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

9 Invited

Modulation of Resistance to Biological Agents

Abstract not received.

10 Invited

Modulation of Resistance to Hormonal Agents

Abstract not received.

11 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.

12 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?

13 Invited

No Axillary Surgery in Breast Cancer?

S. Alran[1], C. Ngô[1], F. Reyal[1], V. Fourchotte[1], A. Tardivon[2], J.Y. Pierga[3], A. Salomon-Vincent[4], A. Fourquet[4]. *[1]Institut Curie, Surgery, Paris, France; [2]Institut Curie, Radiology, Paris, France; [3]Institut Curie, Medical Oncology, Paris, France; [4]Institut Curie, Pathology, Paris, France*

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

surgery'? Clinicians can combine two approaches for a better patients' selection for 'No axillary surgery':

1. By using nomograms predicting the risk of metastatic SLN in order to identify low risk patients. The main nomograms calculating the risk of metastatic SLN integrate the following variables: age of the patients, tumor size, lymphovascular invasion and biological subtypes with three main categories of BC (luminal-like, basal-like, HER2-like). Thresholds have to be determined in order to classify patients as low, intermediate and high risk of metastatic SLN.
2. By using ultrasound-guided needle biopsy of axillary nodes (UNB). Studies have shown that preoperative UNB of axillary nodes has good accuracy and estimates that UNB has a pooled sensitivity of 80 %, specificity of 98,3%, and a PPV of 97,1% assuming a prevalence of node metastases of 47%.

Based on these approaches, we could offer to our patients an individualized axillary surgery according to the combination of the predicting risk calculated by a nomogram and results of UNB. Three options would be possible (1) No axillary surgery in low-risk patients, (2) SLND in intermediate or high risk-patients and (3) immediate axillary lymph node dissection in case of positive UNB.Perspectives studies should be conducted to define and validate the threshold of risk groups. The decision of 'No Axillary Surgery' would eventually be shared with the patient based on her predicted individualized risk within the low-risk group.

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14 Invited

The Sentinel Node Biopsy is Positive: No Axillary Clearance?

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For all cancers, the goals of lymphadenectomy (in order of importance) are staging/prognostication, local control, and the possibility of a survival benefit. Since the pioneering reports of Morton (1991), Krag (1993) and Giuliano (1994), sentinel lymph node (SLN) biopsy has become standard care for axillary lymph node staging at many institutions worldwide. What have we achieved?

First, we have demonstrated that SLN biopsy works. An overview[1] of 69 published studies of SLN biopsy validated by a backup axillary dissection (ALND) confirms an overall success rate of 96%, with a 7% false-negative rate, results which have been confirmed in 5 randomized trials[2–6].

Second, through an extensive literature we have asked and answered the easiest questions. There remain a few areas of debate. These include the management of non-axillary SLN, the timing of SLN biopsy relative to neoadjuvant chemotherapy, pathologic assessment of SLN (intraoperative and postoperative), the significance of SLN micrometastases, and most importantly the need for ALND in SLN-positive patients.

Finally, recent major reports from the ACOSOG Z0010−11 and NSABP B-32 trials are practice-changing.

In Z0010 (n = 5184)[7] and in B-32 (n = 5611)[8], all patients were treated on the basis of routine H&E staining of the SLN, blind to the results of immunohistochemical (IHC) stains. For IHC-positive vs IHC-negative patients, Z0010 found no differences in 5-year OS and B-32 found that 5-year OS, DFS, and DDFS were worse, but by very small margins, 1.2%, 2.8% and 2.8%, respectively.

In Z0011 (n = 813), patients with H&E-positive SLN were randomized to ALND vs no further axillary treatment (all had breast conservation and whole breast but no axillary RT). Additional positive axillary nodes were found in 27% of the ALND patients, but at 6.3 years' followup there were no differences between the ALND and no-ALND arms in axillary (0.5% vs 0.9%), breast (3.6% vs 1.9%) or overall locoregional recurrence (4.1% vs 2.8%, p = 0.53), or in the usage of systemic therapy[9], or in DFS (82.2% vs 83.9%), or in OS (91.8% vs 92.5%)[10].

These results suggest a diminishing role for ALND in SLN-positive patients, particularly those who will receive whole breast RT, and in turn demand a reappraisal of many 'standard' practices, including ultrasound for preoperative axillary node assessment, intraoperative examination of SLN, and the use of nomograms to predict non-SLN status. Whether a policy of 'no ALND' can be extended *beyond* the Z0011 selection criteria to include patients with (for example) T3 tumors, mastectomy, neoadjuvant chemotherapy, and partial-breast RT is a subject for future study.

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15 Invited

The Management of the Axilla Around Neo-Adjuvant Chemotherapy

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The role of treatment of regional lymph nodes in breast cancer is unclear. For clinically node negative disease, Axillary Lymph Node Dissection (ALND) is replaced by the Sentinel Node (SN) procedure. In series where no axillary treatment is performed in case of a positive SN, the incidence of axillary recurrence is extremely low. Large clinical trials of regional treatment are either negative or suffer from lack of events. On the other hand, for clinically node positive or locally advanced disease, aggressive treatment, consisting of neo adjuvant chemotherapy, and locoregional treatment including full ALND and Axillary Radiation Therapy (ART) is generally applied. Several trials have shown that ALND leads to considerable arm and shoulder morbidity, particularly in combination with ART.

Since the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of 2000 it is clear that better locoregional treatment, in particular radiotherapy, improves longterm overall survival of breast cancer. It is unknown whether the survival benefit of locoregional radiotherapy is due to adjuvant treatment of the regional lymph node areas, or to the prevention of local recurrences in the breast or chest wall as such as a result of local irradiation. The recent EBCTCG overview of breast conservation trials with or without local radiotherapy and the lack of events in the regional treatment trials suggest that local treatment may be more important that regional treatment.

We should investigate overtreatment of the axilla not only in patients with clinically node negative disease but also in patients with node positive or locally advanced disease treated with neo adjuvant chemotherapy. In case of yN0 disease after neo adjuvant chemotherapy ART alone or even no axillary treatment at all may well be sufficient. In case of residual axillary disease after neo adjuvant chemotherapy ALND alone or ART alone may be as effective as the combination. These issues should be adressed in randomized clinical trials.