Efficacy of *Nab*-Paclitaxel Does Not Seem to Be Associated with SPARC Expression in Metastatic Breast Cancer

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Abstract. *Aim: To evaluate the predictive value of the expression of the secreted protein acidic and rich in cysteine (SPARC) for nab-paclitaxel in metastatic breast cancer (MBC). Patients and Methods: Forty-four patients with progressive MBC were prospectively treated with nab-paclitaxel. Expression of SPARC in tumor cells was assessed by an immunoreactive score, integrating staining intensity and percentage of positive tumor cells; expression in stroma based on staining intensity. SPARC serum levels were determined before 1st and 2nd cycle of nab-paclitaxel and at progression. By applying several cut-offs the association between SPARC expression or serum levels and clinical end-points was analyzed. Results: No clear association between expression of SPARC in primary or metastatic tumor tissue or in serum and any clinical end-point could be detected regardless of the various cut-offs applied. Conclusion: Efficacy of nab-paclitaxel in MBC does not seem to be associated with expression of SPARC in tumor tissues or serum.*

Breast cancer in the early and even more the metastatic setting is a heterogeneous group of diseases comprising of several molecular-defined subtypes. Thus, an individualized approach with an optimal benefit-risk ratio guided by markers that are predictive for the response to a specific therapy would be ideal.

Taxanes are the preferred chemotherapy option for aggressive metastatic breast cancer (MBC). Opposed to docetaxel and paclitaxel, *nab*-paclitaxel does not mandate any solvent (1) and, thus, offers an improved benefit-risk ratio (2, 3). *Nab*-paclitaxel exploits the natural features of albumin probably by two mechanisms: utilizing the natural carrier for hydrophobic molecules and its active-gp60-receptor-mediated transcytosis across the blood vessel endothelium and taking advantage of albumins binding to the glycoprotein secreted protein acidic and rich in cysteine (SPARC), which is supposed to result in peri- and intra-tumoral accumulation of the cytotoxic agent (1, 4). SPARC is an albumin and calcium binding glycoprotein, also known as osteonectin or BM-40, which modulates the interaction of cells with the extracellular matrix (5). It is no tumor-specific protein *per se,* but plays a key role in tumor growth, metastasis and aggressiveness (6, 7). SPARC is overexpressed in numerous tumor types and was found to be a marker of poor prognosis in several tumors including breast cancer (7, 8). Thus, it was hypothesized that the expression of SPARC could serve as a predictive marker for *nab*-paclitaxel therapy.

There exist pre-clinical data to support this hypothesis (9). However, only few clinical data on the predictive significance of SPARC for response to *nab*-paclitaxel exist up to date.

A retrospective study with tumor samples from 16 patients with head and neck cancer suggested a correlation of expression of SPARC in tumor and response to *nab*-paclitaxel with a higher response rate in SPARC-positive tumors (10).

In a phase I/II trial with 67 chemo-naive patients with metastatic pancreatic carcinoma treated with *nab*-paclitaxel and gemcitabine, SPARC expression of the tumoral and stromal compartment was evaluated in tumor samples from 36 patients. The median overall survival (OS) of patients with a high expression of SPARC was significantly longer than the OS of those in the low-SPARC group. SPARC levels remained a significant predictor of OS in multivariate analysis. However, only stromal SPARC and not SPARC in tumor cells was significantly correlated with OS (11).

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Key Words: Metastatic breast cancer, chemotherapy, nab-paclitaxel, SPARC.

In a study with 31 stage IV melanoma pre-treated patients high SPARC plasma levels at baseline were correlated with a poorer survival after *nab*-paclitaxel and carboplatin chemotherapy (12).

In breast cancer, a retrospective analysis of 667 tumor specimens from the German GeparTrio trial found that a high expression of SPARC in tumor cells was significantly correlated with an increased pathological complete response (pCR) rate to neoadjuvant chemotherapy with docetaxel, doxorubicin and cyclophopsphamide (TAC) or with TAC followed by capecitabine and vinorelbine (13). In contrast, a small neoadjuvant study of 29 patients with locally advanced human epidermal growth factor receptor 2 (HER 2)-positive breast cancer did not show a correlation between expression of SPARC in tumor cells and pCR after neaodjuvant chemotherapy with *nab*-paclitaxel, carboplatin, trastuzumab and bevacizumab (14).

