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A MULTICENTER PHASE II TRIAL OF NAB-PACLITAXEL AND CAPECITABINE AS FIRST LINE TREATMENT IN HER-2 NEGATIVE METASTATIC BREAST CANCER (MBC)

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1. BACKGROUND

1.1.

Breast cancer is the most common form of malignancy occurring in women around the world. In 1999, more than 795.000 new cases (21% of all cancer sites) were diagnosed and 314,000 breast cancer deaths (14.1%) occurred. Each year, more than 180,000 women in the United States are diagnosed with breast cancer (30.4% of all cancer deaths) were estimated to occur in the year 2000 (1). In the European Community, an estimated 135,000 new cases per year (24% of all cancer cases) and 58,000 recorded deaths per year (18% of all cancer deaths) will be reported (2). If current breast cancer rates stay constant, a female born today has a 1 in 8 chance of developing breast cancer sometime during her life.

1.2 Metastatic breast cancer

Despite continuous efforts at early diagnosis and improvements in the treatment of early breast cancer, a significant percentage of women with early disease relapse despite adjuvant treatment and develop metastatic disease. In addition, effectively treating advanced breast cancer remains an ongoing challenge. Infact, metastatic breast cancer (MBC) is an incurable disease, whose median survival in presence of treatment with chemotherapy and/or hormonal therapy is less than 2 years (3). In particular patients with MBC that are considered "triple negative" for the absence of estrogen-progesterone receptor and hepidermal growth factor receptor-2 are a subgroup of patients with a poor prognosis, high risk of early relapse and death.

1.3 "Triple negative breast cancer"

Triple negative breast cancer (TNBC) is a subtype of breast cancer distinguished by negative immunohistochemical assays for expression of the estrogen and progesterone receptors (ER/PR) and human epidermal growth factor receptor-2 (HER2), represents approximately 15% of all breast cancers. Patients diagnosed with TNBC generally experience a more aggressive clinical course exacerbated by the lack of effective targeted therapies. Despite best available therapy TNBC accounts for a disproportionate number of breast cancer related deaths, further highlighting the need for novel therapeutic approaches for the management of this high risk subset of patients (4-6). High rates of triple negative breast cancer have been observed in women who are younger , which may be associated with a greater likehood of BRCA1 expression. (7). Current treatment strategies include many chemotherapy agents, such as the anthracyclines, taxanes, ixabepilone, and platinum agents, as well as selected biologic agents.

It has been demonstrated that regimens based on anthracyclines or taxanes, such as the taxane-fluorouracil-doxorubicin-cyclophosphamide (T-FAC) regimen or doxorubicin-Cyclophosphamide-taxane used in the National Surgical Adjuvant Breast and Bowel project

(NSABP) trials in relatively small series of patients treated in the preoperative setting, are effective with high in breast response rates (8,9).

In the triple negative breast cancers, as opposed to the other subtype, there is a markedly higher response rate but a shorter disease free survival and overall survival (OS). A metanalysis by Di Leo et al. as well as smaller phase II and phase III trials with anthracyclines, have shown variable results for individual agents and regimens in this subtype of breast cancer (10-12). Other studies have investigated the use of adjuvant anthracyclines plus taxane in triple negative breast breast cancer. The Breast cancer International research Group (BCIRG001) trial compared docetaxel-doxorubicin-cychlophosphamide versus Fluorouracil-doxorubicin-taxane (FAC). The addition of taxane yelded an advantage in the triple negative cohort, as was true for the overall trial (13). In a slightly more difficult to interpret trial investigated additional cycles of paclitaxel instead of cyclophosphamide, the addition of more, versus less, paclitaxel was associated with a benefit in the triple negative cohort (14). These three data sets all consistently suggest that, in triple negative disease, there is a benefit of taxanes. On the basis of these evidence it could be useful to verify the utility of newer generation of taxanes in metastatic TNBC.

1.4 Abraxane

Conventional taxane formulations use solvents (e.g. Cremophor for paclitaxel and Tween 80 for docetaxel) to overcome the insolubility of the drug molecules. These solvents are associated with increased toxicity as hypersensitivity reactions, neurotoxicity and additional myelosuppression and may also hinder the ability of circulating drug to cross the endothelial barrier and accumulate in tumours, reducing antitumour activity and increasing risk of sistemic toxicity. The first attempt to overcome the limitations imposed by solvent use was the development of albumin-bound (nab)-paclitaxel. With nab-paclitaxel, the reversible binding of albumin to paclitaxel permits exploitation of endogenous albumin pathways to enhance delivery of the drug to tumors. Albumin is a natural carrier for hydrophobic molecules (15,16) and binds to the gp60 receptor on endothelial cells, signalling the formation of Vesicles (Caveolae) in the membrane that carry the albumin complex across the endothelial membrane (Transcytosis) and into surrounding tissue. The entry and retention of albumin complexes in tumor tissue are facilitated by the enhanced permeation and retention effect, ie the accumulation of albumin complexes and other macromolecules in the tumor interstitium via leaky tumor vasculature coupled with reduced release back into blood vessels due to impaired lymphatic drainage in tumor tissue. The preferential accumulation of albumin bound drug in the tumor interstitium results in high concentrations of active drug being in contact with tumor cells. This process appears to be facilitated by the albumin-binding activity of SPARC (secreted protein acidic and rich in cysteine, also known as osteonectin) (17) a protein with multiple biologic activities, including roles in embryonic development, wound repair and tissue remodelling, SPARCs are overexpressed in many tumor types including breast cancer, and high SPARC expression is associated with a significantly poorer outcome in breast cancer. (18)

