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Microtubule-Associated Protein Expression and Predicting Taxane Response

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14. ABSTRACT  
Taxanes are microtubule targeting agents (MTAs) and potent cytotoxic molecules recognized as highly effective chemotherapeutic agents. In large randomized clinical trials, taxane-based chemotherapies provided benefits in overall and disease-free survival, but they are accompanied by significant adverse effects. Thus the clinical utility of taxane therapy would be enhanced if there were companion diagnostic tests so that only the taxane-sensitive patients (about half of breast cancers) could be treated with this drug. Accumulating evidence indicates that microtubule associated proteins (MAPs) may be responsible for tumor cell resistance to taxanes. Our results indicate that MAP-tau functions as a prognostic factor in both the Yale cohort and the TAX 307 cohort with high MAP-tau expression associated with longer overall survival and TTP. Tau does NOT behave as a predictor of response to taxane-based chemotherapy since differences between low and high MAP-tau groups by treatment arm and response rate were not observed in the TAX 307 clinical trial cohort. Our data supports the use of MAP-tau as a prognostic marker, but does not support its use as a singular predictive factor for response to docetaxel. We have also evaluated the microtubule destabilizer, stathmin, and found high expression is associated with worse outcome. Since stathmin expression is useful in predicting survival, it may serve as marker to accurately select patients for current taxane-based or other anti-microtubule therapies in combination with a microtubule stabilizer such as MAP-tau.  

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Microtubule-associated proteins (MAPs), MAP-tau, breast cancer, tissue microarrays, biomarkers  

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**Introduction**

Breast cancer is the leading cause of cancer death in women between the ages of 20 and 59 accounts for more than 31% of all new cancers diagnosed in women and is the leading cause of death for women worldwide [1, 2]. While breast cancer family history is an important risk factor, sporadic cases account for more than 90% of all breast cancers and the etiology of this cancer remains largely unknown [3].

The current standard of care for breast cancer patients includes administration of taxanes to the majority of breast cancer patients despite the fact that more than 50% of these patients will be unresponsive to treatment. A companion diagnostic to accurately select responders to taxane therapy does not exist. Such a diagnostic remains critical for advancing breast cancer therapy and patient care, in anticipation of the availability of a comprehensive range of breast cancer therapeutics alongside the taxanes, from which clinicians will need to select the optimal combination depending on the specific tumor profile of the patient. Consequently, the development of a companion diagnostic that can accurately determine patient sensitivity/resistance to taxanes remains a critical research objective in breast cancer research.

Microtubule associated proteins, such as MAP-tau and stathmin, have begun to gain attention as potential prognostic and predictive markers for taxane response. In previous work, elevated MAP-tau expression was found to decrease microtubule vulnerability to taxanes such as paclitaxel and make cells resistant to taxane treatment in vitro. When MAP-tau was evaluated in the neoadjuvant setting, it was found to be predictive for response to paclitaxel [5]. However, additional studies confirming these results in the primary and metastatic setting are needed.

The underlying goal of this project is the discovery, molecular characterization, and functional assessment of microtubule stabilizing proteins as biomarkers to accurately select patients for taxane therapy. The assessment of the prognostic and predictive significance of microtubule-associated proteins in relation to microtubule targeting agents will facilitate the development of a clinically relevant panel of markers that can effectively select breast cancer patients for taxane therapy. This research will directly impact the management of cancer through the development of a companion diagnostic that utilizes the biological properties of the patient tumor, MAP expression, to determine the appropriate therapeutic combinations most likely to maximize treatment benefit while minimizing toxicity and other losses to quality of life.

**Body**

**Task 1:** Evaluation of tau as a prognostic and predictive marker for paclitaxel sensitivity using AQUA.

Tasks 1A and 1B evaluated the prognostic value of MAP-tau have been completed. (Please view the 2008 Report for more information).
1C. Validate the predictive significance of MAP-tau for response to taxane therapy using independent breast cancer cohorts from two non-Yale affiliated clinical trials involving paclitaxel chemotherapy.

