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Clinical Trial Protocol

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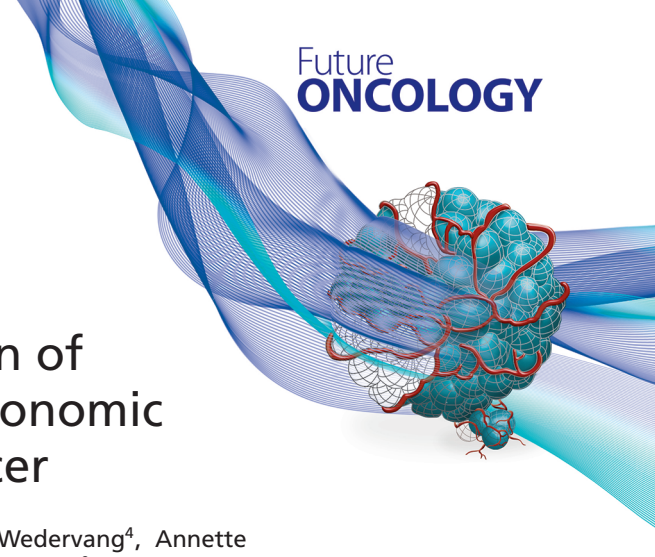

The NAME trial: a direct comparison of classical oral Navelbine versus Metronomic Navelbine in metastatic breast cancer

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Chemotherapy for metastatic breast cancer (MBC) is in general given in cycles of maximum tolerated doses to potentially maximize the therapeutic outcome. However, when compared with targeted therapies for MBC, conventional and dose intensified chemotherapy has caused only modest survival benefits during the recent decades, often compromising the quality of life considerably. Navelbine is an antineoplastic agent that has shown efficacy in the treatment of a variety of cancer types, including breast cancer. Early clinical trials involving both breast cancer and lung cancer patients suggest that metronomic dosing of Navelbine might be at least as effective as classical administration (once weekly, etc.). The NAME trial compares these two strategies of Navelbine administration in MBC patients.

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Keywords: breast cancer • chemotherapy • metronomic • NAME • Navelbine • Phase II trial • vinorelbine

Navelbine (vinorelbine; Pierre Fabre Pharmaceuticals, Castres, France) is an antineoplastic agent that has shown efficacy in the treatment of a variety of solid tumors, including breast cancer [1–3]. Although the drug may be given intravenously, administration by the oral route has been increasingly established for breast cancer patients during the last decade. Results from preclinical studies suggest that the administration of small, frequent doses of chemotherapy (metronomic chemotherapy [mCHT]) may have an effect on endothelial cells in the tumor vasculature [4–6] in addition to the direct effects on tumor cells. Based on the available evidence, giving smaller but more frequent doses of drugs such as vinorelbine should cause a higher dose intensity without corresponding increases in side effects. However, whether anticancer treatment following the metronomic principle is superior to conventional drug dosing, has not yet been validated in larger clinical trials. The NAME study, presented here, has the potential to determine this and thus benefit patients suffering from metastatic breast cancer (MBC).

Breast cancer is among the world's most common cancer types in women [7]. In Denmark and Norway, approximately 4800 and 3600 new breast cancer cases are diagnosed every year, respectively. MBC is currently incurable and cytotoxic therapy prolongs survival only modestly [8]. Very few cytotoxic regimens have shown a clear

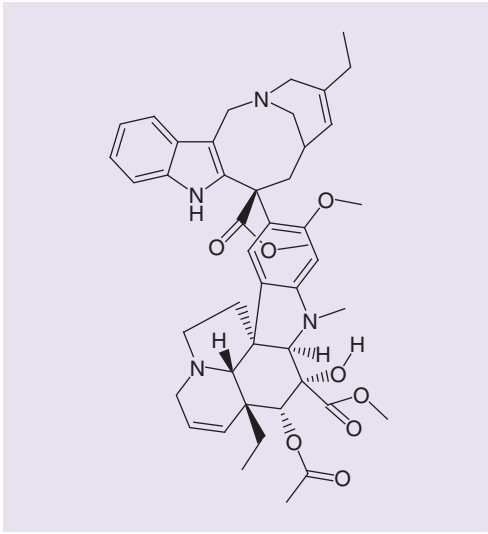

Figure 1. Navelbine (vinorelbine) – chemical structure.

survival benefit. The main goal for treatment of patients with MBC is to relieve symptoms and balance prolonging survival with quality of life. The benefits and disadvantages of chemotherapy need to be carefully considered. In light of this, MBC patients with hormone-sensitive diseases, often are treated with antihormonal regimens (antiestrogens, aromatase inhibitors, etc.) for longer time periods. However, endocrine resistance inevitably occurs and standard chemotherapy regimens will therefore be offered to the majority of patients.

