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ORIGINAL ARTICLE

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Vinorelbine plus platinum compared to vinorelbine plus capecitabine in treatment of patients with metastatic triple negative breast cancer previously treated with anthracycline and taxane: a prospective randomized study

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ABSTRACT

Introduction. This study aims to investigate the efficacy and tolerability of the vinorelbine-based combination chemotherapy with either cisplatin or capecitabine in metastatic triple-negative breast cancer (mTNBC) pretreated with anthracycline and taxane.

Material and methods. This is an open-labeled randomized prospective single-institute study, that included all patients who received chemotherapy for mTNBC in the period between 1st of July 2016 and 30th of June 2017 and were pretreated with anthracycline and taxane. Patients were randomized to either vinorelbine 25 mg/m^2 i.v. on days 1 and 8 plus oral capecitabine 1000 mg/m^2 twice daily, on days 1–14 (NX); or vinorelbine 25 mg/m^2 i.v. on days 1 and 8 plus cisplatin 75 mg/m^2 (NP), every 21 days. The primary endpoint was time to progression (TTP), whereas the secondary endpoints were objective response rate (ORR), safety, and overall survival (OS).

Results. Median TTP was 9.9 months with NP *vs.* 8 months with NX, (p = 0.22). ORR was 40% with NP *vs*. 36% with NX, (p = 0.77). Median OS was 13 months with NP *vs.* 13.2 months with NX (p = 0.599). Both regimens demonstrated similar rates of grade ≥ 3 vomiting and neutropenia. A higher incidence of thrombocytopenia, tinnitus, and kidney function alteration were reported with NP. A higher incidence of anorexia, diarrhea, mucositis, and hand-foot syndrome were reported with NX.

Conclusions. Vinorelbine-based combination chemotherapy regimens with either cisplatin or capecitabine are active in the treatment of mTNBC pretreated with anthracycline and taxane with manageable toxicity profiles. Both regimens have comparable TTP, ORR, OS, and safety profiles.

Keywords: triple-negative breast cancer, chemotherapy, vinorelbine, cisplatin, capecitabine, platinol, Egypt

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Introduction

According to the clinical classification, triple-negative breast cancer (TNBC) is defined by negative estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) [1]. Metastatic triple-negative breast cancer (mTNBC) exhibits more heterogeneity and genetic complexity as compared to early disease [2]. Patients with mTNBC have poor clinical outcomes and a high incidence of visceral and brain metastases [3–5].

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Despite efforts to classify TNBC and dynamic biomarker development, only PD-L1 is applied in clinical practice as a validated biomarker for response to immune checkpoint inhibitor anti-PDL-1 atezolizumab plus nab-paclitaxel in tumors expressing PD- L1 ≥ 1 [6, 7] and anti-PD-1 pembrolizumab plus chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin) in tumors with combined positive score ≥ 10 [8, 9]. Also, germline breast cancer susceptibility gene (gBRCA) mutations in HER-2 negative metastatic breast cancer are targets for Poly [adenosine diphosphate (ADP)-Ribose] Polymerase 1 inhibitor (PARPis) olaparib [10], and talazoparib [11], and most patients are treated with chemotherapy [12]. Combination chemotherapy could be preferred in cases of imminent organ failure mTNBC [13].

Antibody-drug conjugate (ADC) sacituzumab govitecan that directs the active metabolite of irinotecan to cells expressing trophoblast cell surface antigen 2 (Trop-2), which is highly expressed in TNBC, has led to an improvement in outcomes in mTNBC patients who have received two or more prior systemic therapies and at least one of them for metastatic disease with manageable safety profile [14, 15]. The classification of HER-2 negativity expression including IHC 0 and HER2-low IHC 1+ or IHC2+ with ISH negative, make tumors with HER2-low attractive targets for the newer generation of HER-2 directed ADC trastuzumab deruxtecan with improved outcomes [16]. Also, the clinical benefit of sacituzumab govitecan in mTNBC patients was consistent, regardless of their HER2 status [17].

The effect of re-challenge with anthracyclines and taxane in mTNBC might be limited due to drug resistance, as most patients have been treated with them before as part of neoadjuvant/adjuvant chemotherapy [18]. Vinorelbine is a mitotic spindle poison with no cross-resistance to anthracyclines and taxanes [19, 20] and is recommended as a sequential single agent in metastatic breast cancer (mBC) [13]. It has single-agent activity with an objective response rate (ORR) ranging from 25% to 45% in heavily pretreated mBC patients [21].