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Abraxane at dose levels of 80 to 375 mg/m2 were determined in clinical studies. The paclitaxel exposure

(AUC) increased linearly from 2653 to 16736 ng.hr/ml following dosing from 80 to 300 mg/m2. Following intravenous administration of Abraxane to patients with metastatic breast cancer at the recommended clinical dose of 260 mg/m2, paclitaxel plasma concentrations declined in a multiphasic manner. The mean Cmax of paclitaxel, which occurred at the end of the infusion, was 18.7 µg/ml. The mean total clearance was 15 l/hr/m2. The terminal half-life was about 27 hours. The mean volume of distribution was 632 l/m2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of paclitaxel following Abraxane administered intravenously at 260 mg/m2 over 30 minutes were compared with those following 175 mg/m2 of the solvent-based paclitaxel injection administered over 3 hours. The clearance of paclitaxel with Abraxane was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). Differences in Cmax and Cmax corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In a repeat dose study with 12 patients receiving Abraxane administered intravenously at the approved dose, intrapatient variability in systemic paclitaxel exposure (AUCinf) was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses. An analysis of patient exposure (AUCinf) against bodyweight indicated a trend toward reduced AUC at 260 mg/m2 Abraxane, with decreased body weight. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.

The protein binding of paclitaxel following Abraxane was evaluated by ultrafiltration. The fraction of free paclitaxel was significantly higher with Abraxane (6.2%) than with solvent-based paclitaxel (2.3%). This resulted in significantly higher exposure to unbound paclitaxel with Abraxane compared with solvent-based paclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. Based on the published literature, in vitro studies of binding to human serum proteins, (using paclitaxel at 6µM) the presence of ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. (19,20)

1.5 Abraxane clinical data

A phase I clinical study by Ibrahim (21) conducted on 19 patients with solid tumours and breast cancer, showed a maximum tolerated dose of ABI-007 about 70 % higher than that of Crel paclitaxel formulation (300 mg/m2 for an every 3 weeks regimen). Dose limiting toxicities were sensory neuropathy, stomatitis and ocular toxicity (superficial keratopathy and blurred vision at a dose of 375 mg/m2). No patients experienced hypersensitivity reactions. ABI-007 was administered intravenously with no premedication, in shorter infusion period (30 minutes versus 3 hours for polyoxyethylated castor oil based paclitaxel) and with a standard infusion device. Moreover pharmacokinetic parameters showed a linear trend (21). A Phase II trial confirmed that ABI-007 has important antitumor activity in patients with metastatic breast cancer. The overall response rate (at a dose of 300 mg/m2 every 3 weeks) was 48% for all patients and 64% for patients in first line therapy. Time to tumor progression was 26.6 weeks for all patients and 48.1 weeks for patients with confirmed tumor responses; median overall survival was 63.6 weeks. No severe oculare events were noted, and other common taxane-associated toxicities were less frequent and less severe (e.g. myelosuppression, peripheral neuropathy, nausea, vomiting, fatigue, arthralgia, myalgia, alopecia) (22). In a phase III trial, 460 women with measurable metastatic breast cancer (MBC) who had no prior taxane therapy for metastatic disease were randomized to receive either conventional paclitaxel (175 mg/m2 every 3 weeks via 3-hour infusion) with standard premedication with dexamethasone and antihistamines or nab-paclitaxel (260 mg/m2 q3w via 30 –minute infusion) with no standard premedication (23). Approximately three quarters of patients had received prior anthracycline therapy, and more than half of patients had received at least one prior treatment for metastatic disease. The response rate was 33% with nab-paclitaxel (N=229) versus 19% with paclitaxel (N=225; P= 0.001); among patients with at least one prior treatment for metastatic disease, the response rate was 27% in those receiving nab-paclitaxel (n= 132) versus 13% in those receiving paclitaxel (n= 136 P = 0.006). The time to disease progression was significantly prolonged with nab-paclitaxel, from a median of 16.9 weeks to 23 weeks (P= 0.006). There was no significant difference between groups with regard to overall survival (OS) among all patients but nab-paclitaxel was associated with a significant prolongation of TTP (median 56.4 weeks vs 16.7 weeks; Hazard ratio 0.73; P= 0.024) among those patients with at least one prior treatment for metastatic disease (23).