Some of the most established types of chemotherapy for the treatment of MBC are anthracyclines and taxanes. These drugs are unfortunately quite toxic and many patients may have used these drugs in the adjuvant setting, somewhat limiting their efficacy in MBC. Thus, there is a great need for other effective chemotherapy regimens with acceptable side-effect profiles that may be used in the advanced situation of the breast cancer disease. Systematic reviews of available chemotherapeutic treatment options for MBC following progression on anthracyclines and taxanes recommend drugs like capecitabine or vinorelbine in this setting [9]. Eribulin has recently been shown to have some activity in this setting as well [10,11].

In HER-2 negative MBC, there is currently no single, optimal first-line chemotherapy or following line of chemotherapy and the clinician's choice of therapy will be made based on factors like prior therapy lines, time after termination of adjuvant therapy, toxicity, performance status, comorbidity, age and the preferences of the individual patient. In addition, an optimal sequence of chemotherapeutic options has not been established thus far.

The preferable side-effect profile of vinorelbine monotherapy and its proven capacity to stabilize MBC while preserving an acceptable quality of life makes this drug a good candidate for further studies in MBC aiming to improve outcome and side effects during treatment [12]. Its oral administration makes the drug a patient-friendly treatment option requiring less frequent visits to the cancer ward, compared with standard intravenous chemotherapies.

Conventional chemotherapy is often given intravenously every 3 weeks (e.g., anthracyclines, taxanes) or weekly (taxanes). Especially the three-weekly regimens are causing considerable side effects and complications (infections, bone marrow suppression, etc.) and may lead to hospitalization and periods without treatment to allow the patients to recover. Long treatment intervals and also necessary treatment holidays may allow some tumor cell clones to regrow or possibly adapt to therapy.

A novel strategy to avoid the extreme side effects of established chemotherapy regimens is the so-called 'metronomic approach'. Metronomic dosing entails frequent but small doses of chemotherapy without major treatment-free intervals. mCHT is increasingly believed to interfere with the vascular endothelial cells in the tumors and thereby influence tumor angiogenesis and to have stimulatory effects on the immune system [13–19]. mCHT is currently being tested in clinical trials for a variety of human cancer types, however, optimal drugs and dose schedules have yet to be established.

Navelbine

Navelbine (vinorelbine) belongs to the group of vinca alkaloids (Figure 1), blocking cell division in the G2/M-phase

of the cell cycle by inhibiting the assembly of microtubules, which are necessary for cell division. Vinorelbine is considered less toxic compared with taxanes, anthracyclines and other vinca alkaloids. The drug is available for both oral and intravenous administration.

Vinorelbine as intravenous therapy

A Phase I study reported a maximum tolerable dose of 35 mg/m^2 weekly, when vinorelbine was administered as monotherapy [20]. Granulocytopenia was the most significanr dose-limiting factor. The same report recommended the 30 mg/m^2 dose for Phase II trials. A Phase I–II study showed that the maximum tolerable dose was 40 mg/m^2 when given on day 1 and 8 every 3 weeks. Thus, the dose for subsequent studies was set to 35 mg/m^2 [21]. Vinorelbine is commonly used in doses of 30 mg/m^2 weekly, causing clinical response rates between 40 and 60% as first-line therapy in MBC [22–26]. A study from Denmark confirmed a clinical benefit rate of 38% with an intention-to-treat response rate of 12% [21]. Vinorelbine given in combination with other chemotherapeutics has shown high response rates of 62–65% and efficacy at the same level as other combinations. A prospective randomized Phase III trial compared vinorelbine in combination with epirubicin to epirubicin alone. The combination resulted in significantly higher response rates (50 vs 42%). The drug doses in this study were 90 mg/m^2 epirubicin and vinorelbine 25 mg/m^2 on days 1 and 8 [27].

The HERNATA-trial tested vinorelbine in tandem with trastuzumab (Herceptin) in HER-2 positive breast cancer patients and compared this combination with a combination of docetaxel and trastuzumab [28]. While the response rates were very similar between the two arms, the combination with vinorelbine caused significantly fewer side effects and has become the first-line therapy for HER-2 positive MBC in Denmark as a result of this study.