The rationale for including platinum agents is supported by the fact that: 1) most breast cancers, in the setting of germline BRCA1 mutation, are triple negative; 2) some TNBC have some BRCA characteristics resulting in faulty DNA repair pathways; 3) platinum-based chemotherapy is associated with progression-free survival (PFS) benefit in patients with MBC and gBRCA mutation [22, 23].

The rationale for including the anti-metabolite capecitabine is supported by its tolerability, clinical benefit, and superiority when tested, as first-line chemotherapy of mBC, in patients pretreated with anthracycline and taxane [24].

Our study aimed to investigate the efficacy and tolerability of the vinorelbine-based combination chemotherapy with either cisplatin or capecitabine in mTNBC patients previously treated with anthracycline and taxane.

Material and methods

Female patients aged > 18 years with histologically confirmed mTNBC (defined by lack of ER, PR, HER2-neu on biopsies of the primary and confirmed by a biopsy of the metastatic site), previously treated with anthracyclines and taxane in a neo/adjuvant setting were eligible for inclusion in this open-labeled prospective randomized single-institute study. Prior chemotherapy or taxane re-challenge in the metastatic setting was permitted. The present study has included all eligible patients who received chemotherapy for mTNBC in the period from 1st of July 2016 to 30th of June 2017. Other inclusion criteria included adequate organ function, measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [25], and performance status of 2 or better on the Eastern Cooperative Oncology Group (ECOG) scale. Patients with brain metastasis, or with non-measurable disease were excluded. Patients aged 65 years or over were excluded because it is the chronological age that needs geriatric assessment [26].

Patients were randomized using permuted blocks to receive a combination of vinorelbine 25 mg/m^2 on days 1 and 8 and oral capecitabine 1000 mg/m^2 twice daily on days 1–14 every 21 days (NX regimen) or vinorelbine 25 mg/m^2 on day 1 and 8 and cisplatin 75 mg/m^2 on day 1 every 21 days (NP regimen) for up to 6 cycles, until progression or unacceptable toxicity.

Tumor response was assessed clinically every cycle, and computed tomography (CT) scans were required every two months. X-ray, bone scan, magnetic resonance imagining (MRI), and biopsy were required when indicated.

The primary endpoint was time to progression (TTP), whereas the secondary endpoints were objective response rate, safety, and overall survival (OS). Time to progression is the period from the first day of treatment to progression. The objective response rate was calculated as the number of patients with the best overall response of confirmed complete response (CR) or partial response (PR) according to RECIST v1.1. divided by the total number of patients in the group. Patients were evaluated for adverse events throughout the treatment period and were graded using NCI Common Terminology Criteria for Adverse Events v.4.03 [27].

Results

Patient characteristics

By June 30, 2017, fifty female patients with mTNBC had been enrolled, randomized, and treated. Thirty-seven patients received vinorelbine combination first-line chemotherapy of mTNBC, while 13 patients received vinorelbine combination second-line chemotherapy of mTNBC after progression on paclitaxel-carboplatin

Table 1. Patients baseline characteristics in both arms — vinorelbine plus capecitabine (NX) regimen and vinorelbine plus cisplatin (NP) regimen

