Background
Tumor biological changes -- e.g., hormone receptor status (HR), HER2, or grading -- between primary tumor (PT) and metastatic tissue (MT) could impact outcome and treatment choice following first recurrence in breast cancer (BC).

Methods
PRIMET is a prospectively planned, retrospective multicenter quality assurance study comparing BC phenotype in tissue from PT, involved lymph nodes (LN) of primary disease, and disease recurrence (DR). PRIMET comprises 635 patients from the WSG and DETECT trial groups (11 centers), whose BC was diagnosed between 1980 and 2010; follow-up continued until mid-2012. Patients with unilateral primary BC suffering subsequent local-regional and / or distant DR (LDR / DDR) were included. Clinical data in PT and DR, including ER, PR, HER2, and grade, were obtained from a systematic chart review; in two centers, these factors were also measured in LN by central pathology. The impact of changes in tumor biological factors on post-recurrence survival (PRS) was analyzed.

Results
Fig. 1 summarizes characteristics of the collective. Data from 635 patients (including 592 cM0, of whom 46% had LDR only) were available for analysis. Median follow-up in patients alive at last contact was 126 months; median recurrence-free survival (RFS) was 48 months (DDR present: 45 months; LDR only: 50 months). Median PRS was 59 months (DDR present: 45 months; LDR only: 127 months). In patients without LDR within 18 months, median PRS was 29 months, in others 79 months.

HR status in PT/MT groups is shown in Fig. 2. About 19% had a switch, with 13.2% losing hormone sensitivity and 5.5% acquiring it. Moreover, of the HR “switches” (in either direction) with LN biopsy available, about half had already occurred in lymph nodes. HER2 status in PT/MT is shown in Fig. 4. About 22% had a switch including 6.7% (+/-) and 14.9% (-/+). With LN biopsy available, most losses of HER2 overexpression were already observed in LN tissue, whereas acquired HER2 overexpression was observed in about half of LN biopsies (Fig. 4). Triple negative (TN: HR-, HER2-) percentages were 74.4% (non-TN/non-TN), 9.0% (non-TN/TN), 6.1% (TN/non-TN), 10.5% (TN/TN). Compared to HR+/+, loss of HR+ status (HR+/-) was significantly associated with poorer PRS (hazard ratio: 1.62; p=0.01) (Fig. 3). A switch from G3 to G1/2 was associated with significantly better PRS (hazard ratio: 0.47; p=0.02). Tumors that switched to TN or that lost HER2 overexpression showed trends toward poorer PRS (Fig. 5). Persistent TN was associated with poorer PRS than other combinations. Among patients with DDR, metastasis only in bone was associated with better PRS than primary or visceral (CNS, lung, liver, etc.) metastasis. Among patients with visceral metastasis, negative HR status in metastasis was associated with poorer survival than in HR+/- not only for HR-/- (p=0.02), but also for HR+/- (p=0.04) (Fig. 6).

Conclusions
Tumor biology of primary and metastatic tissue differed in a substantial fraction of patients (HR: 19%; HER2: 22%; TN: 18%). More than half of all switches occurred already in the axillary LN. Status changes, particularly loss of HR+ status, had a significant prognostic impact for post relapse survival. We can expect a switch in HR or HER2 status (or both) in about 38% of metastatic tissue biopsies, with important clinical therapeutic consequences, in particular regarding targeted therapies. This trial confirms the necessity of a re-biopsy upon first metastasis with regard to optimal treatment choice and survival as supported by international guidelines such as ABC.

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