To evaluate the TAX 307 cohort, fluorescence-based immunohistochemistry on 140 floated, whole tumor sections was performed. We also evaluated in parallel, 6 YTMA-94-1 control tissue microarrays containing cell lines MB468, BT474, ZR75.1, T47D, and MB231. The TAX 307 tumor sections were accompanied by H&E slides with long term clinical follow up data from patients randomized to the AT arm of TAX 307. Automated quantitative analysis (AQUA) was used to evaluate MAP-tau expression, with cytokeratin staining defining pixels as breast cancer within the array spot and Cy-5 conjugated antibodies used to measured the intensity of MAP-tau expression. Image acquisition was limited to all tumor section areas containing cytokeratin staining. Approximately 15,686 images were collected and analyzed due to the size of the tumor area and the image acquisition matrix utilized by PM2000.

Preliminary data indicating that MAP-tau is not predictive was presented in 2009. This data contradicts previous results from the Lajos Pusztai group at MD Anderson. To strengthen these initial findings, we used a normal breast tissue microarray (YTMA 55) to determine a biologically relevant cutpoint rather than the cohort median AQUA score. The median AQUA score is statistically unbiased, but biologically ambiguous stratification for distinguishing high expressors from low.

In addition to normal breast tissue analysis, a third pilot study* was conducted to classify all case images (~ 15,000) as either normal, invasive, or DCIS tissue. Using the AQUA matrix/quadrant system, it was possible to image the entire tissue whole section of each case with the disadvantage that the presence of a large number of normal tissue images could, in effect, ‘contaminate’ the cohort data, acting as a strong confounder and causing MAP-tau to appear non-predictive for taxane response. However, we found only 3 cases with normal tissue (total of 42 images) and these images were removed from the data set. All other images of normal tissue had been excluded automatically during validation due to insufficient tumor mask percentage. The remaining cases contained mostly invasive tumor tissue and some DCIS (7 mixed cases with invasive and DCIS).

TAX 307 data analysis required both prognostic value (biological outcome of the disease regardless of treatment) and predictive value (tumor response based on treatment) assessment. Predictive value included the evaluation of randomized treatment arms and clinical response data (complete response CR, partial response PR, stable disease SD, and progressive disease PD), as well as interaction effects, randomization subset parity, appropriate stratification for ER, HER2, and treatment, versus MAP-tau expression, and more complex multivariate analysis (in collaboration with Dr. Annette Molinaro, Department of Biostatistics, Yale School of Epidemiology and Public Health).

Two TAX 307 Pilot Studies were conducted. The first study, Pilot 15, evaluated the mean, median, modality/ general population distribution for all acquired images of 15 randomly selected cases, as well as DAPI, cytokeratin, and MAP-tau
immunofluorescence and localization. These results indicated primarily unimodal distributions and excellent immunofluorescence localization.

The second study, Pilot 10, addressed the issue of tissue sampling and representativity in tissue whole section slides: we asked, what is the minimum number of images needed to accurately characterize high or low MAP-tau expression for a TAX 307 case? We found statistically significant correlations between the median score of 10 confirmed invasive tumor images for 44 cases versus the median score of all images for each of the 44 cases (mean = 615 for all images vs 670 for ten invasive-only images; median = 383 for all images vs 341 for ten invasive-only images; we used the non-parametric test, Spearman rho, p < 0.001). These results indicate a strong correlation between the median AQUA score calculated for all- images-only and the ten-invasive-only images. We conclude that 10 images or possibly less can accurately represent a tissue whole section. We did not test for less than 10 images so we do not know the absolute minimum number of images needed. More significantly, we conclude that it is unnecessary for all images of a tissue whole section to be acquired and analyzed in order to obtain representative results for the entire section.

1D. We evaluated a third cohort for MAP-tau predictive value using the CALGB 9840 (Cancer and leukemia Group B) array. This was a phase III study of weekly paclitaxel via 1 hour infusion versus standard 3 hour infusion every 3rd week for metastatic breast cancer. The microarray was comprised of 100 cases of tumor tissue in triplicate. All HER2 positive patients were randomized to receive trastuzumab. Data analysis was submitted to CALGB biostatistics for analysis. Results showed no prognostic or predictive value for MAP-tau, confirming our previous results from the TAX 307 clinical trial.

Outcome/deliverables: Evaluation of

Task 2: Construction of a Taxane Therapy tissue microarray as a training cohort for future predictive markers beyond tau.