Patients characteristics	NX (n = 25)	NP (n = 25)	p
Age			
Mean ± SD	47.8 ± 8.7	50 ± 9.4	0.41
Median (range)	50 (30–62)	49 (30–64)	
Age Groups			
≤ 45	10 (40%)	8 (32%)	0.76
>45	15 (60%)	17 (68%)	
Menopausal status			
Pre	14 (56%)	12 (48%)	0.77
Post	11 (44%)	13 (52%)	
Type of initial surgery			
MRM	18 (72%)	20 (80%)	0.50
BCS	7 (28%)	5 (20%)	
Histological subtype			
IDC	24 (96%)	22 (88%)	0.28
Others*	1 (4%)	3 (12%)	
T-stage at primary diagnosis			
T0	1 (4%)	0	0.62
T1	3 (12%)	3 (12%)	
T2	18 (72)	19 (76%)	
T3	2 (8%)	3 (12%)	
T4	1 (4%)	0	
N-stage at primary diagnosis			
N0	7 (28%)	7 (28%)	0.11
N1	2 (8%)	8 (32%)	
N2	11 (44%)	5 (20%)	
N3	5 (20%)	5 (20%)	
AJCC TNM at primary diagnosis			
IA	0	1 (4%)	0.22
IIA	6 (24%)	8 (32%)	
IIB	2 (8%)	6 (24%)	
IIIA	10 (40%)	5 (20%)	
IIIB	1 (4%)	0	
IIIC	5 (20%)	5 (20%)	
Prior local recurrence	7 (32%)	7 (32%)	1
Prior regimen for MBC			
0	18 (72%)	19 (76%)	0.75
1	7 (28%)	6 (24%)	
Number of metastatic sites			
1	5 (20%)	8 (32%)	0.542
2	15 (60%)	14 (56%)	
≥ 3	5 (20%)	3 (12%)	
Type of metastasis			
Visceral	10 (40%)	12 (48%)	0.83
Non-visceral	4 (16%)	4 (16%)	
Both	11 (44%)	9 (36%)	
Site of disease (multiple sites are possible)			
Lung	14 (56%)	17 (68%)	0.382
Liver	13 (52%)	11 (44%)	0.571
Lymph nodes	10 (40%)	6 (24%)	0.225
Chest wall	7 (28%)	5 (20%)	0.758
Pleural	4 (16%)	3 (12%)	0.666
Bone	7 (24%)	6 (24%)	0.747

*Others included metaplastic, medullary, and adenoid cystic carcinoma; AJCC TNM — American Joint Committee On Cancer; BCS — breast conserving surgery; IDC — invasive ductal carcinoma; M — metastasis; MRM — modified radical surgery; MBC — metastatic breast cancer; N — node; SD — standard deviation

(6 patients), paclitaxel weekly (5 patients), and gemcitabine-carboplatin (2 patients). The median age of the total population was 49.5 years (range 30–64 years). HER-2 negative expressions including IHC 0 and HER2-low (IHC 1+ or IHC2+ with ISH negative), were equal in both treatment arms, and accounted for 72%, and 28% in each group, respectively. Table 1 illustrates patient characteristics in both groups.

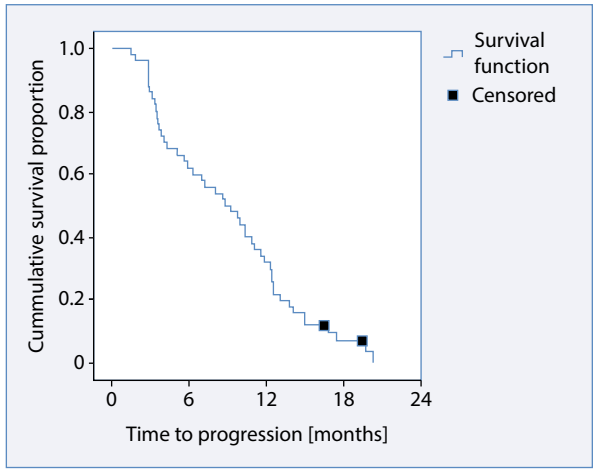

Figure 1. Time to progression of the total population

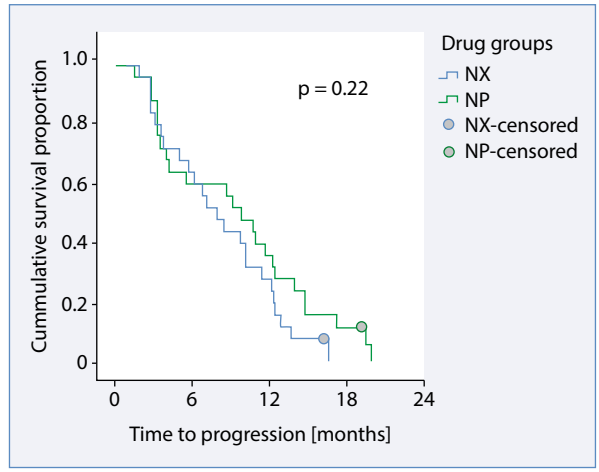

Figure 2. Time to progression of vinorelbine plus capecitabine (NX) regimen compared with vinorelbine plus cisplatin (NP) regimen

Safety

Twenty-five patients received a total of 131 NX cycles (range 2–6 cycles). Vinorelbine doses were delayed in 19 patients during their course of treatment due to neutropenia. Amongst them, 11 patients (44%) received granulocyte colony-stimulating factor (G-CSF) secondary prophylaxis due to grade 3 (< 1000–500/mm^3) or 4 (< 500/mm^3) neutropenia. Vinorelbine doses were reduced by 25% in 5 patients (20%) due to persistent grade 3 neutropenia after G-CSF secondary prophylaxis.

