Report Synopsis of Study VinoMetro

EudraCT-Nr.: 2016-000284-17

Vorlage-Nr.: 4041603

1) **Name of Sponsor/Company:** University Medical Centre of the Johannes Gutenberg-University Mainz Department of Obstetrics and Gynaecology Langenbeckstraße 1 55131 Mainz	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** Navelbine® Oral (soft capsules)		
3) **Name of Active Substance:** Vinorelbine tartrate		

5) **Title of Study[2]:**

Phase II study of metronomic treatment with daily oral vinorelbine as first-line chemotherapy in patients with advanced/metastatic HR+/HER2- breast cancer resistant to endocrine therapy.

Eine Phase II Studie: Metronomische Behandlung mit täglichem oralem Vinorelbin als Erstlinien-Chemotherapie bei Patientinnen mit fortgeschrittenem/metastasiertem, HR-positivem und HER2-negativem Mammakarzinom resistent gegenüber Hormontherapie.

Amendment 1 (Protocol V2.0 from 25 July 2017): Additional safety measures implemented. Patients were instructed by the investigator to record their body temperature daily on a chart and to seek immediate medical assistance in case of fever (increased body temperature > 38°C). The chart was checked by the investigator at each visit and the review was documented on the chart and in the patients´ files. The clinical monitor periodically checked the documentation on the chart and in the file. Haematological parameters were controlled on a weekly basis (trial schedule was changed). Flow cytometry analysis was no longer performed.

6) **Principal Investigator(s):**

Coordinating Investigator (LKP, according to the German Medicinal Products Act): Univ.-Prof. Dr. Marcus Schmidt

7) **Study centre(s):**

01-Mainz:

Univ.-Prof. Dr. Marcus Schmidt, Universitätsmedizin Mainz, Klinik und Poliklinik für Geburtshilfe und Frauengesundheit, Langenbeckstraße 1, 55131 Mainz.

02-Ravensburg/Wangen:

Prof. Dr. Thomas Decker, Schwerpunktpraxis für Hämatologie und Onkologie Ravensburg, Elisabethenstraße 19, 88212 Ravensburg; Schwerpunktpraxis für Hämatologie und Onkologie Wangen, Am Engelberg 29, 88239 Wangen im Allgäu.

8) **Publication (reference):** na.

9) **Studied period (years)[3]:** Date of first enrolment: 31 Jan 2017 Date of last completed: 15 Apr 2019 Note: Recruitment stopped on 05 Jul 2017 due to occurence of a SUSAR; Amendment 1 (Protocol V2.0 from 25 July 2017); Premature termination of the trial on 16 Aug 2018 due to termination of the agreement by the marketing authorisation holder of Navelbine® oral. No financial resources were available any more. At this time, 2 patients were still under treatment. Further treatment of these patients was ensured.	10) **Phase of development:** II

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

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On 15 April 2019 the last patient had her last follow-up visit.	

11) **Objectives:**

The primary objective was to estimate the efficacy of metronomic treatment with daily oral vinorelbine in terms of clinical benefit rate (CBR) based on local radiological assessment using RECIST 1.1 in patients with advanced/metastatic HR+/HER2- breast cancer resistant to endocrine therapy. The primary endpoint was the CBR (CR+PR+SD) at 24 weeks after start of treatment.

Secondary objectives were: i) To further assess the efficacy of metronomic treatment with daily oral vinorelbine in terms of overall response rate (ORR), disease control rate (DCR), duration of disease control (DoDC), duration of stable disease (DoSD), duration of response (DoR), progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS); ii) To assess the safety and tolerability of metronomic treatment with daily oral vinorelbine; iii) To assess the effect of metronomic treatment with daily oral vinorelbine on patient's symptoms and health-related quality of life (HRQoL); iv) Exploratory: To characterise histopathological parameters and biomarker profiles in tumour tissue and blood, potentially relevant to a clinical benefit from the treatment; v) Exploratory (associated separate project): To assess the feasibility and acceptance of the use of the eHealth system CANKADO in the frame of metronomic treatment with daily oral vinorelbine and to evaluate potential differences in adherence, efficacy and safety parameters of users of CANKADO in comparison with patients who do not want to participate in this eHealth system.