A retrospective cohort of 90 patients treated with taxane monotherapy at Cornell Medical Center was assembled and tissue samples from this cohort were used to construct a TMA. In order to validate the predictive significance of the MAP/TAX Biomarker Assay for response to therapy, we will construct and assess an independent, prospective TMA cohort. YTMA 172 from Cornell Medical School/Dr. Linda Vahdat.

i. Cataloguing of all tissue samples: COMPLETED
ii. Transported all tissue samples to Yale: COMPLETED
iii. Lori Charette meeting to plan for TMA construction: COMPLETED
iv. H&E tumor assessment, marking, and pathologist review: COMPLETED
v. H&E replacements IN PROGRESS
Outcome/deliverables: Novel taxane tissue microarray block with 100-150 TMAs. Each TMA contains 90 histospots in replicate (total of 180 histospots) with microtubule-stabilizing protein cell line controls.

Task 3. Analysis of additional tubulin isoforms and other microtubule stabilizing proteins as potential biomarkers for predicting response to taxanes.

Screen MAPs (n=11) for predictive significance using a Yale taxane therapy TMA in order to select appropriate markers for the development of a multiplexed, expression-based assay (MAP/TAX Biomarker Assay).

In-depth literature search for antibodies used for IHC and/or in immunoblotting and search for commercial availability. RBC: remains to be completed.

Stabilizers
1. MAP-tau: Antibody and titration, immunofluorescence of boutique and large cohort arrays, image capture, AQUA, and statistical analysis: COMPLETED
2. Dis1/TOG Currently on backorder.
3. CLIP-170 IN PROGRESS
4. EB1/Bim1p Currently on backorder.
5. XMAP215 Not commercially available.

Destabilizers
1. Stathmin: Antibody and titration, immunofluorescence of boutique and large cohort arrays, image capture, AQUA, and statistical analysis: COMPLETED
2. KIF2c/MCAK Antibody and titration, immunofluorescence of boutique; large cohort arrays; COMPLETED
3. Kinesin13 IN PROGRESS
4. Katanin Currently on backorder.
5. APC Currently on backorder.
6. Myosin Va Antibody and titration, immunofluorescence of boutique and large cohort arrays, image capture, AQUA, and statistical analysis: COMPLETED

Outcome/deliverables: Eleven MAPs were selected for evaluation with four MAPs titered and evaluated for prognostic value, two MAPs in progress and five MAP antibodies currently unavailable for evaluation.

Task 4: Determine the prognostic value of the different components for each microtubule stabilizing antibody utilizing Kaplan-Meier survival curves, univariate and multivariate analysis in conjunction with the clinical information in the database. COMPLETED
a. Determine the protein expression levels of the different components for microtubule stabilizing antibody using AQUA to quantitate fluorescence intensity in three subcellular compartments (nucleus, cytoplasm, membrane) **COMPLETED**

b. Determine the prognostic value of the different components and of each microtubule-stabilizing antibody utilizing Kaplan-Meier survival curves, univariate and multivariate analysis in conjunction with the clinical information in the database **COMPLETED**

Timeline: Months 28-36
Outcome/deliverables: Data indicates that MAP-tau and stathmin are strong prognostic factors for survival in patients with breast cancer. Alone, MAP-tau is not predictive for taxane response but a combination of MAP-tau and stathmin may have predictive value.
Figure 2. MAP-tau Expression in Yale University Cohort

A
Cytokeratin & Mask
Tumor Mask
DAPI
Target: MAP-tau
AQUA score: 789
Frequency distribution for MAP-tau expression in Yale University cohort

B

Preselected cutpoint based on normal breast tissue MAP-tau expression

C

MAP-tau expression in Yale University cohort

Yale University Overall Survival (Probability)

Follow-Up (Months)

$P = 0.003$
D. MAP-tau expression stratified by ER status in Yale University cohort

E. MAP-tau expression in ER positive cohort
F  MAP-tau expression in ER negative cohort

G  MAP-tau expression stratified by HER2 status in Yale University cohort
H  MAP-tau expression in ER positive patients stratified by HER2 status in Yale University cohort

- HER2 NEG/TAU HI
- HER2 NEG/TAU LO
- HER2 POS/TAU HI
- HER2 POS/TAU LO

20 years

I  MAP-tau expression in ER negative patients stratified by HER2 status in Yale University cohort

- HER2 NEG/TAU HI
- HER2 NEG/TAU LO
- HER2 POS/TAU HI
- HER2 POS/TAU LO

20 years
Figure 3

MAP-tau expression for patient case 24 from TAX 307S cohort

Frequency distribution for MAP-tau expression in TAX 307S

Preselected cutpoint based on normal breast tissue MAP-tau expression
**Figure 4**