Another US neoadjuvant study in 123 HER2-negative breast cancer patients evaluated the feasibility and safety of a bi-weekly schedule of neoadjuvant *nab*-paclitaxel with gemcitabine and epirubicin followed by bi-weekly *nab*-paclitaxel and gemcitabine postoperatively. Seventy-seven tumor samples were available for immunohistochemical staining. There was no statistically significant correlation between SPARC staining of tumor cells or stromal fibroblasts and the pCR rate. The authors reported that SPARC-positive tumors showed a trend to improved progression-free survival (PFS) that was strongly associated with tumoral SPARC but not stromal SPARC (15). In a further publication of this study a SPARC microenvironment signature (SMS) integrating SPARC staining of an array of microenvironment components was correlated with PFS and OS and discriminated patients in a low and high risk group with significantly higher survival in the low risk group (16). However, SMS might be too complex to be applicable in routine clinical practice.

Data on SPARC as a predictive factor for *nab*-paclitaxel in MBC come from a phase II study in 29 patients with triple-negative MBC treated with combination of *nab*-paclitaxel, carboplatin and bevacizumab. SMS was evaluated in specimens of primary tumors and metastatic lesions. SMS in primary tumors did not correlate with outcomes. SMS in metastatic sites available from 20 patients correlated with PFS. Paired biopsies from primary and metastatic lesions from 14 patients suggested a better outcome in terms of overall response rate (ORR) if SMS in primary and metastatic lesions was similar (17).

We prospectively evaluated if SPARC assessed in a way applicable to routine clinical practice could serve as a predictive marker for *nab*-paclitaxel in MBC. We tested the association of SPARC expression in tumor cells, stroma or serum with the outcome of MBC patients treated with single-agent *nab*-paclitaxel.

Patients and Methods

Study design and objectives. This prospective single-Center translational study was performed to evaluate expression of SPARC in tumor cells, stroma and serum as a predictive factor for *nab*-paclitaxel. The study was approved by the ethics committee. All patients had to provide asigned informed consent and had to have progressive metastatic breast cancer with indication for chemotherapy and no pretreatment or contraindication to *nab*-paclitaxel. *Nab*-paclitaxel was administered on days 1, 8, 15 of a 28-day cycle at a scheduled dose of 150 mg/m2 until progression or the occurrence of not manageable toxicity. It was at the treating physician's decision to reduce the dose upfront if deemed necessary. In case of toxicities of grade 3 or more, or neurotoxicity grade 2 or more, the dose was reduced by 20%. Response to therapy was evaluated after every third cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (18).

Evaluation of SPARC expression in tumor tissue and SPARC serum levels. Expression of SPARC by tumor cells and stroma was evaluated by immunohistochemical staining of sections from tissue of primary tumors and metastatic lesions using a murine monoclonal antibody against SPARC (NCL-O-NECTIN, 1:100, Novocastra, Leica Biosystems, Wetzlar, Germany). Expression in tumor cells was quantified by an immunoreactive score (IRS) from 0-12 integrating staining intensity and percentage of positive tumor cells as described previously (13, 19). Expression in stroma was semi-quantified as 0 for negative, 1+ for weak and 2+ for strong staining intensity. SPARC serum levels, in μg/ml, were determined by ELISA (Osteonectin EIA, Immundiagnostik, Bensheim, Germany) before the start of *nab*-paclitaxel, before cycle 2 and at progression.

Statistical analysis. Descriptive statistics were used to summarize patient and tumor characteristics. The ORR was defined as complete or partial response (CR+PR) according to the RECIST criteria version 1.1 (18), disease control rate (DCR) as CR+PR+ stable disease (SD), clinical benefit rate (CBR) as CR+PR+SD lasting more than 6 months. PFS was defined as the interval between the first dose of *nab*-paclitaxel and the time of disease progression or death, OS as the interval between the first dose of *nab*-paclitaxel and death. PFS and OS were assessed using the Kaplan-Meier method censoring for patients with no documented event at the time of last follow-up.