12) **Methodology:**

This was a national, multi-centre, open-label, single arm phase II clinical trial to estimate the efficacy of metronomic treatment with daily oral vinorelbine in terms of clinical benefit rate (CBR) based on local radiological assessment using RECIST 1.1 in patients with advanced/metastatic HR+/HER2- breast cancer resistant to endocrine therapy. A total of 9 patients were enrolled in this study. All patients who fulfilled the inclusion criteria and none of the exclusion criteria were included. Oral vinorelbine was administered at a daily dose of 30 mg (flat dose without any adaptation to body weight or body surface area) without breaks. Treatment was continued until disease progression, occurrence of unacceptable toxicity, patient's refusal or investigator's decision to stop the treatment. In terms of study assessments, a treatment cycle was defined as 28 days of therapy. Dose adjustments to 20 mg per day and dose delays were permitted in those patients who were unable to tolerate the dosing; if the toxicity was tolerable for the patient, the initial dose was maintained.

Tumour measurements by CT scan or MRI were performed at screening (thorax and abdomen/pelvis; within 28 days prior to the first intake of study medication) and repeated every 12 weeks (± 7 days) from start of treatment until progression or until the patient started another anticancer therapy. Moreover, again consistent with clinical routine, a whole-body bone scintigraphy was performed at baseline (a scan performed within 3 months prior to first intake of study drug was accepted). Further potential imaging at screening and throughout the study was also performed according to their clinical indication. Clinical response was determined using the revised RECIST guidelines version 1.1.

With regard to safety, physical condition including ECOG performance status, vital signs, standard haematology and standard biochemistry were assessed at screening, at regular visits during the treatment phase and at the end of treatment.

13) **Number of patients (planned and analyzed):**

Planned:	N = 45
Enrolled:	N = 9
Analyzed:	N = 9

14) **Diagnosis and main criteria for inclusion:**

Documented advanced/metastatic HR+/HER2- breast cancer resistant to endocrine therapy.

Inclusion criteria:

1. Written (personally dated and signed) informed consent prior to the performance of any trial specific procedure.
2. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and/or the follow-up schedule.
3. Female patient ≥ 18 years of age.
4. ECOG performance status 0-1, which the investigator assesses as being stable at time of screening.
5. Estimated life expectancy ≥ 16 weeks.
6. Histologically confirmed adenocarcinoma of the breast.
7. Documented locally advanced or metastatic disease, previously untreated by palliative chemotherapy and not amenable to any curative treatment.
8. Hormone receptor positive disease determined by ≥ 1% positive stained cells for oestrogen and/or progesterone receptor by immunohistochemistry on the primary tumour or on a metastatic site.
9. HER2-negative disease (assessed by 0-1+ IHC or 2+ IHC with negative FISH or CISH) on the primary tumour or on a

metastatic site.