With regard to toxicitites, nab-paclitaxel was associated with a significantly reduced frequency of grade 3-4 neutropenia. Sensory neuropathy of any grade was significantly more common with nab-paclitaxel. Of 24 patients with grade 3 neuropathy; 14 had documented rapid improvement (median 22 days) with 10 of these patients resuming treatment of a reduced dose. Overall, 6 of 233 patients (3%) discontinued nab-paclitaxel due to sensory neuropathy; there were no cases of severe motor neuropathy. Despite the absence of premedication in the nab-paclitaxel group, hypersensitivity reactions were virtually noexistent (grade 2 in less than 1%of patients). Overall adverse event rates in each group did not differ from patients aged < 65 years and those aged ≥ 65 years, raising no additional safety concerns about the use of nab-paclitaxel in older patients (23).

Comparable findings were recently reportes in a Chinese trial comparing solvent-based paclitaxel (175 mg/m2) and nab-paclitaxel (260 mg/m2 q3w) in 210 patients with MBC (24). The primary study outcomes were ORR and toxicity. ORR was 54% with nab-paclitaxel versus 29% with paclitaxel (P= 0.001); TTP (median 7.6 months vs 6.2 months; P= 0.078) and progression free survival (PFS median 7.6 months vs 6.2 months P= 0.118) were non significantly increased with nabpaclitaxel. Alopecia and peripheral neuropathy were the most common toxicities and were of similar frequency in the two treatment groups (24).

In a trial comparing weekly nab-paclitaxel, q3w nab-paclitaxel and conventional docetaxel in first line treatment for MBC, 300 patients were randomized to receive 300 mg/m2 of nab-paclitaxel q3w (N=76), 100 mg/m2 of nab-paclitaxel weekly 3 of 4 weeks (N= 76), 150 mg/m2 weekly 3 of 4 weeks (N= 74) or 100 mg/m2 of docetaxel q3w (N=74) (25). The objectives of the trial were to obtain comparative toxicity and preliminary antitumor response data for nab-paclitaxel versus docetaxel, weekly versus q3w nab-paclitaxel, and higher dose versus lower dose weekly nab-paclitaxel. On both investigator assessment and independent radiologic review, ORR was higher with all nab-paclitaxel regimens than with docetaxel. The risk of disease progression was significantly reduced with nab-paclitaxel q3w (HR, 063; P=0.046) and nab-paclitaxel 150 mg/m2 weekly (HR, 046; P=0.002) versus docetaxel, with no difference between weekly nab-paclitaxel 100 mg/m2 and docetaxel; the risk was significantly reduced (HR, 0.55; P= 0.009) with the higher dose versus lower dose weekly nab-paclitaxel regimen (25). With regard to toxicity all nab-paclitaxel regimens were associated with significantly lower rates of grade 3-4 treatment related toxicities, with the nab-paclitaxel 100 mg/m2 weekly regimen being associated with a significantly lower rate than the nab-paclitaxel q3w regimen. All nab-paclitaxel regimens were associated with a significantly reduced frequency of neutropenia compared with docetaxel. Febrile neutropenia occurred in 1% of each of the nab-paclitaxel groups compared with 8% of the docetaxel group. Rates of neutropenia were significantly higher with q3w nab-paclitaxel and the higher weekly dose compared with the lower weekly dose. There were no significant differences between nab-paclitaxel groups and the docetaxel group with regard to the frequency of peripheral neuropathy; the rate of peripheral neuropathy was significantly lower in the lower dose weekly nab-paclitaxel group than in the other nab-paclitaxel groups (25).

The median time to improvement of peripheral neuropathy was 16 days in the nab-paclitaxel q3w group, 22 days in the lower dose weekly nab-paclitaxel group, 23 days in the higher dose weekly nab-paclitaxel group and 41 days in the docetaxel group. This trial showed that in first line treatment two regimens of nab-paclitaxel (150 mg/m2 weekly and 300 mg/m2 q3w) increase progression free survival (PFS) compared with docetaxel with an inproved safety profile; moreover it has demonstrated that 100 mg/m2 weekly of nab-paclitaxel is well tolerated and is associated with a PFS similar to that with docetaxel.

The combination of nab-paclitaxel with chemotherapy and biologic agents has been investigated in some phase II trials. The combination of nab-paclitaxel and gemcitabine has been shown to improve OS compared with paclitaxel alone in anthracyclines pretreated patients with MBC (26). The phase II NCCTG N0531 trial examined the combination of nab-paclitaxel (125 mg/m2 via 30 minutes infusion on day 1 an 8 q3wly) plus gemcitabine (1000 mg/m2 on days 1 and 8 q3wkly) in 50 patients with MBC who had no prior chemotherapy for metastatic disease and could not have received taxane therapy within 6 months of study entry (27). Available data reported at Asco Symposium in 2007 showed a confirmed response rate of 50% (95% CI 36-64%), including complete response (CR) in 4 patients (8%) and partial response in 21 patients (42%).

The median PFS was 7.9 months (95% CI, 5.4-10 months), the PFS at 6 months was 60% (95% CI, 48%-76%) the median OS was not reached. Grade 3 neuropathy occurred in 4 patients (8%). Dose delay was required in 33 patients and dose reduction was required in 29 patients mostly due to hematologic adverse events (27). Thus far, the findings indicate that the combination has clear activity in MBC with manageable toxicities, including a relative absence of significant non-hematologic adverse events.