Capecitabine doses were interrupted in 10 patients (40%) during their course of treatment and continued at 75 % of the initial starting dose due to either grade 2 or 3 non-hematological toxicity (vomiting, hyperbilirubinemia, increased creatinine, hand food syndrome, neutropenia, oral mucositis, and diarrhea) using NCI Common Terminology Criteria for Adverse Events v.4.03 [27].

Twenty-five patients received a total of 133 NP cycles (range 2–6 cycles). Vinorelbine doses were delayed in 22 patients during their course of treatment due to neutropenia. Amongst them, 13 patients (52%) received G-CSF secondary prophylaxis due to grade 3 or 4 neutropenia. Vinorelbine doses were reduced by 25% in 3 patients (12%) due to persistent grade 3 neutropenia after G-CSF secondary prophylaxis. The dose of cisplatin was reduced by 25% in 12 patients (48%) if serum creatinine was between 1.5 to 2 mg/dL but creatinine clearance was ≥ 50 mL/min. Cisplatin was stopped in one patient because creatinine clearance was < 50 mL/min.

Time to progression

The median TTP of 50 patients who received vinorelbine-based therapy was 8.7 months (95% CI 5.5–11.8), and TPP at 1 year was 41% (Fig. 1).

The median TTP of the NP group was numerically higher than in the NX group; however, it was not statistically significant [9.9 months (95% CI 6.4–13.3) *vs.* 8 months (95% CI 5–10.7)], respectively. TTP at 1 year was 56% and 52% for the NP and NX regimens, respectively (p = 0.22) (Fig. 2).

Objective response rate

For the total population, the ORR was 38%, including 1 CR and 18 PR. The ORR was 40 % with the NP regimen included (1 CR and 9 PR,) and 36% with the NX regimen included (9 PR) (p = 0.77).

Overall survival

Median OS of 50 patients who received vinorelbine-based therapy was 13 months (95% CI 12–14), and OS at 1 year was 57%. (Fig. 3).

Median OS was similar in both groups, 13 months (95% CI, 11.6–14.4) *vs.* 13.2 months (95% CI 9.5–16.8). OS at 1 year was 62% and 56% for the NP and NX regimens, respectively (p = 0.599) (Fig. 4).

Toxicity

The most predominant grade 1 or 2 adverse events (AEs) reported were hematological (anemia 62% *vs.* 76%, neutropenia 48% *vs.* 48%, and thrombocytopenia 40% *vs.* 68% in the NX and NP regimens, respectively), gastrointestinal (anorexia 72% *vs.* 76%, nausea/vomiting 62% *vs.* 60%, diarrhea 48% *vs.* 32%, oral mucositis 48% *vs.* 24%, elevated bilirubin 20% *vs.* 16%, elevated transaminases 24% *vs.* 8%, in the NX and NP regimens, respectively). Other grades 1 or 2 AEs were peripheral neuropathy 80% *vs.* 68%, creatinine