**A**
Baseline for comparing TAX 307 with TAX 307S

TAC vs FAC treatment in TAX 307S cohort

Time to Tumor Progression (Months)

- **FAC Treatment**
- **TAC Treatment**

$p = 0.312$

**B**
MAP-tau expression in TAX 307S cohort

Time to Tumor Progression (Months)

- **MAP-tau expression score HI AQUA score ≥ 462**
- **MAP-tau expression score LO AQUA score < 462**

$p = 0.013$
C MAP-tau expression stratified by treatment in TAX 307S cohort

TAX 307S Cohort

Probability of Progression Free Survival

Time to Tumor Progression (Months)

$P = 0.006$

D MAP-tau expression in ER positive patients stratified by treatment in TAX 307S cohort

TAX 307S Cohort

Probability of Progression Free Survival

Time to Tumor Progression (Months)

$P = 0.006$
**E**

**MAP-tau expression in ER negative patients stratified by treatment in TAX 307S cohort**

![Graph showing Kaplan-Meier survival curves for different treatment groups.](image)

*P* = 0.662

**F**

**MAP-tau expression in TAC treated patients stratified by ER status in TAX 307S cohort**

![Graph showing Kaplan-Meier survival curves for different ER status groups.](image)

*P* = 0.221
MAP-tau expression in FAC treated patients stratified by ER status in TAX 307S cohort

Probability of Progression Free Survival

Time to Tumor Progression (Months)

ER POS/TAU HI
ER NEG/TAU LO
ER NEG/TAU HI
ER POS/TAU LO

$P = 0.108$
Key Research Accomplishments

This work demonstrated the following:

- In the Yale Cohort (YTMA 49-4 and YTMA 49-5) comprised of early stage breast cancer patients, MAP-tau functions as a prognostic marker. MAP-tau is a microtubule stabilizing protein (Appendix D).

- In the TAX 307 clinical trial cohort comprised of metastatic breast cancer patients, MAP-tau is a strong prognostic marker but is not predictive for taxane response (Appendix D).

- Increased MAP-tau expression is associated with better outcome in breast cancer patients and with longer time to tumor progression and is an independent predictor of survival (Appendix D).

- MAP-tau is a useful prognostic marker in early and metastatic breast cancer. However, it is not a predictive marker for taxane response (Appendix D).

- Stathmin, a microtubule destabilizing protein, is strongly prognostic and is an independent predictor of survival. The predictive value of stathmin for taxane response is currently being evaluated using a taxane-treated cohort (Appendix E).

- Examining additional microtubule associated proteins for predictive value and evaluating stabilizer to destabilizer ratios may provide a better model for taxane response prediction.

- Examining tissue heterogeneity using both whole tissue sections and tissue microarrays can clarify the usefulness of TMAs in cancer diagnosis and treatment.

Reportable Outcomes


3. TAX 307 whole tissue sections stained with T1029 MAP-tau Mab (Appendix A and Figs. 1-5).

4. Whole Section Tissue database with 15, 604 images. (Figs. 1-5)
5. 6 control slides created: YTMA 94-1 tissue microarray with 120 histospots (Fig 4).


7. PhD dissertation research project that is specifically and uniquely breast cancer-focused in Department of Experimental Pathology program at Yale University with mentoring and training emphasis in breast cancer research that would not be possible without this grant.

**Conclusion**

Our research findings indicate that increased MAP-tau expression is associated with better outcome and that MAP-tau is a prognostic marker in early and metastatic breast cancer settings. However, MAP-tau alone is not predictive for taxane response in either the early or metastatic breast cancer settings. We have also examined the microtubule destabilizing protein, stathmin, and found strong prognostic value. This marker will be tested on a taxane-treated tissue microarray to evaluate predictive power for taxane response. Additional microtubule related proteins have also been examined and show prognostic value for multiplexing with MAP-tau. We hope to determine if specific combinations of microtubule stabilizing and destabilizing proteins, rather than simply one protein marker such as MAP-tau, may provide improved molecular signatures for taxane responsiveness.

The dual functionality of MAP-tau in combination with other MAPs may translate into increased tumor molecular screening information for patients with breast cancer resulting in better treatment options. Consequently, these microtubule associated proteins may serve as valuable biomarkers for personalized molecular assessment of breast cancer tumors. We have systematically evaluated MAP-tau and stathmin, a stabilizer and destabilizer, and are working to systematically evaluate several other microtubule proteins with prognostic value.
References

Appendices
Appendix A

Automated Quantitative Analysis (AQUA)

What is an AQUA Score?