1.6 Capecitabine Clinical data

Capecitabine is an oral prodrug that is converted to fluorouracil by an enzymatic pathway ending with thymidine phosphorylase, which is present at higher levels in sensitive tumor cells than in normal cells. Capecitabine showed significant activity with an objective tumor response rate of 20% in a single arm trial of women with heavily pretreated breast cancer (28). In addition to its localized tumor activation, capecitabine has demonstrated synergistic activity in vivo with a wide range of other cytotoxic and biologic agents, including taxanes, anthracyclines, mitomycin C, oxaliplatin, bevacizumab, cyclophosphamide, gemcitabine, vinorelbine, epidermal growth factor receptor inhibitors and trastuzumab. Finally, the favourable toxicity profile of capecitabine contributes to its prominent role in the treatment of MBC (29). First line capecitabine has similar efficacy to that of anthracyclines and taxanes in the treatment of MBC. Studies report a response rate of 30-58% for first line capecitabine (30, 31) and a response rate of 36% for combined first-/second line capecitabine (32). This is comparable with other agents, including first line anthracyclines, with response rates of 36%-41% (33,34); docetaxel, with response rate of 23-42% in anthracycline pretreated MBC (35); and paclitaxel with a response rate of 14%-34% in anthracycline pretreated MBC (36). Capecitabine is well tolerated with a favourable safety profile (37). Among the > 700 taxane-pretreated patients treated in the five clinical trials submitted to the regulatory authorities for capecitabine's approval in MBC, there were no treatment-related deaths. Complete hair loss and myelosuppression were rare (38-40). The most common adverse event was hand-foot syndrome (or palmar-plantar erythrodysestesia), a cutaneous side effect that may be debilitating but is always reversible. Grade 2 hand-foot syndrome can be treated effectively with dose interruption, with resumption at a lower dose if necessary after recovery. Gastrointestinal adverse events (diarrhea and stomatitis) were the next most common side effects seen but were largely mild to moderate intensity and could be effectively managed with medical intervention (e.g., loperamide and rehydratation for diarrhea, mouthwash and fluconazole for stomatitis). Togheter with appropriate dose modification, the incidence of grade 3 or 4 adverse events can be minimized without compromising efficacy

1.7 Rationale of the study

Despite attempts to improve further the efficacy of taxane-based therapy in patients with anthracycline-pretreated metastatic breast cancer, including combination of a taxane with other cytotoxic drugs, no cytotoxic drug has until now improved survival compared with single agent docetaxel. A phase III study demonstrated that combination therapy of capecitabine plus docetaxel is more effective than single agent docetaxel in patients progressed after anthracyclines treatment. (41) Moreover a phase III study demonstrated superior efficacy and safety of weekly nab-paclitaxel compared with docetaxel, with a statistically and clinically significant prolongation of PFS in patients receiving nab-paclitaxel 150 mg/m2 weekly compared with docetaxel 100 mg/m2 q3w (25). A phase II trial examined the combination of nab-paclitaxel (125 mg/m2 via 30 minute infusion on days 1 and 8 q3w) plus oral capecitabine (825 mg/m2 twice daily on days 1-14 q3w) in 50 patients with measurable MBC who had received no prior chemotherapy for metastatic disease, no prior capecitabine and no adyuvant fluoropyrimidine or paclitaxel therapy within 6 months (42). The primary outcome was ORR. Among 46 evaluable patients, 28 had a response (ORR,

60.8%) with a CR occurring in 2 (4.3%) and PR occurring in 26 (56.5%); stable disease occurred in 10 patients (21.5%) and progressive disease occurred in 8 patients (17.4%). The median PFS was 270 days; the median OS had not been reached at the time of analysis. The regimen was well tolerated, with few grade 3-4 adverse events being reported (42).
On the basis of these findings we want to investigate the association of nab-paclitaxel 150 mg/m2 day1 and 8 every 21 days plus capecitabine 825 mg/m2 twice daily days1-14 every 21 days as I line patients with Her-2 negative advanced breast cancer. The objective of the study was to test the efficacy and tolerability of the drugs with a different schedule respect to the previous study and in particular who planned to enroll preferably triple negative breast cancer in order to assess the efficacy of this combination regimen in this subtype. There are moreover some suggestions about the presence of increasing level of Caveolin -1 (CAV-1) in triple negative breast cancer (43). CAV-1 is a receptor-mediator of transcytosis of nab-paclitaxel, so we will to examine the relationship between level of CAV-1 and benefit of nab-paclitaxel in all patients enrolled (ER+/Er-) but especially in the group of triple negative breast cancer (44).