The association between SPARC expression and clinical end-points was assessed. To divide patients into disjoint prognostic groups, several cut-offs for SPARC negativity/positivity were applied as detailed in Table II. Expression of SPARC comprised of expression in tumor cells or stroma of primary tumors, metastatic lesions, most recent tumor material available (primary tumor or metastatic lesion) and, if available, change from expression in primary tumor to metastatic lesion plus SPARC serum levels at predefined time-points and the change in serum levels from baseline to beginning of cycle 2.

Association between SPARC expression and ORR, DCR or CBR was analyzed by the Fisher's exact test. Applicability of SPARC, as an indicator for response to *nab*-paclitaxel, was determined by the area under the receiver operating characteristic curve (AUROC analysis) using all applicable cut-off points. The relationship between SPARC expression and PFS or OS was determined by stratified Kaplan-Meier-analysis.

Table I. *Clinicopathological characteristics*.

Characteristics	Patients N (%)
Median age, years (range)	61 (35-79)
Performance status	
0	29 (66)
1	14 (32)
2	1 (2)
Hormone receptor status	
Positive	28 (64)
Negative	15 (34)
Unknown	1 (2)
HER2 status	
Negative	36 (82)
Positive	8 (18)
TNBC	11 (25)
Pattern of metastasis	
Visceral	34 (77)
Non-visceral	10 (23)
Number of metastatic sites	
>3	10 (23)
2-3	25 (57)
1	9 (20)
Treatment line*	
1st line	19 (43)
2nd line	11 (25)
≥3rd line	14 (32)
Nab-paclitaxel regimen	
Monotherapy	41 (93)
Combination with biological#	3 (7)
Starting dose of nab-paclitaxel	
260 mg/m^2 q3w	1 (2)
150 mg/m^2 q1w	37 (84)
125 mg/m^2 q1w	2 (5)
100 mg/m^2 q1w	3 (7)
70 mg/m^2 q1w	1 (2)
Patients with ≥1 dose reduction or delay	23 (52)
Number of cycles per patient	
Median, range	3, 1-11
Mean, standard deviation	3.75±2.46
Number of applications per patient	
Median, range	8.5, 1-32
Mean, standard deviation	11.11±7.48

HER2, Human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer. *Median number of treatment lines 2 (range 1-8), #Bevacizumab n=2, trastuzumab n=1.

Table II. *SPARC expression in primary tumor and metastatic lesions*.

	SPARC Low score	SPARC Low N (%)	SPARC High score	SPARC High N (%)
Tumor cells				
Primary tumor				
n=37	0	30 (81)	≥1	7 (19)
	0-2	32 (86)	≥3	5 (14)
	0-3	34 (92)	≥4	3 (8)
	0-4	36 (97)	≥5	1 (3)
Metastatic lesions				
n=22	0	19 (86)	≥1	3 (14)
	0-1	20 (91)	≥2	2 (9)
	0-2	21 (95)	≥3	1 (5)
Most recent tumor material*				
n=43	0	38 (88)	≥1	5 (12)
	0-1	39 (91)	≥2	4 (9)
	0-2	41 (95)	≥3	2 (5)
Stroma				
Primary tumor				
n=37	0	6 (16)	≥1+	31 (84)
	0-1+	9 (24)	2+	28 (76)
Metastatic lesions				
n=22	0	3 (14)	≥1+	19 (86)
	0-1+	6 (27)	2+	16 (73)
Most recent tumor material*				
n=43	0	6 (14)	≥1+	37 (86)
	0-1+	12 (28)	2+	31 (72)

SPARC expression of tumor cells was evaluated by an immunoreactive score (IRS) from 0-12, SPARC expression of stroma was semiquantified by 0, 1+ and 2+. *SPARC score of tumor cells or stroma of either metastatic or primary tissue depending on what was the most recently available tumor material.

Results

Patients, tumor characteristics and treatment. Overall, 44 patients were enrolled from May 2012 to July 2013. Major patient, tumor and treatment characteristics are summarized in Table I and reflect a typical population of patients with MBC seen in clinical practice. *Nab*-paclitaxel was given as first-line therapy in 19 (43%) patients, second-line in 11 (25%) and third-line or further in 14 (32%) patients. One patient received a three-weekly schedule of *nab*-paclitaxel instead of the scheduled weekly regimen. Most patients (84%) started with *nab*-paclitaxel at 150 mg/m^2. The median number of cycles administered was 3 (range=1-11) and the median number of *nab*-paclitaxel applications was 8.5 (range=1-32). The dose of *nab*-paclitaxel was reduced or delayed in 23 (52%) patients.

