A novel serum protein-based assay for monitoring response to therapy and recurrence of breast cancer

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Introduction

Monitoring recurrence and evaluating response to therapy are important aspects of clinical decision making in the treatment of Breast cancer (BC). Serum tumor markers such as cancer antigen 15-3 are used by many physicians, but without clear recommendations from clinical societies. We used an in-house developed modular proteomic array platform, to identify a protein biomarker (BF-09 antigen) that was differentially expressed in BC tissues versus normal counterparts, present in early and late stages and measurable in serum[1-2]. The present study is designed to assess the performance of our assay in (neo)adjuvant and metastatic treatment follow-up.

Materials and Methods

The concentration of our BC biomarker was measured by ELISA assay in a pilot study using retrospective serial serum samples from 85 BC patients obtained from a biobank at the IRCCS San Raffaele Pisana Research Center (Italy). 313 samples from 72 patients (72.2% stage I-III; 27.8% stage IV) had enough information for primary analysis. Change in biomarker concentration was correlated with clinically recorded outcomes at different points before and/or after surgery and treatment. A significant increase or decrease in BF-09 concentration was defined as a change equal or superior to 2.5 times the %CV of the assay as compared to a previous point and interpreted as progression or no progression, respectively. Sensitivity (SE), specificity (SP), accuracy, negative (NPV) and positive predictive values (PPV) of the assay were calculated using MedCalc version 23.1.3 with a BC recurrence prevalence rate of 16.6%. Lead time was calculated as the time from first BF-09 serum rise to clinical recurrence or neoadjuvant response for patients with available samples. 95% confidence intervals (CI) were calculated using MedCalc version 23.1.3. Differences between median BF-09 levels were determined by 2-sided Wilcoxon rank sum test.

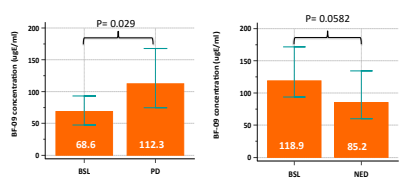


Figure 1. Adjuvant treatment follow-up. Median BF-09 serum level at baseline (BSL, within 1 year of AT start) and (left) relapses/PD or long-term NED (right). Statistically significant difference between medians by Wilcoxon test of paired samples when (p<0.05). Overlaid error bars represent 95% confidence interval.

Application	SE (%) / 95% CI	SP (%)/ 95% CI	PPV (%)/ 95% CI	NPV (%)/ 95% CI
NAT (N=24)	70/ 34.7-93.3	79/ 49.2-95.3	39.4/ 18.1-67.7	92.9/ 83.1-97.2
AT (N=35)	75/ 47.6-92.7	89/ 66.9-98.7	58.7/ 27.1-84.4	94.7/ 88.4-97.7
Early BC FU (N=59)*	73/ 52.2-88.4	85/ 68.1-94.9	49/ 29.3-67.0	94.1/ 89.2-96.8
MBCT* (N=40)	75/ 58.8-87.3	NA	NA	NA
All groups (N=99)*	74/ 62.0-84.2	85/ 68.1-94.9	49.4/ 30.0-68.9	94.3/ 91.5-96.2
All groups /HR+HER2- (N=66)*	78/ 61.5-89.2	89/ 69.9-97.6	57.2/ 31.3-79.7	95.2/ 91.6-97.3

Table 1. BF-09 Assay performance as measured by changes in detecting PD during neoadjuvant (NAT), adjuvant (AT) and metastatic treatment (MBCT) follow-up. Test performance in 72 patients (99 disease status events) grouped by therapy phases. Early BC follow-up includes stages I-III while All Groups includes stages I-IV. *Per sample sensitivity (SE)/Specificity (SP). N= number of follow-up events.

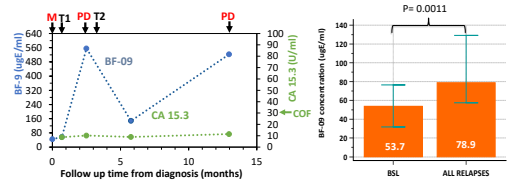


Figure 2. Metastatic treatment follow-up. (Left). BF-09 and CA 15-3 dynamics during MBCT follow-up as illustrated in one stage IV patient with lung metastasis. T1: FEC+ Dexrazoxane; T2 TXT + Capecitabine. PD to lung. **(Right)** Median BF-09 serum level at baseline (BSL, diagnosis of metastasis) and points nearest all relapses in 30 patients (40 relapses). Statistically significant difference was found between medians by Wilcoxon test of paired samples (p<0.05). Overlaid error bars represent 95% confidence interval.

Results and Conclusions

- The overall per-sample (N=99, 66 PD, 33 NED) performance of the BF-09 assay for progressive disease/recurrence (PD) was calculated for each therapy setting (neo/adjuvant and metastatic). Sensitivity ranged from 70-78% at 79-89% specificity with 39.4-58.7% PPV and 92.9-95.2% NPV and an overall accuracy of 83-86.7%. Median lead time in detecting relapses was 9.4 months (range 0.8-27 months).
- The results of this pilot study showed the clinical validity of the BF-09 biomarker in various clinical settings. Further testing is needed to confirm these results in a prospective trial population.

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References

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[2] Chavany et.al. A Serum Biomarker for the Early Detection of Breast cancer. Cancer Res (2024) 84 (9_Supplement): PO5-07-08.

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