Vinorelbine as oral therapy

An oral formulation of vinorelbine has been developed and is now widely established in clinical practice worldwide. It consists of a soft gelatin capsule filled with the drug. Factors affecting the bioavailability of the oral administration of vinorelbine include solubility, absorption through the mucosa of the gastrointestinal tract, the first-pass metabolism in mucosa and the liver and the distribution of the drug in various tissues. The bioavailability of oral vinorelbine is 43% (+/− 14%) and there is bioequivalence of 80 mg/m^2 orally and 30 mg/m^2 intravenously as well as 60 mg/m^2 orally and 25 mg/m^2 intravenously [29]. Comparative studies of intravenous administration and oral treatment with vinorelbine have been conducted in non-small-cell lung cancer patients. In a Phase II study [30], 114 patients with metastatic or advanced disease were randomized to either oral vinorelbine (60 mg/m^2 weekly, with the option of a dose-escalation to 80 mg/m^2) or intravenous vinorelbine (30 mg/m^2 weekly) monotherapy. The authors reported a response rate of 14 and 21%, respectively and a median survival of 9.3 and 7.9 months, respectively. The 1-year survival rate was 41 and 29%, respectively. The differences, however, were not statistically significant. In the aforementioned study and an analysis of four other Phase II studies, toxicity was compared between oral and intravenous administration of vinorelbine. Taken together, the evidence suggests a comparable toxicity, but that oral administration is accompanied by a predominance of gastrointestinal side effects. Grade III–IV nausea and vomiting occurred in 11 and 8% of the patients when treatment was given orally while the corresponding toxicity was 0 and 3% when given intravenously. Neither trial prescribed prophylactic anti-emetics to its subjects. The toxicity was clearly dose-related as expected. A dose increase from 60 to 80 mg/m^2 was recommended only for patients with good tolerability at the 60 mg dose. Freyer and colleagues concurred in their breast cancer study where vinorelbine was administered orally as first-line treatment of MBC. Vinorelbine could be given as 60 mg/m^2 weekly and increased to 80 mg/m^2 if there was no grade IV neutropenia. Freyer and colleagues reported a response rate of 31% [31].

The NAME trial

The Name trial is an investigator-initiated, prospective, randomized Phase II, nonblinded multinational, multicenter study approved in Denmark and Norway. Women diagnosed with HER-2 negative, MBC (n = 200) will be enrolled according to the study protocol.

Background & rationale for mCHT in patients with MBC

During the recent decade, we have seen an increasing interest in the concept of mCHT for MBC. Several Phase II trials involving compounds like 5-fluororacil, capecitabine, vinorelbine, cyclophosphamide and erlotinib have been published (Table 1) [32–37]. However, so far there are no clinical trials reported that used daily therapy with

Table 1. Metronomic vinorelbine (Navelbine) in patients with metastatic breast cancer – selected studies.

Study	Phase/clinical setting	Treatment arms	n	Main results	Ref.
Addeo *et al.*	Phase II; first line	VNB 70 mg/m^2 d 1, 3 and 5 (1 week on/1 week off)	34	ORR: 38% (28–48) CBR: 68% (60.7–81.9) TTP: 7.7 months (6.9–9.05)	[32]
De Iuliis *et al.*	Pretreated with several lines; Phase II	VNB 30 mg q2d; contiuously	32	ORR: 68.7% CBR: 78.1% TTP: 9.2 months	[37]
Addeo *et al.*	Second line and first line with brain mets.	TMZ 75 mg/m^2 + WBRT VNR 70 mg/m^2 d 1,3 and 5 + TMZ 75 mg/m^2 d 1–21	32	ORR: 52% (38–67) CBR: 77% (62.7–88.9)	[33]
Cazzaniga *et al.* (VICTOR-1 trial)	First or second line; Phase I–II	VNR 40 mg d 1, 3 and 5 + CAPE 500 mg TID	34	CBR: 58.1%	[34]
Cazzaniga *et al.* (VICTOR-2 trial)	First or second line; Phase I–II	VNR 40 mg d 1,3 and 5 + CAPE 500 mg TID	85	CBR: 81% (first line) CBR 73% (second line)	[35]
Montagna *et al.* VEX-trial	Treatment-naive patients vs pretreated	VNR 40 mg d 1,3 and 5 + CAPE 500 mg TID + CTX 50 mg/d	42 vs 46	TTP: 26.5 vs 9.6 months	[36]

CAPE: Capecitabine; CBR: Clinical benefit rate; CTX: Cyclophosphamide; d: Day; ORR: Overall response rate; qxd: Every x day; TID: Three-times daily; TMZ: Temozolomide; TTP: Time to progression; VNR: Vinorelbine; WBRT: Whole-brain radiotherapy.

