methotrexate and cytosine arabinoside for CNS metastases and LC and progressed. Before the starting of IT trastuzumab administration, the patient presented with headache, gait disturbance, disequilibrium, dysarthria, neck stiffness and reduced flexion of lower limbs. After the first three doses she recovered lower limb motion, resumed her daily physical activities and CSF cytology has been negative ever since. In January 2009 she started capecitabine and iv trastuzumab for worsening lung metastases, later changed in July 2009 to cisplatin/etoposide/trastuzumab for progressive brain metastases, which she is still on. She refused the placement of an Ommaya reservoir, and weekly LP are still being performed with excellent tolerance. So far the patient has received 50 administrations of IT trastuzumab without adverse events. There was an increase in gadolinium leptomeningeal enhancement over time, which was not associated with functional CNS deterioration; this has faded since cisplatin/etoposide was begun. The patient maintains excellent performance, exercises regularly, performs manual tasks and speaks fluently without dysarthria.

Conclusion: Administration of IT trastuzumab is feasible, safe and led to a dramatic functional improvement in a heavily pre-treated HER2+ MBC patient with LC. Further studies are warranted to confirm clinical activity and optimize trastuzumab delivery into the CNS, including dose, schedule and duration of treatment.

487 Poster

Efficacy of first-line capecitabine plus bevacizumab in patients with ER/PgR-positive metastatic breast cancer (MBC) and those previously treated with hormone therapy

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Background: The RIBBON-1 phase-III study of bevacizumab (A) or placebo (p) was performed in two independently powered cohorts, with patients receiving capecitabine (X) or taxane/anthracycline. Progression-free survival (PFS), the primary endpoint, was significantly greater with A combined with chemotherapy in both cohorts. In this analysis, we assess the efficacy of first-line X-containing regimens only in women pretreated with hormone therapy.

Methods: Key inclusion criteria were: age $\geqslant$18 years; HER2-negative locally recurrent/MBC; ECOG score 0 or 1. Patients who had received prior chemotherapy for locally recurrent/MBC or with CNS metastases were excluded. Patients were randomised to X 1,000 mg/m^2 b.i.d. on Days 1−14 per 3-week cycle or p, plus A 15 mg/kg q3w, and stratified according to disease-free interval ($\leqslant$12 or >12 months), prior adjuvant chemotherapy (yes or no), and number of metastatic sites (<3 or $\geqslant$3). The primary endpoint of the study was investigator-assessed PFS. The cohort was independently powered to detect a statistically significant increase in PFS at the 0.05 level.

Results: In total, 615 patients were enrolled in the X cohort (XA: 409; Xp control: 206) and 74% of them had ER/PgR-positive status. Around 50% of patients had received prior hormone therapy for early breast cancer (XA 49.6%; control 52.9%) or locally recurrent/MBC (XA 46.0%; control 43.2%). Overall, PFS was significantly greater with the XA combination than Xp (hazard ratio [HR] 0.69, p = 0.0002; 8.6 vs 5.7 months). Subgroup analysis showed that in patients with ER/PgR-positive status, PFS was greater with XA than with control (HR 0.69 [0.55–0.87]; 9.2 vs 6.2 months for XA vs Xp, respectively). Similarly, PFS was greater with XA in the subgroup of patients receiving prior adjuvant hormone therapy (HR 0.71 [0.54–0.93]; 9.5 vs 6.1 months). Analysis of patients with ER/PgR-negative status also revealed an improvement in PFS with XA (HR 0.70 [0.48–1.01]; 6.1 vs 4.2 months), in-line with the significant overall benefit observed in the X cohort.

Conclusions: In the RIBBON-1 study overall, XA combination therapy achieved a significant improvement over Xp in PFS as first-line therapy for HER2-negative MBC. Here, we show that the XA combination provides clinical benefit in patients with hormone-positive or hormone-negative MBC, as well as in those previously treated with adjuvant hormone therapy.