Efficacy and safety. Forty-two patients were evaluable for response. No CR was observed. Ten patients achieved PR, 13 SD and 6 SD lasting 6 months or more corresponding to ORR of 23%, DCR of 52% and CBR of 36%. The median PFS was 5.7 (95% confidence interval (CI)=2.95-7.93) months. The median OS was 10.2 months (95%CI=7.64; upper limit could not be calculated), however, 72% of OS events were censored.

There was no grade 4 non-hematological toxicity and no grade 5 toxicity at all. The most frequent grade 3 non-hematological toxicities were peripheral polyneuropathy (7%), dyspnea (7%), nausea (5%) and infection (5%). One

patient had grade 4 neutropenia, 11 (25%) patients grade 3 neutropenia. No case of febrile neutropenia was documented.

SPARC expression and serum levels. Several cut-offs for SPARC were applied. Table II gives an overview on the distribution of SPARC expression in the respective subgroups. Applying the established thresholds of IRS for hormone-receptor positivity, a positive SPARC expression of IRS ≥3 in tumor cells was detected in 5/37 (14%) primary tumors and 1/22 (5%) metastatic specimens, a positive SPARC expression of 2+ in stroma was detected in 28/37 (76%) primary tumor specimens and 16/22 (73%) metastatic tissue specimens.

The median SPARC serum levels were 0.76 μl/ml (range, 0.23-3.33; n=44) at baseline, 0.75 μl/ml (range=0.16-2.77; n=43) after cycle 1 and 0.84 μl/ml (range=0.22-10.80; n=29) at progression. Analysis of the intraindividual changes in SPARC serum levels from baseline to the time-point after cycle 1 (median=0.02, 25% quantile –0.15, 75% quantile 0.16) or to progression (median=–0.01, 25% quantile –0.12, 75% quantile 0.15) did not show fluctuation of SPARC levels over time.

Association of SPARC and clinical end-points. No relationship between expression of SPARC in primary or metastatic tumor tissues or SPARC serum levels and any clinical end-point could be detected regardless of the various cut-offs applied. Table III gives an overview of all *p*-values of the analyses of the association between expression of SPARC, as defined by various cut-offs and each clinical en-point. Only the *p*-value for DCR and SPARC in stroma of the most recent specimen analyzed was of borderline significance ($p=0.05$) when the cut-off of 0 *vs*. ≥1+ for SPARC negativity/positivity was applied. The AUROC analysis did not reveal SPARC as an indicator for response to *nab*-paclitaxel.

Discussion

Our data do not provide evidence for a predictive value of SPARC expression in tumor cells or stroma from either primary tumors or metastatic lesions for treatment of MBC with *nab*-paclitaxel except for one singular borderline positive finding, which could have resulted from multiple testing. In addition, we did not find an association of SPARC serum levels and any efficacy endpoint of *nab*-paclitaxel therapy.

One major limitation of our study is clearly the low patient number, which makes it difficult to draw definitive conclusions. However, this limitation also applies to studies that did report a correlation of SPARC and outcome to *nab*-paclitaxel (10-12, 14-17). In our study SPARC seemed to be differentially expressed on tumor cells and in stroma, a finding which has also been reported by others for breast cancer and for pancreatic carcinoma (7, 11, 13). Regardless of any cut-off applied, the proportion of SPARC-positive tumor cells in both primary tumors and metastatic lesions in our study was low. Overall, definitions a high SPARC score in the tumoral compartment was found in 3% to 19% of primary tumors and/or metastatic lesions. This compares to 26.4% of the samples from primary breast cancer tumors found to be SPARC positive due to an IRS of tumor cells of ≥5 in the German GeparTrio study (13). Yardley *et al*. reported a proportion of 83% SPARC-positive tumors by immunohistochemistry (IHC) from a neoadjuvant trial in HER2-positive breast cancer (14). In another neaodjuvant study, 85% of evaluated tumors were found to be SPARC-positive based on the IHC staining of tumor and/or fibroblasts surrounding tumor cells. Using the so called SMS, *i.e*. a composite SPARC score derived from IHC staining of 7 cellular tumor components, the same investigators categorized 30 of 68 (44%) patients as low risk regarding OS due to SMS (16). A study in metastatic triple negative breast cancer found 5 of 20 (25%) patients to be low risk regarding PFS due to the SMS of metastatic lesions (17).