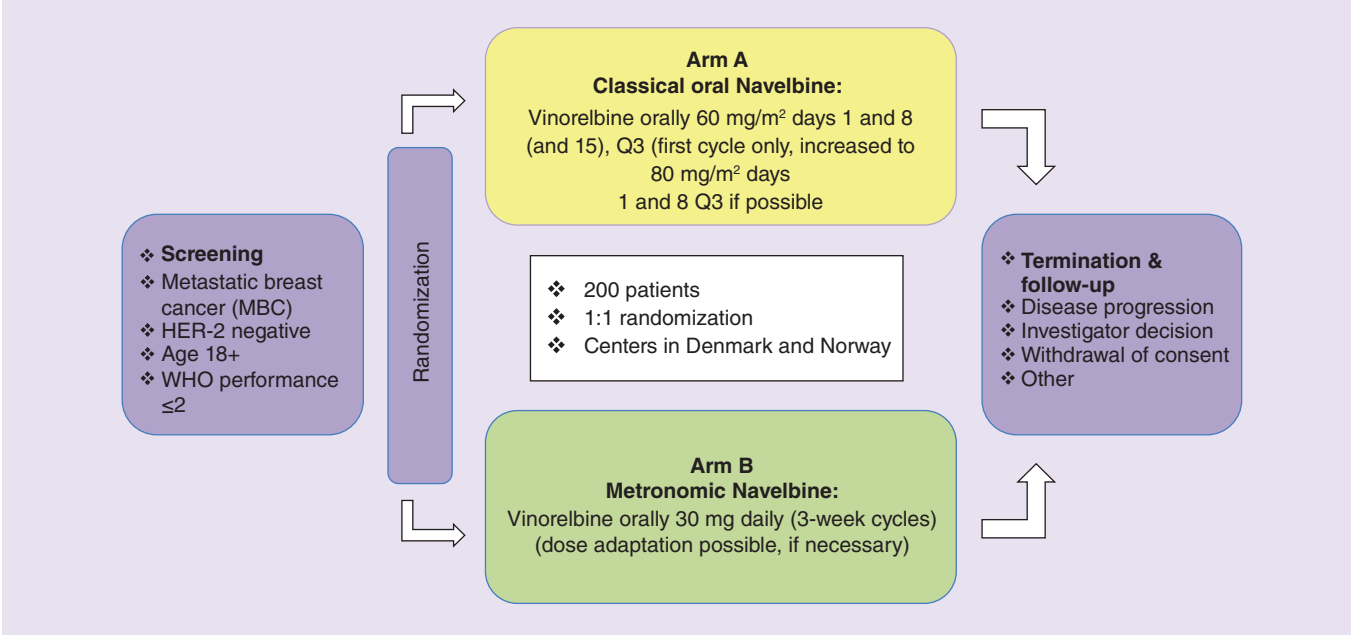

Figure 2. Study design – the NAME trial.
Q3: Every 3 weeks.

vinorelbine for MBC. In contrast, a Phase I trial with daily therapy of vinorelbine has been published for lung cancer patients by Gütz *et al.* [38]. In this dose escalation study, patients were treated daily with vinorelbine for 3 weeks followed by a 1-week break. The study included 27 patients from three German cancer centers. About 78% of the patients had stage IV disease with relapse and 93% had received prior chemotherapy. The median age of the study population was 65 years. Patients were treated with daily doses of vinorelbine between 20 and 50 mg. The investigators recommended a daily dose of 30 mg which could be subsequently increased to 40 mg daily for some patients [38]. No significant accumulation of vinorelbine was observed.

Study design

The NAME trial is a randomized, open label, multicenter, multinational, Phase II clinical trial (Figure 2).

Box 1. General inclusion and exclusion criteria (NAME trial).