2.OBJECTIVES

2.1 Primary objective

The primary objectives of this study are:

- **the efficacy of combination in terms of response rate (RR) according to RECIST criteria (45)**
- **the progression free survival (PFS) expressed as the time from enrollement in the study to the date of progression or death for any cause**

2.2 Secondary objective

The secondary objectives of this study are

- **overall survival (OS) defined as the time from enrollement in the study to date of death or lost at follow-up**
- **tolerability and safety of the combination regimen according to CTC criteria (46)**

3.STUDY DESIGN

3.1 Overview of study design and dosing regimen

This will be a single arm, openlabel multicenter phase II trial. After Informed consent signature and after the verification of the correspondence to inclusion/exclusion criteria, patients will be enrolled in the trial. *nab*-Paclitaxel will be administered at a dosage of 150 mg/m2 day1, and day 8 in 30 minutes i.v. every 21days in association with capecitabine 825 mg/m2 twice daily days 1-14 every 21 days. We planned to reduce the dosage of nab-paclitaxel as follows: to 125 mg/m2 in case of grade 2 neurotoxicity and to 100 mg/m2 in case of grade 3

neurotoxicity not recovering after 28 days. No premedication to prevent hypersensitivity reaction will be required before administration of nab-paclitaxel. The study is planned to administer 6 cycles of therapy, assessment will be done after 3 cycles of treatment. In case of stable disease or partial/complete response at the end of the planned treatment (6 cycles) the treatment could be continued for two cycles more according to clinicians.

3.1.1 Dose Interruptions and Modifications

Recommendations for nab-paclitaxel dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following sections.

As a general rule, if dose reduction of nab-paclitaxel is necessary, the dose should be reduced stepwise by one dose level, and the subject should be monitored for 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, nab-paclitaxel may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

Once the dose has been reduced no re escalation is allowed.

If a subject's treatment has been interrupted for more than 21 days, the investigator must contact the GOIM headquarter to review the subject's condition in order to resume the treatment.

Table 1:

Dose Level	Nab-paclitaxel (mg/m^2)
0	**150**
-1	**125**
-2	**100**

3.1.2 Dose Interruptions/Modifications for Specific Toxicities for Nab-paclitaxel

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 3.

3.1.3 Dose Reductions and guidelines for for Hematologic Toxicity

Neutropenia

Table 2:

Adverse event	Grade			
	1	2	3	4
Neutrophils / granulocytes (ANC / AGC)	< LLN - 1500/mm^3 < LLN - 1.5 x 10^9/L	< 1500 - 1000/mm^3 < 1.5 - 1.0 x 10^9/L	< 1000 - 500/mm^3 < 1.0 - 0.5 x 10^9/L	< 500/mm^3 < 0.5 x 10^9/L

Febrile neutropenia (fever of unknown origin without clinically or micro biologically documented infection) ANC < 10^9/L; fever ≥ 38.5°C			**Present**	**Life-threatening consequences (e.g. septic shock, hypotension, acidosis, necrosis)**

Severe neutropenia is defined as:

- **Neutrophils <0.5 x 10^9/L longer than 7 days.**
- **Neutrophils <0.1 x 10^9 /L longer than 3 days.**
- **Every grade 3 neutropenia concomitant with fever (3 oral temperature determinations > 38°C during a 24-hour period or a single elevation above 38.5°C).**

Table 3: Use of G-CSF and Dose reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC < 500 cells/mm^3 (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent neutropenia (ANC < 1500 cells/mm^3) OR For patients whose next treatment within the cycle (Day 8) is omitted due to persistent neutropenia (ANC < 1000 cells/mm^3). OR Neutropenia < 500 cells/mm^3 for > 1 week	**Any Occurrence**	**At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is □ 1500 cells/mm^3.** **If G-CSF is given concurrently with weekly Nab-paclitaxel, administration may begin the day after Nab-paclitaxel is given and should stop at least 48 hours prior to when Nab-paclitaxel is given the following week.**

***See NCI Toxicity Criteria Scale for definition of Grade 3 and Grade 4 events.**

For Q3W study drug administration, administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care) 24 hours after chemotherapy until recovery to the predetermined neutrophil count.

- **Anemia**

Occurrence of anemia strongly correlates with fatigue symptoms and reduced quality of life. Therefore supportive treatment with erythropoetin-stimulating factors (ESF) is recommended in case of the development of anemia.

Table 4:

Adverse Event	**Grade**			
	1	**2**	**3**	**4**
Hemoglobin	**< LLN - 10.0 g/dL** **< LLN - 6.2 mmol/L** **< LLN - 100 g/L**	**< 10.0 - 8.0 g/dL** **< 6.2 - 4.9 mmol/L** **< 100 - 80 g/L**	**< 8.0 - 6.5 g/dL** **< 4.9 - 4.0 mmol/L** **< 80 - 65 g/L**	**< 6.5 g/dL** **< 4.0 mmol/L** **< 65 g/L**

Anemia

Table 5:

Adverse event	**Action to be taken for subsequent cycles**
Hemoglobin 8 - 10 g/dL	**Start with ESF for all subsequent cycles. Use supplementation with 200 mg iron per day. ESF therapy should be stopped if Hb levels exceed 12 g/dL.**
Hemoglobin < 8 g/dL or clinical signs of anemia	**Blood transfusions until hemoglobin rises above 9 g/dl. Start or continue with ESF + iron. ESF therapy should be stopped if Hb levels exceed 12 g/dL.**

For blood transfusions, patients will receive leukocyte-reduced and filtered concentrates of erythrocytes from single donors. The reason, number, and frequency of erythrocyte transfusion must be documented.
Cytotoxic treatment should be stopped as long as hemoglobin levels are below 8.0 g/dL (□ XX mmol/L). If hemoglobin has not recovered to ≤ grade 1 on day 42, study treatment should be discontinued.
Treatment with nab-paclitaxel should be on hold as long as hemoglobin levels are below 8 g/dL.