488 Poster

Characteristics of metastasis in the breast from extramammary malignancies

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Background: Breast metastasis from extramammary neoplasm is rare. We present the cases of metastasis to the breast after review of results in one institute and we want to show the difference of previous report.

Material and Methods: The surgical and pathology databases of Samsung Medical Center from November 1994 to March 2009 were investigated to identify all patients with a diagnosis of metastasis to the breast.

Results: Thirty three patients with breast metastases from extramammary neoplasm were studied. Gastric carcinoma was most common metastatic origin in this study. There were 4 cases with microcalcifications in their metastatic lesions. This is the first report of microcalcification of metastatic lesions to the breast from hepatocellular carcinoma and gastric cancer.

Conclusions: Pathologic examination and considering known clinical history may be helpful to differentiate the primary breast cancer and metastatic cancer. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis. An accurate diagnosis of breast metastases, differentiating primary from metastatic breast carcinoma, is important for proper management.

489 Poster

Bevacizumab (BV) in combination with chemotherapy in the treatment of HER2-negative metastatic breast cancer (mBC): PFS subgroup results from two phase III studies

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Background: Three multicentre, randomised phase III trials of taxane (T), capecitabine (Cap), or anthracycline (Anth) +/− BV established that combination with BV improves progression-free survival (PFS). Outcomes in clinically important subsets are important to demonstrate the consistency of treatment effect and may guide physicians when considering treatment options for patients. Here we compare the activity of BV in various clinically relevant patient subgroups across two phase III studies in mBC.

Methods: Kaplan-Meier methodology was used to estimate median PFS (mPFS) for patient subgroups from the AVADO and RIBBON-1 studies. Patients received BV in combination with docetaxel (D) or placebo (PL) in AVADO and C, T or Anth in RIBBON-1. PFS data based on investigator assessments were used for both trials. For the overall study results, stratified hazard ratios (HRs) are presented with the same stratification factors as the variables that were used for the randomisation, whereas unstratified HRs are presented for the subgroups. Updated data from the April 2009 cut-off (median follow-up 25 months) are shown for AVADO.

Results: In both studies, and in all subgroups shown, an improvement in PFS resulted from combination of BV with chemotherapy.

	AVADO		RIBBON-1			
PFS	PL+D (N = 241)	BV* +D (N = 247)	PL+Cap (N = 206)	BV*+Cap (N = 409)	PL+T/Anth (N = 207)	BV*+T/Anth (N = 415)
Triple-negative disease, n	111		137		142	
Median	6.1	8.1	4.2	6.1	6.2	6.5
HR	0.68		0.72		0.78	
95% CI	0.46–0.99		0.49–1.06		0.53–1.15	
Age $\geqslant$65 years, n	86		153		124	
Median	7.7	10.3	6.2	9.1	8.5	10.1
HR	0.68		0.69		0.83	
95% CI	0.43–1.08		0.47–1.02		0.52–1.34	
Prior adjuvant T, n	77		245		94	
Median	6.7	9.6	4.2	8.7	6.7	9.1
HR	0.51		0.62		0.65	
95% CI	0.32–0.82		0.45–0.84		0.39–1.07	

*15 mg/kg q3w; CI=confidence interval.

Conclusions: Although combination of BV with chemotherapy consistently improved mPFS across a number of clinically relevant subsets, regardless of the chemotherapy backbone used, absolute improvements in HRs and mPFS varied within subsets and across the trials.

490 Poster

Long term survival and incidence of brain metastasis in HER2-positive (HER2+) metastatic breast cancer patients (MBC) treated with trastuzumab (T): an institutional based review

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Background: HER2+ status is associated with poor prognosis, high incidence of visceral and brain metastasis. However the addition of

trastuzumab to chemotherapy (CT) significantly improves survival in early and advanced breast cancer. The purpose of this retrospective study was to explore the pattern of outcome in a cohort of MBC patients treated with T-based chemotherapy in a single institution. T was approved in Europe in 2000 and in 2001 all pts had access to T according HER2+ status.