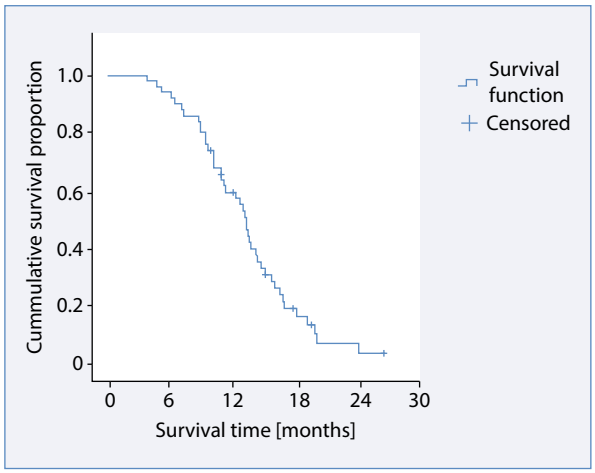

Figure 3. Overall survival of the total population

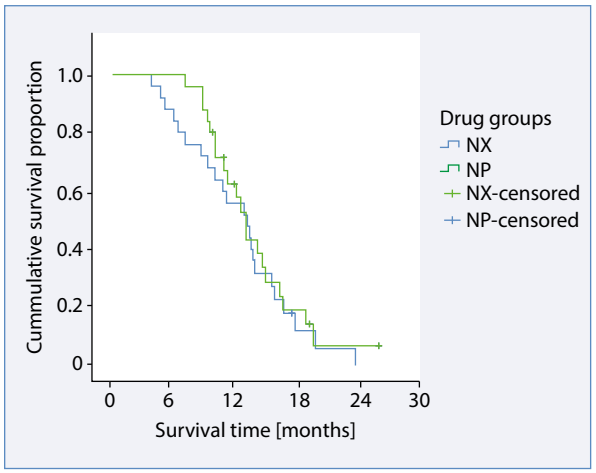

Figure. 4. Overall survival of vinorelbine plus capecitabine (NX) regimen compared with vinorelbine plus cisplatin (NP) regimen

Table 2. The highest grade (G) the of most common adverse event reported at any time

Adverse event*	NX (n = 25)				NP (n = 25)			
	G1 [%]	G2 [%]	G3 [%]	G4 [%]	G1 [%]	G2 [%]	G3 [%]	G4 [%]
N/V	8	54	28	4	24	36	32	4
Diarrhea	24	24	–	–	28	4	4	–
Oral mucositis	28	20	–	–	8	16	–	–
Neutropenia	16	32	40	4	12	36	40	12
Anemia	20	42	16	–	28	48	12	–
Thrombocytopenia	28	12	12	–	48	20	4	–
Neuropathy	48	32	4	–	40	28	12	–
Anorexia	28	44	4	–	40	36	–	–
Creatinine increased	48	8	–	–	48	–	4	–
Hypocalcemia	28	4	–	–	24	16	4	–
Hypercalcemia	12	4	–	–	4	4	–	–
Elevated transaminases	24	–	–	–	8	–	–	–
Elevated bilirubin	16	4			16	–		
Hand foot syndrome	24	8	–	–	–	–		
Extravasation	–	12	–	–	–	16	–	–
Tinnitus	8					32		
A. Fibrillation	–	4	–	–	–	–	–	–
Decreased EF	–	4	–	–	–	–	–	–

*NCI Common Terminology Criteria for Adverse Event version 4.03 was utilized; A. fibrillation — atrial fibrillation; EF — ejection fraction; NP — vinorelbine plus cisplatin; NX — vinorelbine plus capecitabine; N/V — nausea/vomiting;

increase from baseline 56% *vs.* 48%, hypocalcemia 32% *vs.* 40%, tinnitus 8% *vs.* 32%, and hand-foot syndrome 32% *vs.* 0%, in the NX and NP regimens, respectively (Tab. 2).

Higher incidences of thrombocytopenia, anemia, hypocalcemia, and tinnitus were reported in the NP compared to the NX arm.

A higher incidence of any grade of diarrhea, oral mucositis, hand-foot syndrome, and elevation of transaminases was reported in the NX regimen in comparison to the NP regimen.

Grade 3/4 AE reported in > 20% of patients were nausea/vomiting and neutropenia, which were not statistically significantly different between the two regimens (Tab. 3).

Table 3. Grade (G) 3/4 adverse events reported in > 20% of patients

Adverse event*	NX (n = 25)	NP (n = 25)	p
Nausea/vomiting	8 (32%)	9 (36%)	0.76
Neutropenia G3	11 (44%)	13 (52%)	0.57
Neutropenia G4	1 (4%)	3 (12%)	0.28

*NCI Common Terminology Criteria for Adverse Event version 4.03 was utilized; NP — vinorelbine plus cisplatin; NX — vinorelbine plus capecitabine

Other grades 3 AE reported in < 20% of patients were anemia (16% *vs.* 12%), thrombocytopenia (12% *vs.* 4%), neuropathy (4% *vs.*12%), anorexia (4% *vs.* 0%), diarrhea (0% *vs.* 4%), hypocalcemia (0% *vs.* 4%) and creatinine increase (0% *vs.* 4%), in the NX and NP regimens, respectively.