10. Availability of archival (from the most recently obtained sample) or fresh tumour tissue from patients included in the trial for the analysis of relevant metronomic biomarkers; one tumour block (preferred) or a minimum of 12 (recommended: 15) unstained slides to be provided.
11. Relapse ≤ 12 months from end of adjuvant endocrine therapy or progression during/after ≥ 1 line of endocrine therapy in the metastatic setting and/or no longer candidate for further endocrine therapy.
12. Prior (neo-)adjuvant chemotherapy is allowed, if the interval between end of chemotherapy and date of registration is > 12 months.
13. Prior treatment with everolimus and/or palbociclib in the frame of hormonal therapy is allowed.
14. Complete staging before registration (CT/MRI thorax and CT/MRI abdomen/pelvis ≤ 28 days before registration; bone scan ≤ 3 months before registration).
15. Presence of ≥ 1 measurable lesion as per RECIST 1.1, which has not been previously irradiated.
16. Adequate bone marrow, hepatic and renal functions as defined by the following laboratory values:
    - Absolute neutrophil count (ANC) ≥ 1,500/mm^3
    - Platelet count ≥ 100,000/mm^3
    - Haemoglobin ≥ 10 g/dL
    - Total serum bilirubin ≤ 1.5 x ULN (≤ 3 x ULN in case of liver metastases)
    - Liver transaminases ≤ 2.5 x ULN (≤ 5 x ULN in case of liver metastases)
    - Alkaline phosphatase ≤ 5 x ULN
    - Creatinine ≤ 1.5 x ULN (creatinine clearance should be assessed based on the Cockroft-Gault-formula in case of borderline values and should then be ≥ 50 mL/min)
17. Women of childbearing potential must be using a highly effective and medically accepted contraception method to avoid pregnancy during 2 months preceding registration, throughout the study period and up to 3 months after last dose of study treatment; reliable contraception comprises sexual abstinence, double barrier methods (i.e. condom plus diaphragm) or vasectomised partner.
18. Women of childbearing potential must have a negative serum or urine pregnancy test at screening within 72 hours prior to start of study treatment.
19. Ability of the patient to understand the character and the individual consequences of this clinical trial.

15) **Test product, dose and mode of administration, batch number:**

Navelbine® soft capsules (Vinorelbine oral) for oral administration, starting dose 30 mg once daily (flat dose without any adaptation to body weight or bopdy surface area) without breaks. A treatment cycle was defined as 28 days of treatment. Dose adaptations of vinorelbine and treatment interruptions were based on toxicity.

16) **Duration of treatment:**

Continuously daily intake of 30 mg oral vinorelbine until one of the following occurred: Disease progression, occurrence of unacceptable toxicity, patient´s refusal or investigator´s decision to stop the treatment.

17) **Reference therapy, dose and mode of administration, batch number:**

Not applicable, all patients received the test product.

18) **Criteria for evaluation[4]:**

a) Efficacy: Clinical benefit rate (CBR) according to RECIST 1.1. Secondary endpoints were estimation of objective response rate (ORR), disease control rate (DCR) (overall and at 12 weeks), duration of disease control (DoDC), duration of stable disease (DoSD), duration of response (DoR), progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS).

b) Safety: Determination of frequency and severity of (serious) adverse events [(S)AEs] and the number of laboratory values worsening from baseline based on the Common Terminology Criteria (CTC) grade. Assessment of clinical toxicities and safety laboratory during scheduled visits at the study centres. In this trial, all (serious) adverse events that occurred between the first intake and up to 30 days after the last intake of trial medication were documented. All events were reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03). The incidences of treatment interruption and dose reduction were also recorded for all patients.

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

19) **Statistical methods:**

The analysis of the primary endpoint, i.e. the proportion of patients with clinical benefit (CBR; i.e. SD, PR or CR according to RECIST 1.1) at 24 weeks after start of study treatment, was based on the efficacy set (i.e. those patients having received ≥ 1 dose of study treatment and being evaluable according to RECIST). The disease control rate (DCR) was provided together with the corresponding 95% confidence interval (CI).

The minimum required level of efficacy (p0) was set to a DCR of 35% based on a prior trial investigating the standard-monotherapy with oral vinorelbine in the first-line setting of patients with HR+/HER2- metastatic breast cancer: vinorelbine oral 80 mg/m^2 weekly (after 3 administrations at 60 mg/m^2) in 64 patients (30% pretreated with neo-/adjuvant chemotherapy; 60% of them treated with AC-based therapy) – PFS-rate at 6 months approx. 38%.

An increase in DCR by 20% when using the metronomic treatment was considered to be of clinical relevance and accordingly the target DCR (p1) was set to 55%. Simon's two-stage minimax design was scheduled for the primary analysis. The null hypothesis that the true response rate is 0.35 (p0) was tested against a one-sided alternative. In the first stage, 21 patients were to be accrued. If there were ≤ 8 patients with clinical benefit at 24 weeks in these 21 patients, the study would have been stopped. Otherwise, 18 additional patients would be accrued for a total of 39. The null hypothesis would be rejected if ≥ 19 patients showed clinical benefit at 24 weeks in 39 patients. This design yielded a type I error rate of 0.05 and power of 0.80 when the true response rate was 0.55 (p1). Taking into account an anticipated dropout rate of approx. 15%, a total of 45 patients were accrued for this trial.