- Each pixel within the mask is assigned a user-defined subcellular compartment (or unassigned)
- The intensity of the “target” of interest is measured on a scale of 0-255 in each pixel in each compartment
- The final score is normalized by dividing the total target intensity by the area of each subcellular compartment.
- The final score is proportional to a number of molecules per unit area.

Methods and Instruments
AQUA Analysis of Tissue

The AQUA software linked to the fluorescence microscopy system allows for quantification of the protein of interest within the tumor region of each tissue microarray core.

Step 1: Cytokeratin is used to separate epithelial tumor from surrounding stroma, creating a tumor mask.

Step 2: Different fluorescent tags (like DAPI, Cy-5 tyramide) are used to demarcate subcellular compartments (nuclear, membrane, cytoplasmic, etc).

Step 3: Due to the thickness of the tissue sections and the resulting overlap of compartments, a rapid exponential subtraction algorithm (RESA) is used to subtract an out-of-focus image from an in-focus image, providing improved pixel assignment to subcellular compartments. An AQUA score is generated for each compartment ranging from 0-255 (see box What is an AQUA score...)

Step 4: At the Cy-5 wavelength, which is outside the range of tissue autofluorescence, the target of interest is tagged and measured within the subcellular compartments by the PLACE algorithm.

The resulting AQUA score is the measurement of the biomarker pixel intensity within a compartment divided by the total area of the compartment (to normalize for differences in tumor area in each spot).
Appendix B
TAX 307 Patient Characteristics and Study Design

- Cases obtained from the TAX 306 Study Group (2003) (Dr. Lyndsay Harris, Yale Breast Cancer Center)
- Patients randomized to:
  1) FAC: 5-Fluorouracil + doxorubicin (DNA intercalation & anthracycline) + cyclophosphamide (alkylating agents); 56 patients total
  OR
  2) TAC: docetaxel + doxorubicin (DNA intercalation & anthracycline) + Cyclophosphamide (alkylating agent); 62 patients total

- Study Design:
  - Multicenter: 58 total in Europe, S. Africa, S. America, Australia, Canada
  - Randomized (centralized)
  - Non-blinded
  - Phase III

- Primary endpoints: Time to treatment progression (TTP)

- Secondary endpoints: overall response rate (ORR), time to treatment failure (TTF), toxicity, survival, quality of life (QoL)

- Inclusion criteria:
  - adjuvant or neoadjuvant non-anthracycline chemo OK
  - prior hormonal therapy OK, but not concurrent
  - NO previous taxanes

- TAX 307 cohort: 140 cases from both TAC and FAC arms

- Censored:
  - Adverse events
  - Withdraw consent
  - Other reasons
  F=8 (14.2%), T=18 (29%)

- Uncensored:
  - Disease Progression
  - Max Number of cycles
Appendix C

**TAX 307 Whole Tissue Sections**

**Methods**

- 140 cases:
  - Floated, whole tumor sections
  - PLUS slides inconsistently used
- 85 matching H&E slides
- 6 control slides: YTMA 94-1; Cell lines for secondary normalization + staining quality control
- Staining:
  - 6 consecutive batches:
    - 25 slides/batch + 1 YTMA 94-1
    - 1 week period: early November 2006
- Target:
  - MAP-tau mouse monoclonal antibody
  - US Biological; 1:750 dilution (titrated)
- Image Capture:
  - HistoRx Image Grabber
- Quantitative analysis of specimens:
  - HistoRx AQUA
Appendix D

AACR 2009 Late-breaking Abstract

Character limit: 2600 characters
Total count: 2453 characters
Word Count: 357

Category: Molecular biomarkers for diagnosis, prognosis, and prediction
Subclassification: CL13-03 Biomarkers predictive of benefit from therapy
Keywords: biomarker, MAP-tau, taxane, prognostic, predictive
Short title: MAP-tau expression is prognostic but not predictive

Title: MAP-tau expression is prognostic but not predictive for taxane response in metastatic breast cancer

Authors: Maria T. Baquero¹, Karen Lostritto,² Mark Gustavson¹, Annette Molinaro⁴, Robert L. Camp¹, Pharma Authors, Lyndsay Harris³ and David L. Rimm¹