- **Thrombocytopenia**

Table 6:

Adverse event	**Grade**

	1	2	3	4
Platelets	**< LLN - 75000/mm^3 < LLN - 75.0 x 10^9/L**	**< 75000 - 50000/mm^3 < 75.0 - 50.0 x 10^9/L**	**< 50000 - 25000/mm^3 < 50.0 - 25.0 x 10^9/L**	**< 25000/mm^3 < 25.0 x 10^9/L**

Transfusions of platelets are indicated if platelets drop below 15.000/µl or (petechial) bleeding is observed. The number and type (pooled or single donor products) should be documented.
All study medications should be stopped in case of grade 3 or 4 thrombopenia.
Platelets have to recover to ≥ 100 x 10^9/L before the start of the next chemotherapy cycle. If this results in a delay of the next treatment application, a full blood count has to be repeated every second day, to restart treatment as soon as possible. If platelets have not recovered on day 35, treatment should be discontinued.

Table 7:

Thrombocytopenia Grade 3 or Grade 4*	**1st Occurrence**	**Dose reduction to next lower level**
	Recurrence	**Dose reduction to next lower level**

3.1.4 Sensory Neuropathy

Nab-paclitaxel should be withheld in patients who experience Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 1) in subsequent cycles after the sensory neuropathy improves to Grade 1. The time to resolution to Grade 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 2-3 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 1) in subsequent cycles after the sensory neuropathy improves to Grade 1.
Note: the investigator may elect to dose modify for Grade 3 sensory neuropathy.

3.1.5 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged. It is not recommended to administer nab-paclitaxel to patients with prior hypersensitivity to a taxane.

3.1.6 Nausea/Vomiting

NCI-CTCAE grade 2 nausea is defined as oral intake significantly decreased; grade 3 as no significant intake, requiring IV fluids; grade 4 is not applicable. NCI-CTCAE grade 2 vomiting is defined as 2-5 episodes in 24 hours over pre-treatment; grade 3 as ≥ 6 episodes in 24 hours over pre-treatment, or need for IV fluids; grade 4 as requiring parenteral nutrition, or physiologic consequences requiring intensive care; hemodynamic collapse.

For grade ≥ 2 nausea and vomiting, primary prophylaxis with metoclopramide or alizaprid is at the discretion of the investigator, but is recommended. If > grade 2 nausea or vomiting is experienced by the patient, despite primary prophylactic treatment, the dose of capecitabine should be reduced. If primary prophylaxis is not given, patients must be supplied with antiemetics (again metoclopramide or alizaprid are recommended, with 5-HT3 antagonists administration at the discretion of the investigator) in order to help themselves in case nausea or vomiting occurs at home. Adequate secondary prophylactic treatment must be initiated once nausea or vomiting has occurred. If the adverse event then recurs despite secondary prophylaxis, then dose modifications should also be according to Table 1.

3.1.7 Liver Function Tests

In cases with abnormal liver function, liver imaging has to be performed to rule out the eventuality of occurrence of metastatic disease.
When a separate LFT panel is tested, it should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is 2.0x UNL. Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to assure subject safety.

- **Grade 1 abnormal bilirubin and/or ALAT: re-test LFTs every week, continue study treatment**
- **Grade 2 abnormal bilirubin and/or ALAT: hold nab-paclitaxel, re-test LFTs every week until improvement to Grade 1. Re-start nab-paclitaxel at a lower dose level CHECK LFT weekly. Grade 3 or 4: stop nab-paclitaxel permanently**

3.1.8 Other Toxicities

If toxicities are grade 3, except for anemia, treatment should be withheld until resolution to grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level

3.2 Rationale for dose selection

The dose regimen of nab-paclitaxel is 150 mg/m2 day 1 and 8 every 21 days. This dose comes from data of superior efficacy of nab-paclitaxel 150 mg/m2 weekly compared with docetaxel 100 mg/m2 3wkly (25)
The dose regimen of Capecitabine is 825 mg/m2 twice daily days 1-14 every 21 days. This dosage comes from the evidence that the reduction of capecitabine from the standard dosage of 1250 mg/m2 twice daily days 1-14 did not influence the efficacy of the drug itself. (47)

3.3 End of study

The study will end when the last patient has died or 4 weeks after last patient assumed the last treatment dose.