Inclusion criteria

- Women with histological confirmed metastatic breast cancer. The tumor cells should be tested HER-2 negative from the primary tumor or by biopsy of metastatic sites (measured with IHC 0-1 or IHC 2+ with consecutive, negative FISH or CISH)
- Expected life time of more than 12 weeks
- Age 18+
- WHO performance status ≤2
- Patients, who, after oral and written information about the trial, agree to be included in the study (written informed consent)
- Patients who are suitable for vinorelbine therapy
- Patients with only one solitary metastatic lesion must have an cytological or histological confirmation of the diagnosis
- Negative pregnancy test (urine test)

Exclusion criteria

- Previous treatment with vinorelbine
- Parallel treatment with other anticancer therapies
- Patients with peripheral sensory neuropathy (>grade 2)
- Malabsorption syndromes or previous surgery with resection of stomach or small intestine (potentially affecting the absorption of vinorelbine)
- Difficulty with swallowing tablets
- Pregnant or breast-feeding women
- Women with childbearing potential who are not using adequate contraception
- Clinical symptoms of CNS-metastasis requiring large doses of steroids
- Decreased bone marrow function defined by WBC count $<3.0 \times 10^9$/l or neutrophil counts $<1.5 \times 10^9$/l or platelets $<75 \times 10^9$/l
- Hepatic impairment defined by bilirubin >1.5-times UNL
- Renal impairment defined by serum-creatinine >1.5-times UNL
- Creatinine clearance <50 ml/min
- Other severe medical conditions, including serious heart disease, unstable diabetes mellitus, uncontrolled hypercalcemia, clinically active infections or organ transplanations
- Participation in other clinical trials with experimental therapy arms within the last 30 days

CISH: Chromogenic *in situ* hybridization; FISH: Fluorescence *in situ* hybridization; UNL: Upper normal limit.

Primary, secondary or tertiary objectives

Treatment will be given first or second line (chemotherapy). The primary objective is to evaluate and compare the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD], SD >3 months) in the two arms. Secondary objectives are to compare the duration of disease control, time to progression, response rate (RR), duration of response (DR), overall survival (OS) and side effects for the two regimens. Evaluation of the global health status/quality of life (QoL), on the basis of the EORTC QOL C30 questionnaire will be performed. At last, a translational study to explore the potential of biomarkers during metronomic therapy is planned. The patients will be treated until disease progression or to unacceptable high toxicity, unless the patient wishes discontinuation of treatment for other reasons.

Key eligibility criteria

Patients with metastatic, HER-2-negative breast cancer, who experience progression of their disease and who are candidates for first- or second-line treatment with chemotherapy are eligible for this trial. Inclusion and exclusion criteria for the NAME trial are summarized in Box 1.

Dose & schedule of therapy

Patients enrolled in the NAME trial are randomized to one of the two following treatment arms (see also Table 2 for more details concerning the drug doses used in the two study arms):

- Control arm (arm A), or Classical treatment: Navelbine orally: vinorelbine (60 mg/m^2) on day 1 and day 8 (and day 15), every 3 weeks for the first cycle followed by 80 mg/m^2 on day 1 and day 8, every 3 weeks for the following cycles.

Table 2. Standard doses of vinorelbine according to dose levels and body surface in arm A and B of the NAME trial.

Arm A							
Vinorelbine 60 mg/m2 (Day 1+8 q3)				Vinorelbine 80 mg/m^2 (Day 1+8 q3)			
Body surface	Dose level			Body surface	Dose level		
m^2	0	-1 (75% dose)	-2 (50% dose)	m^2	0	-1 (75% dose)	-2 (50% dose)
≤1.54 m^2	90 mg	70 mg	40 mg	≤1.54 m^2	120 mg	90 mg	60 mg
1.55–1.71 m^2	100 mg	80 mg	50 mg	1.55–1.71 m^2	130 mg	100 mg	60 mg
1.72–1.90 m^2	110 mg	80 mg	50 mg	1.72–1.90 m^2	140 mg	110 mg	70 mg
>1.90 m^2	120 mg	90 mg	60 mg	>1.90 m^2	160 mg	120 mg	80 mg
Arm B							
Dose level							
0	-1	-2					
30 mg	20 mg	20 mg					
Daily	Daily	Every other day					

- Experimental arm (arm B), or Metronomic treatment: vinorelbine orally: with 3-week cycles of daily doses of 30 mg (patients with body surface ≤1.54 m^2 or ≥65 years of age start on 20 mg vinorelbine daily).

Efficacy evaluations

The response of breast cancer patients with metastatic disease during vinorelbine therapy in the two arms of the NAME trial will be evaluated by CT scans of the chest and abdomen according to the established RECIST criteria. Additional MRI-scans and x-rays may be performed whenever clinical useful. At baseline, measurable and evaluable metastases must be documented by identification of at least one bidirectionally measurable lesion. Solitary lesions must be verified by cytology/histology. All tumor measurements will be performed approximately every 3 months in accordance to standard procedures in oncology in both Denmark and Norway.