Methods: Women with de novo or recurrent breast cancer treated with trastuzumab at Institut Curie between 2001 and 2006 with HER2+ status (IHC 3+ or FISH +) were identified from the Institut Curie database. Disease was classified in two groups: patients who received T upfront and those who received T after one or several CT regimens. Overall survival (OS) was defined as the time from the date of the first metastasis to the date of death or last follow-up and was estimated using the Kaplan-Meier product method.

Results: The final analysis included 244 patients. Median age was 53.4 yrs (29−80). Median time from primary and first metastasis was 22 mths (0–238). Visceral metastasis were present in 153 pts (63%) and 125 pts (51%) presented multiple sites. One hundred pts (42%) developed brain metastasis during the course of disease. One hundred and sixty five pts (68%) received T as first line, 79 pts (32%) after a median of one line of CT (median 1, range 1−5). One hundred and twenty four pts (52%) received more than 3 regimens. The median overall survival was 53 mths (4–113), similar in both groups. However there is a major bias: pts with very aggressive disease not treated upfront with T not have not been offered delayed T and don't appear in the analyzed population. Patients who developed brain metastasis had a median survival of 41 mths (11−90). Complete characteristics of pts will be presented.

Conclusions: The introduction of T has altered the natural history of HER2+disease. Even outside a clinical trial, our results show that the addition of T to CT improves the prognosis of MBC patients with HER2+ disease. Prolongation of T after progression with other CT appears beneficial, even in pts with a high disease burden. The high incidence of brain metastases remains an issue in such a population and new strategies of prevention and treatment need to be addressed.

491 Poster

Affecting factors to the survival of breast cancer with brain metastasis

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Background: Brain metastasis (BM) associated with breast carcinoma commonly occur in later stage of metastatic disease and strongly affect survival of the patient. Recently, several studies reported that breast cancer subtypes may be related with central nervous system recurrence rate and survival after BM. Aim of this study was to identify tumor characteristics and the affecting factors to the survival of breast cancer patients with BM at our oncology hospital.

Material and Methods: Medical records of 123 primary breast cancer patients with brain metastasis receiving treatment in a cancer center between january 2004 to August 2009 were rewieved retrospectively. 105 patients whose steroid hormon receptors (estrogen receptor (ER) and progesteron receptor (PgR) and HER-2 status of their tumors were assesed hve been included in the study.

Results: Median age at the diagnosis of breast cancer was 42 (range 24−78 years). Except one male patient, all of the patients were women. Only seven patients had metastatic disease at the presentation. Sixty (57.1%) patients had HER-2 positive tumors. Thirteen (12.4%) patients had triple negative tumors. Sixtyeight (64.7%) patients had ER and/or PgR positive tumors. BM was the first site of relaps in 16 (15.2%) patients. Sixtyfive (61.9%) patients had multiple BM, 10 (9.5%) had both metastasis of brain parenchyma and the leptomeninges. Seventeen (16.2%) patients underwent brain surgery or cyber- or gamma-knife surgery for BM. Ninetythree (90.3%) patients received whole-brain radiotherapy. No HER-2 positive patients received adjuvant trastuzumab therapy. Fortyfour patients was given trastuzumab for treatment of metastatic disease.

Median disease free survival (DFS) was 18.3 months (range 0–183 months). Median overall survival was 35.1 months (range 1–208). Median survival after BM was 6.2 months (range 0−50 months). Median survival of four groups of patients after BM were as follows respectively:

for triple negative group was 5.47 months (range 0−26 months);
for ER and/or PR positive and HER-2 negative group was 9.6 months (range 0−50 months);
for ER and/or PgR positive and HER-2 positive group was 8.2 months (range 0−23 months);
for ER and/or PgR negative and HER-2 positive group was 7.1 months (0−18 months).

Multiple linear regression (backward) model showed that having young age (r: −1.93; CI%95: −0.375–0.001); p = 0.056), ER positivity (r: 2.34; CI%95: 0.62−7.5; p = 0.021) and adjuvant chemotherapy (r: 1.68; CI%95: −0.06–7.4; p = 0.09) affected the survival positively. Patients treated with cranial RT had longer survival with BM (4.9±5.07 vs. 9.9±9.3 months) but the difference was marginally significant (p = 0.09).