3.4 Centers involved

We planned to involve 22 following centers:

CENTRI PARTECIPANTI ALLO STUDIO

I 22 centri partecipanti allo studio sono:

- **U.O. Oncologia Medica, Ospedale "Vito Fazzi", Lecce, Dott. Lorusso: oncologialecce@libero.it**
- **U.O. Oncologia Medica, Ospedale "Perrino", Brindisi, Dott. Cinieri S: saverio.cinieri@ieo.it**
- **U.O. Oncologia Medica, IRCCS "Giovanni Paolo II", Bari, dott. Giotta: francescogiottalibero.it**
- **U.O. Oncologia Medica, IRCSS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (Foggia), Dott. Maiello: oncologia@operapadrepio.it**
- **U.O. Oncologia Medica, Ospedale "Moscati", Taranto, Dott. Pisconti: oncologianord@virgilio.it.**

- **U.O di Oncologia Ospedale Garibaldi Nesima Superiore , Catania Dott. Roberto Bordonaro oncoct@hotmail.com**

- **U.O Oncologia Ospedale "La Maddalena" Palermo Dott. Vittorio Gebbia vittorio.gebbia@tin.it**

- **Az Osp. "Cardarelli", Napoli, G. Cartenì cartenigiacomo@gmail.it**

- **Osp. "Di Miccoli", Barletta, Dott. M. Brandi mf.brandi@tiscali.it; m.brandi @aulbatuno.it**

- **Osp. "Sacro Cuore di Gesù", Benevento, Dott. A. Febbraro antoniofeffraro@virgilio.it**

- **Osp. "Civile", Castellaneta A.Rinaldi oncologia.castellaneta@gmail.com**

- **Centro Catanese di Oncologia "Humanitas" , Catania, Dott. M. Caruso mcaruso.cco@tiscali.it**

- **Osp. "Civile", Cefalù, Dott.L. Blasi livio.blasi@hsrgiglio.it**

- **Osp. "Riuniti di Foggia", Foggia, Dott. S.Romito santeromito@tiscali.it**

- **Ist.Naz. Tumori "fondaz.Pascale" Napoli, Dott. F.Perrone francesco.perrone@usc-intnapoli.net**

- **Un. Degli Studi di Napoli " Federico II", Napoli, S.De Placido sdponco@urina.it**
- **Ops. "Buccheri La Ferla", Palermo, Dott. N. Borsellino nicolo.borsellino@tin.it**
- **Policlinico Un., Palermo, Dott. A. Russo lab-oncologia@usa.net**
- **Osp. Civile, Paola (CS), Dott. G.Filippelli g.filippelli@tiscali.it**
- **Centro di Riferimento Oncologico, Rionero (PZ), Dott. M. Aieta aietamichele@libero.it**
- **Osp. "Riuniti", Sciacca, Dott. F. Verderame francescoverderame@ospedaledisciacca.it**
- **"ASL NA/3", Frattamaggiore, Dott.S. Del Prete saldelprete@yahoo.it**

4. STUDY POPULATION

This study will be included stage IV metastatic breast cancer Her-2 negative and triple negative with no previous treatment for metastatic disease.

4.1 Inclusion criteria

1. **Age ≥ 18 years**
2. **Documented diagnosis of Her-2 negative metastatic breast cancer (ER+ or Er-) or "triple negative " breast cancer (ER/Pgr-, Her-2-)**
3. **No prior chemotherapy for metastatic disease**
4. **Previous hormonal therapy as adjuvant or as I line treatment is allowed**
5. **Previous therapy with taxanes is allowed as adjuvant or neoadjuvant treatment if completed from at least 6 months**
6. **Previous treatment with anthracyclines is not mandatory**
7. **PS 0-1**
8. **adequate organ function**

4.2 Exclusion criteria

1. **Documented brain metastases**
2. **sensory neuropathy more than grade 1**
3. **Positive pregnancy test**

5.STATISTICAL CONSIDERATIONS

The study has designed as a two stage design according to Simon hypothesis. To obtain a response rate of 40% with a statistical power of 90% we planned to enroll in a first time 54 patients preferentially "triple negative subtype" (48). Primary endpoint will be progression free survival (PFS) defined as the time from the enrollment in the study until progression or death for any cause and response rate (RR) defined according to RECIST criteria (45). Secondary endpoints will be overall survival (OS) defined as the time from the enrollment in the study until death or lost at follow-up and toxicity evaluated according to CTC criteria (46). If the Simon Hypothesis will be verified we have planned to enroll further 40 patients. Efficacy analysis will be primarily based on

intent-to-treat (ITT) analysis set defined as all consented subjects allocated to treatment. All consented subjects allocated to treatment who do not receive at least one dose of treatment will be excluded from the Safety analysis set. An interim analysis has been planned after enrollement of first 54 patients. Moreover we have planned to analyse the basal level of CAV-1 and its modifications during treatment. The method of detection used to assess serum CAV-1 is adirect sandwich ELISA test (49)

6.SCHEDULE OF ASSESSMENTS AND PROCEDURES

6.1 Baseline examination

All subjects must sign and date the most current informed IEC-approved written informed consent before any study specific assessments or procedures are performed. Patients must fulfill all the entry criteria for participation in the study. The following baseline data will be collected:

- **Date of informed consent**
- **Demographics (age, ethnicity)**
- **Relevant medical history (included menopausal status pre or post)**
- **Primary and mBC history including prior adjuvant treatment**
- **Serum pregnancy test within 3 weeks prior to the first dose of experimental regimen**
- **Physical examination (included neurological status, weight, blood pressure, PS)**
- **Laboratory tests (hematology, biochemistry)**
- **Echocardiography**
- **Concomitant medications**
- **Tumor assessment according to RECIST criteria**
- **Collection of sample at baseline for the dosage of Caveolin-1**

6.2 Clinical Assessments and Procedures

The investigator shold be perform assessments of disease every tree cycles through CT scan and collecected sample for the dosage of caveolin-1 every month.