Secondary efficacy analyses included:

a) Kaplan-Meier analyses were performed to evaluate PFS, TTF and OS; the corresponding medians and 95% confidence intervals (CIs) were given.

b) ORR was summarised as percentage rate and 95% CI.

c) DoDC, DoSD and DoR were also analysed descriptively.

Safety assessments were based on the incidence of (serious) adverse events, the number of laboratory values outside of pre-defined ranges and number of clinically meaningful laboratory changes as determined by the investigator. Safety assessments were based on the safety population, which consisted of patients having received ≥ 1 dose of oral vinorelbine and having had ≥ 1 post-baseline safety assessment. There were interim analyses planned after 10 patients for safety reasons and after completion of 21 patients after the 1st stage of Simon's design. However, due to the low number of recruited patients no interim analyses were performed.

20) **Summary – Conclusions[5]:**

I. Patient characteristics

All patients were female and the mean age was 65.2 (± 8.21).

a) TNM-Staging/Grading:

2 patients (22%) had T1c and 7 (78%) T2. 3 patients had N0 (33%), 2 N1 (22%), 2 N2 (22%) and 2 N3 (22%). All patients had no metastases. 5 tumours (56%) were graded 2nd grade and 4 tumours (44%) were graded 3rd grade.

There were 15 previous surgical therapies in 9 patients. 13 showed no residual tumour, 1 showed a microscopic residual tumour and 1 showed a macroscopic residual tumour.

b) Receptor status for primary diagnosis:

8 patients (89%) were oestrogen receptor (ER) positive and 1 ER (11%) negative. 2 (22%) were human epidermal growth factor receptor 2 (HER2) 1+ (negative), 2 (22%) were HER2 2+ (not clear) and 5 (56%) were HER2 negative. 7 (78%) were progesterone receptor (PR) positive and 2 (22%) were PR negative.

c) Receptor status for metastatic disease:

This assessment was performed for 6 out of 9 patients. All 6 patients were ER positive. 3 were HER2 1+ (negative), 1 was HER2 2+ (not clear), 1 was HER2 negative and 1 was not assessed. 3 were PR positive and 3 were PR negative.

d) Therapies:

8 patients (89%) received an adjuvant chemotherapy and 1 (11%) did not. All patients received endocrine therapy, antibody therapy or targeted therapy and all patients received radiotherapy.

e) Lesions:

All patients had at least 1 measurable lesion. The median number was 2 and ranged from 1 to 3. Most of them (9/17) were located in the liver. The median size of the lesions were 50 mm and ranged from 15 to 71 mm. All patients had at least 1 non-measurable lesion in various locations. The median number was 2 and ranged from 1 to 3.

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

II. Patient disposition and extent of exposure

Figure 1 shows the patient disposition. 1 patient reached treatment cycle 18 and another patient treatment cycle 10. All other patients discontinued at cycle 5 or earlier. The median days under treatment was 95 days, ranging from 12 to 509 days. The median total amount of study medication was 2.430 mg resuling in a median average daily dose of 27.30 mg. The compliance could be rated as very good with a median of 95%, ranging from 49% to 100%.