It becomes obvious that definitions and terminology for SPARC positivity or a high expression of SPARC differ considerably. Thus, clinical data on the predictive significance of SPARC are not only few but also hardly comparable. While some reports base SPARC positivity on intensity of IHC staining of tumor cells (10), others take both staining of tumor cells and fibroblasts as a positive signal (15). A more differentiated approach is to evaluate the staining intensity and proportion of positive cells and integrate both parameters in an immunoreactive score, as it is common practice for evaluating hormone receptor positivity (13). The third highly sophisticated approach is the SMS, which is a combined score integrating 42 variables taking into account staining by two antibodies and assessment of the maximum staining intensity, the percentage of cells at the maximum intensity and an overall score of seven tissue components, *i.e*. tumor cells, fibroblasts, inflammatory cells, acellular stroma/matrix, blood vessels, nerve tissue and normal tissue within the tumor by two pathologists (11, 16, 17). In our opinion a predictive marker should be applicable for broad routine clinical practice, which is why we chose the immunoreactive score, as reported by Untch *et al*. (13).

As of today there is no evidence for SPARC as a predictive marker from randomized trials. Data from the pivotal trial in metastatic pancreatic cancer (20) are awaited this year. However, findings from one tumor entity may not apply to another. The German GeparSepto trial comparing neoadjuvant paclitaxel *vs*. neoadjuvant *nab*-paclitaxel includes a translational program on SPARC and will provide evidence for its predictive significance in neoadjuvant therapy of early breast cancer (21). Data from large

Table III. *Relationships between SPARC expression and efficacy parameters for chemotherapy with nab-paclitaxel.*