Ecocardiography will be performed at the end of treatment in absence of cardiac comorbities or cardiological symptoms

7.4 Tumor Response Criteria

7.4.1 The objective response rate will be assessed every three cycles and defined According to CTC criteria (46) as follows: a complete response (disappearance of target lesions) or partial response (≥ 30% reduction in the volumetric sum of all measurable lesions). Progressive disease is defined as the occurrence of any of the following: ≥ 20% increase in the volumetric sum of all evaluable lesions, new lesions, progression of non measurable lesions. Stable disease is defined as neither sufficient shrinkage to qualify for PR nor suffcient increase qualify for PD.

7 ADVERSE EVENTS

7.1 Definitions

An Adverse Event is any untoward medical occurrence in a patient administered a medical product and which does not necessarily have a causal relationship with this treatment. It also includes any undesirable clinical or laboratory change which does not commonly occur in the patient.

Adverse Events will be graded according to NCI CTC (46).

7.2 Adverse Reaction (AR)

Adverse reactions are all untoward and unintended responses to a medicinal product related to any dose administered.

All expected Adverse Reactions are listed in the Investigator's Brochure (IB) for an unapproved investigational medicinal product or in the Summary of Product Characteristics (SmPC) for an authorized product. If the nature or the severity of an adverse reaction is not consistent with the applicable product information, the adverse reaction is defined as unexpected. The base for the decision is the current version of the corresponding reference document that has been submitted and approved by the competent authority and the ethics committees.

7.3 Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event.

Important medical events are those which may not be immediately lifethreatening, but are clearly of major clinical significance.

Pregnancy and AEs of special interest must also be documented as a serious adverse event.

7.1 EXCEPTIONS

1) Hospitalization which is due to a planned study visit and for no other reason and without prolongation does not constitute a Serious Adverse Event.

2) An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be handled/documented as a Serious Adverse Event.

3) Any local invasive or distant relapse of breast cancer, any contralateral breast cancer, any secondary malignancy (non breast) and any death irrespective of its cause do not need to be handled/documented as a Serious Adverse Event.

7.1.1 Suspected Unexpected Serious Adverse Events (SUSAR)

All unexpected serious adverse events judged by either the investigator or the sponsor to have a reasonable suspected causal relationship to an investigational or an accompanying medicinal product qualify as suspected unexpected serious adverse reactions (SUSAR). All Suspected Serious Adverse Reactions, which might be unexpected, must be reported immediately, regardless of the time which has elapsed during the clinical trial (treatment and follow-up phase).

7.1.2 Death on Study

Any death occurring during the active treatment part of the study and within 30 days following the last treatment must be reported to the sponsor within 24 hours, regardless of the relation to study drug(s), and have to be reported on the death report form section of the CRF. The cause of death should be documented (cancer-related, treatment-related, cancer- and treatment-unrelated). Autopsy reports should be collected whenever possible and sent to the sponsor.

Deaths that are not occurring due to tumor progression during the study or the follow-up period have to be reported as serious adverse events.

7.1.3 Documentation/Reporting of Events

All AEs, including SAEs, occurring within the period of observation for the clinical study must be recorded in the Adverse Event form. The period of documentation begins after the first treatment and ends with the last administration of study medication. For all Adverse Events the relationship to study medication must be clarified. This must be documented in Adverse Event form. The Adverse Event Form completed in every part must be send to Coordinator Center (Ospedale "Vito Fazzi" Lecce- Dott.ssa Valeria Saracino) at the followig fax number 0832-661962.

Expedited reporting for SAEs and SUSARs are explained in detail below.

7.1.4 SAE Reporting

All serious adverse events occurring during the study treatment period or within 30 days following the last therapy must be reported immediately. Any late SAE (occurring after this 30-day period) possibly or probably related to the study chemotherapy should follow the same reporting procedure.

Progression of a patient's underlying condition leading to one of the above should also not be reported as a serious adverse event, but documented as primary study endpoint.

7.1.5 SUSAR Reporting

SUSARs have to be reported to the competent authorities and the corresponding ethics committees by the sponsor within 15 days, and within 7 days in case of fatal or life-threatening events. SUSAR reporting can be delegate to an adequate qualified person and organization. In this case the responsibility and commitment still lies at the sponsor of the study. The sponsor or the pharmaceutical manufacturer, as designee of the sponsor, decides whether the SAE is unexpected to study treatment and therefore qualifies as a SUSAR. After this evaluation of expectedness by the manufacture, all SUSARS will be reported to the competent authorities and the corresponding ethics committees by the sponsor, within 1 working day for fatal or life-threatening events, within 3 working days for non-fatal-SUSARs.

Address for reports on serious adverse events:

Pharmacovigilance Manager Celgene Srl (Italy)

Fax: +39 02 63471119

Tel: +39 02 91434340

Email: drugsafety-italy@celgene.com

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