Conclusion: Survival after BM of the patients with triple negative and HER-2 positive breast cancer are shorter than steroid hormon receptor positive and HER-2 negative breast cancer with BM. New effective treatment strategies are required for these poor risk groups.

492 Poster

Chemotherapy and bevacizumab combinations in second-line or more for metastatic breast cancer: efficacy and toxicity results

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Background: In first line metastatic breast cancer (MBC), bevacizumab (B) in combination with chemotherapy [taxanes (T), anthracyclines or capecitabine (C)] is more efficient in comparison with the same mono chemotherapies regimens. However, such combinations are not approved in subsequent lines of therapy even if the patients were treated in first line MBC without B before the BT combination approval. in order to evaluate the efficacy and toxicity profile of these combinations in at least second lines of treatments for MBC we have extract from our chemotherapy database the population of patients treated with bevacizumab-chemotherapy combinations for MBC.

Methods: A retrospective analyzis was performed on all the MBC patients treated with B combined with chemo, between 1/2007 and 12/2008, in the oncology departments of APHP Tenon hospital in Paris. Statistics were descriptive for the population, the efficacy and the toxicity.

Results: 55 patients received B combined with T in 34 cases (62%) or C/5FU in 16 cases (29%). Median age was 57.3 years [37.7–76.8]; 55.2 years [37.7–76.8] in the B-T treated group and 60.9 years [48.5–76.8] in the B-C/5FU treated group. Median number of previous lines was 4 [2−11]. At a median follow up of 11 months [0−28] 65% of all the patients are still alive. According to the presciber evaluation the median duration of the clinical benefit, measured as the delay between the first day of B-chemo combination and the date of progression or last news date, was of 4.2 months [0.7–16.6]; 4.2 months [0.7–16.6] in the B-T treated group and 5 months [0.7−8.3] in the B-C/5FU treated group. 27 patients (49%) had an objective response and 13 (24%) had no clinical benefit and readily progressed under therapy. We didn't find predictive factor for clinical benefit of the combination but we didn't find that previous taxane therapy for MBC was associated with a worst efficacy of B-chemotherapy regimens. Considering the toxicity profile, we didn't find different outcomes comparing to the reported results in the randomized phase III trials concerning the first line MBC treatments with chemotherapy and B.

Conclusions: in this retrospective analysis, in heavily pretreated MBC patients the combination of B-chemotherapy seems feasible without an increasing level of toxicity. However, this strategy had to be evaluated in a porspective trial considering the absence of approval of B-chemotherapy combinations beyond 1st line MBC treatment.

493 Poster

Prognostic factors to predict outcomes in patients with HER2-overexpressing metastatic breast cancer treated with trastuzumab containing chemotherapy as first or second line therapy: prognosis grouping according to the prognostic factors

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Background: To investigate prognostic factors to influence overall survival (T-OS) in patients with HER2 overexpressig metastatic breast cancer (HO-MBC) who underwent first or second line trastuzumab containing chemotherapy.

Patients and Methods: From January 2003 to May 2008, clinical and laboratory findings of 89 patients at the time of trastuzumab administration were analyzed to correlate with T-OS.

Results: In univariate analysis, estrogen and progesterone receptor positivity (p = 0.047), lung metastasis (p = 0.006), liver metastasis (p = 0.006), 3 or more metastatic sites (p = 0.002), elevated aspartate aminotrasferase (AST) (p = 0.005), elevated alkaline phosphatase (0.039), and elevated total bilirubin (p = 0.001) were significant factors to affect T-OS. In multivariate analysis, presence of lung metastasis (p = 0.004, hazard ratio=5.440, 95% CI = 1.722–17.180) and elevated AST (p = 0.004, hazard ratio=4.035, 95% CI = 1.549–10.514) were significant poor risk factors for T-OS. Based on risk factors in multivariate analysis, three prognosis groups were categorized: good prognosis group (risk factor = 0),