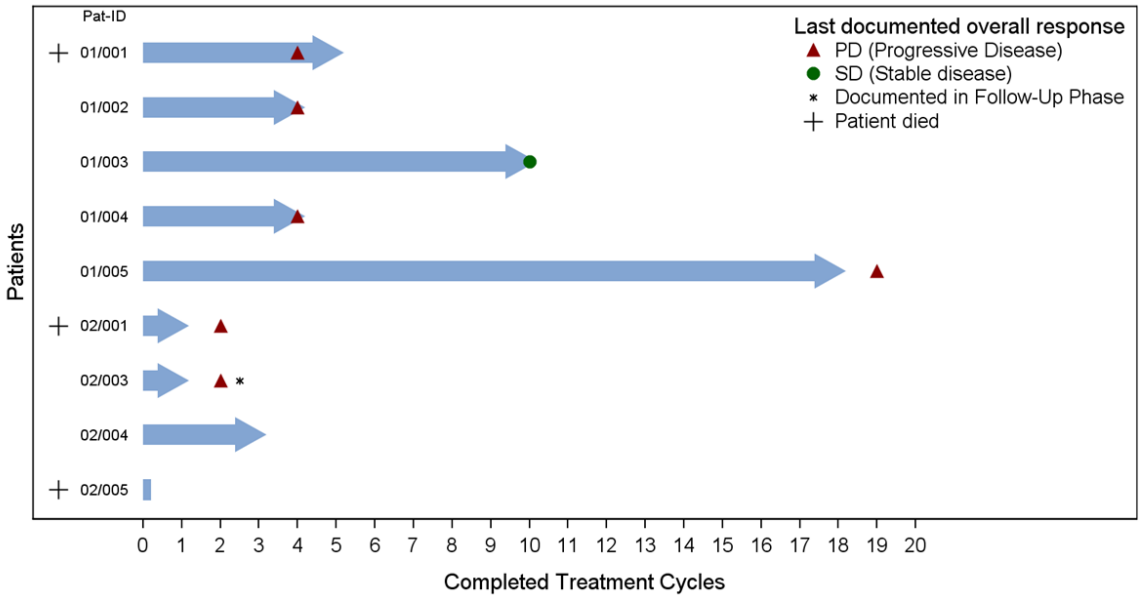

Fig. 1: Patient disposition (enrolled population). Each bar represents a patient in the enrolled population.

III. Efficacy results

a) Disease Control Rate/Clinical Benefit Rate (DCR/CBR):

Table 1 displays the results of the Disease Control Rate/Clinical Benefit Rate (DCR/CBR). 2 patients (22%) achieved complete response (CR), partial response (PR) or stable disease (SD) after 24 weeks. In fact, both patients were on SD. The 90% confidence interval ranged from 4% to 55% and could not deliver great precision because of the low patient number.

Tab. 1: Results of the DCR/CBR.

Variable	**All patients (N=9)**
Clinical benefit rate at 24 weeks after start of study treatment	
Yes	2 (22.22%)
No	7 (77.78%)
90% Lower Confidence Limit	0.0410
90% Upper Confidence Limit	0.5496
p-Value (p0=35%)	0.2108

b) Progression-free survival (PFS):

Figure 2 displays the Kaplan-Meier curve for progression free survival (PFS). The median time to progression or death due to any reason was 84 days (95% CI: 16 to 504 days).