SPARC expression of	SPARC ccore cut-offs	ORR		DCR		CBR		PFS		OS	
		p-Value for correlation	AUROC	*p*-Value for correlation	AUROC	*p*-value for correlation	AUROC	HR	*p*-value	HR	*p*-Value
Tumor cells of primary tumor		N=35		N=35		N=35		N=35		N=37	
	0 *vs.* ≥1	0.3397	0.583	0.3800	0.583	0.3834	0.591	1.333	0.5473	2.711	0.3264
	0-2 *vs.* ≥3	0.5855		0.6399		0.3370		1.466	0.4575	2.343	0.4089
	0-3 *vs.* ≥4	1.0000		1.0000		0.5412		1.010	0.9877	1.119	0.9153
	0-4 *vs.* ≥5	1.0000		1.0000		0.3714		2.290	0.4137	<0.001	0.3988
Tumor cells of metastatic tissue		N=21		N=21		N=21		N=21		N=22	
	0 *vs.* ≥1	0.5489	0.406	1.0000	0.450	0.2286	0.375	0.639	0.5739	0.285	0.1453
	0-1 *vs.* ≥2	1.0000		0.4286		0.4857		0.809	0.8421	0.243	0.2138
	0-2 *vs.* ≥4	1.0000		0.2381		1.0000		0.223	0.1418	0.147	0.0731
Tumor cells in most recent tumor material*		N=41		N=41		N=41		N=41		N=43	
	0 *vs.* ≥1	0.5801	0.555	1.0000	0.523	1.0000	0.505	0.817	0.7477	0.667	0.6022
	0-1 *vs.* ≥2	0.2454		1.0000		0.6366		0.901	0.8889	0.812	0.8447
	0-2 *vs.* ≥3	0.4329		0.5049		1.000		0.404	0.2137	0.492	0.4982
Change in SPARC expression from primary tumor to metastatic tissue		N=15		N=15		N=15		N=15		N=16	
	Decrease *vs.* increase/ no change	1.0000	0.511	0.2308	0.300	1.000	0.444	0.633	0.4531	<0.001	0.1842
Stroma of primary tumor		N=35		N=35		N=35		N=35		N=37	
	0 *vs.* ≥1+	1.000	0.592	0.3912	0.563	1.000	0.521	1.01	0.9859	1.614	0.5458
	0-1+ *vs.* 2+	0.3907		0.6855		1.000		1.062	0.8976	1.795	0.4037
Stroma of metastatic tissue		N=21		N=21		N=21		N=21		N=22	
	0 *vs.* ≥1+	0.5489	0.463	0.1278	0.613	1.000	0.472	1.268	0.7151	<0.001	0.3425
	0-1+ *vs.* 2+	0.5975		0.5975		1.000		1.237	0.6941	<0.001	0.2289
Stroma of most recent tumor material*		N=41		N=41		N=41		N=41		N=43	
	0 *vs.* >1+	0.3072	0.581	0.0500	0.614	0.3759	0.550	1.276	0.6229	0.636	0.6621
	0-1+ *vs.* 2+	0.6937		0.2847		0.7342		1.237	0.5981	0.680	0.6189
Change in SPARC expression in stroma from primary tumor to metastatic tissue		N=15		N=15		N=15		N=15		N=16	
	Decrease *vs.* increase/ no change	0.7538	0.511	0.4436	0.600	1.000	0.583	2.262	0.2146	<0.001	0.7055
		N=42		N=42		N=42		N=42		N=44	
Serum level prior to tx	< or ≥1st quartile	1.000	0.500	1.000	0.430	0.2696	0.603	1.267	0.6447	0.681	0.7203
	< or ≥median	1.000		1.000		0.3408		1.503	0.2836	1.486	0.4918
	< or ≥3rd quartile	1.000		0.2383		1.000		1.040	0.9239	1.204	0.7837
		N=41		N=41		N=41		N=41		N=43	
Serum level after cycle 1	< or ≥1st quartile	0.6622	0.489	0.7017	0.453	1.0000	0.564	1.533	0.4086	0.942	0.9563
	< or ≥median	1.000		0.7337		0.7513		0.811	0.5921	1.524	0.4873
	< or ≥3rd quartile	0.6834		1.000		0.4724		1.086	0.8399	2.154	0.3174
		N=41		N=41		N=41		N=41		N=43	
Absolute change in serum level from beginning to after cycle 1	< or ≥1st quartile	1.0000	0.585	0.1241	0.540	0.7125	0.560	1.762	0.1607	1.112	0.8929
	< or ≥median	0.2772		1.0000		0.3408		0.979	0.9547	0.962	0.9496
	< or ≥3rd quartile	1.0000		0.7011		1.000		0.934	0.8721	1.598	0.5451
		N=29		N=29		N=29		N=29		N=29	
Serum level at progression	< or ≥1st quartile	1.0000	0.568	1.0000	0.500	0.3898	0.681	1.769	0.2373	1.455	0.7447
	< or ≥median	0.6817		1.0000		0.2723		1.073	0.8674	0.583	0.6365
	< or ≥3rd quartile	0.6460		1.0000		0.1086		1.373	0.4940	3.004	0.3247

*SPARC Score of tumor cells or stroma of either metastatic or primary tissue depending on what was the most recently available tumor material. ORR, Overall response rate (complete response + partial response); DCR, disease control rate (complete response, partial response + stable disease); CBR, clinical benefit rate (complete response, partial response + stable disease lasting for more than 6 months); PFS, progression-free survival; OS, overall survival. *p*-Values of 1.0000 are to be interpreted as >0.9999.

prospective trials in MBC on SPARCs value as a predictive marker of *nab*-paclitaxel therapy are clearly warranted. However, it would be beneficial to have a consensus on how to evaluate SPARC expression to better-determine the prognostic and predictive significance of SPARC. Ideally, this approach should be applicable in broad routine clinical practice.

Conflicts of Interest

The Authors have declared no conflicts of interest.

Acknowledgements

This study was supported by the Celgene Corporation, Summit, NJ, USA. The Authors received editorial support in the preparation of this manuscript from Dr. Susanne Hell, funded by Celgene Corporation. Celgene was not involved in the design of the study, the collection, analysis and interpretation of data or in the decision to submit the paper for publication. The authors were fully responsible for all content and editorial decisions for this manuscript. The paper reflects the views of the authors. No restrictions were set by the sponsor.

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Received June 25, 2014
Revised July 30, 2014
Accepted August 4, 2014