Discussion

In the current study, the median TTP was 1.9 months longer in the vinorelbine-cisplatin (NP) group (9.9 months) compared to 8 months in the vinorelbine-capecitabine (NX) group; but the difference was not statistically significant (p = 0.22). ORR was numerically higher with NP 40% *vs.* 36% with NX (p = 0.77) but not statistically significant. Median OS was similar in both groups, 13 *vs.* 13.2 months, and OS at 1 year was 62% and 56% for the NP regimen and NX regimen, respectively (p = 0.599), compared to OS reported by Du et al. [28] in a retrospective analysis of 48 mTNBC patients who received NP *vs.* NX and were pretreated with anthracyclines and taxanes (PFS = 5.3 *vs.* 3.0 months; p = 0.023), (ORR = 33.8% *vs.* 7.7%; p = 0.029), and (OS = 27.7 *vs.* 14.8 months; p = 0.077). Our observed TTP rate was higher than that reported by Hu et al. [29] for gemcitabine — cisplatin *vs.* gemcitabine-paclitaxel (PFS = 7.73 *vs.* 6.47 months).

Key grade > 3 AEs were mainly vomiting and neutropenia, other grade 3 AEs reported were neuropathy, anemia, thrombocytopenia, and diarrhea. All these grade 3 AEs were manageable, no treatment-related death and no neutropenic fever were reported. Only 2 patients required unplanned hospitalization. One because of grade 4 vomiting and grade 3 diarrhea in the NX arm, and the other one because of grade 3 hypocalcemia in the NP arm. However, some patients required a 25% reduction in vinorelbine dose because of persistent grade 3 or 4 neutropenia after G-CSF prophylaxis which were numerically higher in NX than NP arm. Moreover, about one-fourth of patients required a 25% dose reduction in cisplatin dose due to an increase in creatinine 1.5–2 mg/dL. Only one patient stopped cisplatin because of creatinine clearance < 50 mg. Capecitabine was interrupted in 40% of patients due to grade 2 or 3 non-hematological AEs, mostly vomiting, diarrhea, and oral mucositis.

Nevertheless, dose reduction limited toxicity, and patients on both regimes in our study benefited from the alleviation of symptoms associated with mTNBC, such as dyspnea, pain, chest wall masses, and compression symptoms. This highlights the advantage of both treatment regimens and their potential, especially when they are used to achieve a rapid response, for example, in the setting of a visceral crisis and imminent organ failure. In our study, vomiting and neutropenia in both arms, diarrhea, loss of appetite and hand-foot syndrome in the NX arm, and drowsiness, thrombocytopenia and kidney function alteration in the NP arm were all manageable.

A limitation of our study is the small study group and its single-center character. Also, at the time when the study began in 2016, performing germinal BRCA mutation testing and PD-L1 assay was not often required to make treatment decisions. Another limitation of our study is the absence of analysis of patient-reported quality of life using a highly validated cancer-specific instrument.

Conclusions

Vinorelbine-based combination chemotherapy regimens with either cisplatin or capecitabine are active in the treatment of mTNBC pretreated with anthracycline and taxane with manageable toxicity profiles. Both regimens have comparable TTP, ORR, OS, and safety profiles.

Article Information and Declarations

Data availability statement

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request

Ethics statement

The study was approved by the institutional review board of the Egyptian National Cancer Institute, Cairo University, organization No. IORG0003381, IRB

No. IRB00004025, FWA No. 00007284, approval No. 201516044.3, the study was constituted and operated according to ICH-GCP guidelines and complied with the declaration of Helsinki. Written informed consent to participate in the study was obtained from all patients. Results and other study material was not included items that reveal the identities of the patients.

Author contributions

AMD, HMZ, and AAG have substantial contributions to the conception and design of the work. AAA performed and revised the histopathological and immunohistochemical examination of tumor tissues. AMD, HMZ, AAG, and MNA have a substantial contribution to collecting and analyzing data. AMD drafting the article. HMZ and AAG revised it. All Authors have approved the submitted manuscript.

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None.

Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary material

None.

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