Safety evaluations

Adverse events (AE) and laboratory abnormalities will be monitored throughout the entire study. All AEs will be evaluated using the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 on a scale of five grades and detailed in the electronic case report form (eCRF) forms. AEs not listed in the CTCAE must be classified accordingly to five grades (mild, moderate, severe, life-threatening and death) as described in the study protocol. Symptoms clearly related to the progression of the underlying malignancy will not be reported as serious adverse events (SAEs). Hospitalization, solely due to the progression of breast cancer should not be reported as an SAE. However, if in doubt, symptoms will be reported by the responsible oncologists as SAEs. Due to the severity of the primary diagnosis advanced breast cancer, a number of events may be excluded from SAE reporting like hospitalization due to bone marrow depression, fever or nausea and vomiting. These side effects will, however, always be reported in the eCRF system. After completion of the study treatment period, the responsible physician shall follow-up all reported AEs and SAEs according to the procedures defined in the NAME protocol. Local laboratories will be used for all biochemical testing during the trial. All abnormalities will be reported in the eCRF system as defined in the study protocol.

Statistical analysis

The clinical efficacy of each given therapy during the trial will be evaluated after 9 weeks on therapy (three series of classical vinorelbine). RECIST 1.1 criteria will be used to evaluate all effects [39]. All areas of metastasis are to be monitored and the lesions will be categorized as either measureable or nonmeasureable. The overall response rate will also be evaluated using RECIST 1.1. Clinical chemistry alone may not be used to define response to therapy. Descriptive statistics will be used to summarize subject characteristics, AEs and duration of responses, etc. The response rate and its 95% CI will be reported in the planned publication.

Conclusion

Vinorelbine (Navelbine) is a well-established vinca alkaloid for the treatment of MBC. The drug is usually given either orally or intravenously on days 1 and 8 every 3 weeks. The NAME trial aims to investigate the potential efficacy of administering vinorelbine according to a metronomic dose schedule, meaning small doses administered

every single day. Our hypothesis is that metronomic therapy with vinorelbine has the potential to be at least as effective as classical vinorelbine, while with less associated side effects.

Executive summary

Background

- Breast cancer is one of the most common cancer types among women in the world. Metastatic breast cancer is currently incurable and available chemotherapy is only prolonging survival at a modest level.
- Metronomic chemotherapy is a new approach aiming at stabilization of the advanced breast cancer disease while decreasing side effects compared with traditional administration.

Vinorelbine/Navelbine

- Vinorelbine (Navelbine) is a well-established member of the vinca alkaloids, blocking cell division in the G2/M-phase of the cell cycle by inhibiting the assembly of microtubules necessary for the cell division. The drug is established both as intravenous therapy and oral therapy mostly for lung cancer and breast cancer.

The NAME trial

- The NAME trial is an investigator-initiated, multinational, prospective, randomized, open-label, Phase II trial running in Denmark and Norway.
- A total of 200 women with HER-2 negative, metastatic breast cancer will be enrolled.
- The patients are randomized to two treatment arms:
  - Arm A: first cycle: Navelbine 60 mg/m^2 p.o. on days 1 and 8 (15) every 3 weeks; all following cycles: Navelbine 80 mg/m^2 p.o. on days 1 and 8 every 3 weeks.
  - Arm B: 30 mg Navelbine given orally and daily; (dose adaptation may be performed according to protocol).
- Treatment will be given until disease progression has been confirmed using RECIST criteria or until the investigator terminates the treatment for other reasons according to the protocol.
- The trial has been approved by all national authorities in both Denmark and Norway.

Conclusion

- The NAME trial will clarify the role of metronomic chemotherapy with Navelbine in patients with metastatic breast cancer.

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Clinical trial identification

EUDRACT no: 2016-002165-63. Health Board no: 2017040059. Approved by the Danish Research Ethics Committee and Data Protection Agency June 2017. The trial was also approved in Norway by the regional ethics committee (2017/1829) and the National Medical Agency of Norway (SLV 18/06310-16) in 2018.

Financial & competing interests disclosure

The study is an investigator-initiated study, but financially supported by the pharmaceutical company Pierre Fabre. J Geisler received consulting fees from Novartis Pharmaceuticals, Pfizer Inc., AstraZeneca, Merck, MSD, Roche, BMS and Pierre Fabre. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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