INTRODUCTION: Taxanes are microtubule stabilizing agents and potent cytotoxic molecules recognized as highly effective chemotherapeutic agents. Varying response rates of 40-60%, depending on treatment setting, suggest the need for a clinical diagnostic with predictive value to determine patient sensitivity to taxane therapy. Microtubule associated proteins (MAPs) mediate polymerization and endogenously alter microtubule stabilization/destabilization. Recently, MAP-tau (Tau), a microtubule stabilizing protein, has been investigated as a useful predictive marker for taxane sensitivity. However, studies evaluating the prognostic and predictive value of Tau have presented conflicting results. Here we measure Tau levels in a retrospective cohort and a prospective taxane clinical trial to determine prognostic and predictive value of Tau.

METHODS: Tau protein expression levels were quantitatively assessed using AQUA technology in two cohorts: a 480-case Yale retrospective collection and a 140-case clinical trial, TAX 307 [a randomized clinical trial comparing FAC versus TAC treatment as first line chemotherapy for metastatic breast cancer]. Tissue microarray and whole section MAP-tau scores were correlated with clinical and pathologic variables.

RESULTS: Prognostic evaluation of the Yale cohort using univariate analysis and median score cutpoint indicated a direct correlation between high MAP-tau expression and overall survival (HR = 0.73, 95% confidence interval [CI] = 0.62-0.85; p< 0.0001). Kaplan Meier analysis indicated 10-year survival in 65% of the patients with high Tau compared to 47% for those with low Tau. In the TAX 307 cohort, patients with high expression exhibited a significantly longer time to tumor progression (TTP) regardless of treatment arm (31.7 v 23.1 months, p= 0.02) with mean TTP of 26.5 months. Response rates did not differ by Tau expression (43% low Tau vs 57% high Tau; p=0.27) or by treatment arm.
CONCLUSIONS: Tau functions as a prognostic factor in both the Yale cohort and the TAX 307 cohort with high Tau expression associated with longer overall survival and TTP. Tau does NOT behave as a predictor of response to taxane-based chemotherapy since differences between low and high Tau groups by treatment arm and response rate were not observed. Our data supports Tau as a prognostic marker, but does not support the use of Tau as a predictive factor for response to docetaxel.
Appendix E

AACR 2010 Abstract

Title: High expression of the microtubule destabilizing protein stathmin is prognostic for worse outcome in breast cancer

Authors: Maria T. Baquero, Jason Hanna, Seema Agarwal, Elizabeth Killiam, Robert L. Camp, and David L. Rimm

INTRODUCTION: Taxanes are microtubule targeting agents (MTAs) and potent cytotoxic molecules recognized as highly effective chemotherapeutic agents. In large randomized clinical trials, taxane-based chemotherapies provided benefits in overall and disease-free survival, but they are accompanied by significant adverse effects. Thus the clinical utility of taxane therapy would be enhanced if there were companion diagnostic tests so that only the taxane-sensitive patients (about half of breast cancers) could be treated with this drug. Accumulating evidence indicates that microtubule associated proteins (MAPs) may be responsible for tumor cell resistance to taxanes. Here we use a large retrospective cohort to measure expression levels of stathmin, a microtubule destabilizing protein, and to determine prognostic value, as a first step toward development of a companion diagnostic.

METHODS: Stathmin expression was measured in a large retrospective breast cancer cohort (n= 645) with 20 year follow-up using tissue microarray technology (TMA) in two-fold redundancy and quantitative immunofluorescence (AQUA). Patient stathmin expression levels were correlated with clinical, pathological, and disease free survival variables.

RESULTS: Stathmin expression exhibited nonparametric distribution with high correlation (R= 0.70) between redundant TMA cores. Prognostic evaluation of the cohort using univariate analysis indicated an inverse correlation between high stathmin expression and overall survival (HR = 1.30, 95% confidence interval [CI] = 1.02-1.65; p< 0.028). Kaplan Meier survival analysis showed 10-year survival of 54% for patients with high stathmin expression versus a 65% survival rate for low expressers (log rank,
P<.0058). Multivariate analysis indicated that high stathmin expression, nodal status, HER2 expression, and tumor size are independent predictors of survival.

CONCLUSIONS: Stathmin expression in breast tumor tissue functions as a prognostic factor where high expression is associated with worse outcome. Since stathmin expression is useful in predicting survival, it may serve as marker to accurately select patients for current taxane-based or other anti-microtubule therapies.