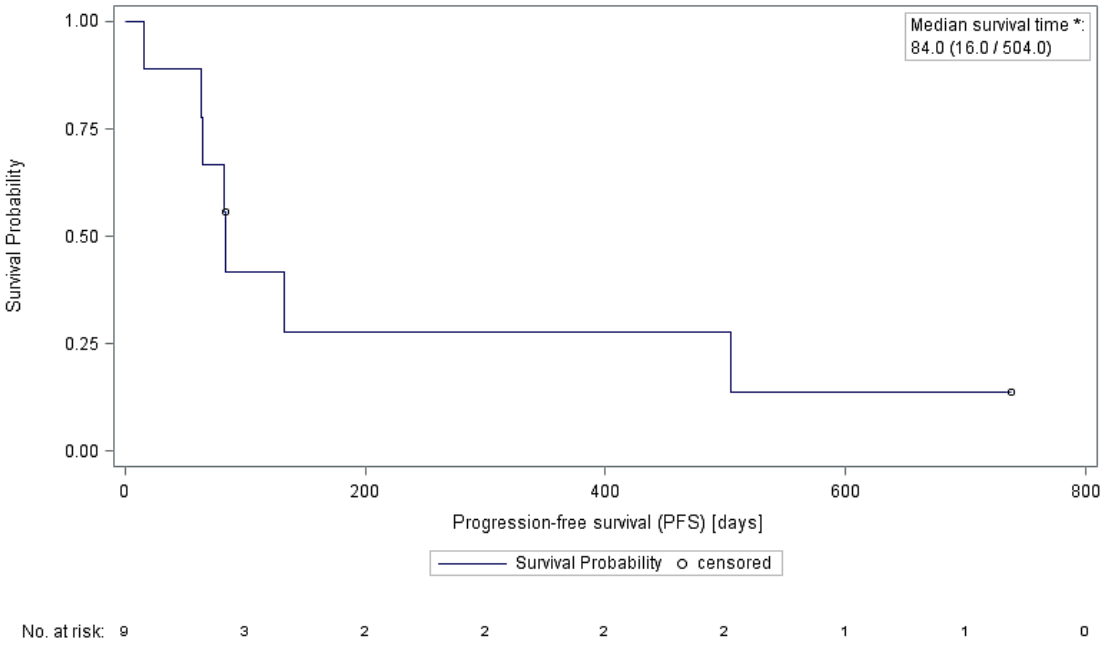

Fig. 2: Kaplan-Meier curve for progression-free survival (PFS). Analysis Set = enrolled population (N=9). *Statistics: Median survival time including 95% confidence interval.

c) Time to treatment failure (TTF):

Figure 3 displays the Kaplan-Meier curve for time to treatment failure (TTF). The median time to treatment failure was 94 days (95% CI: 11 to 258 days).

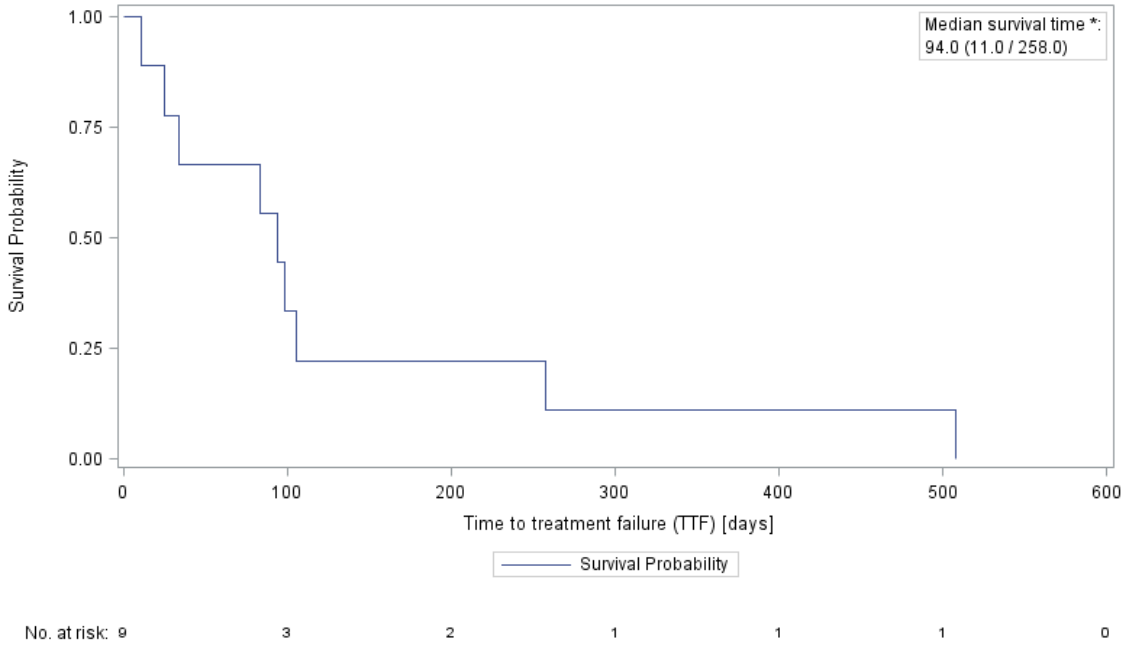

Fig. 3: Kaplan-Meier curve for time to treatment failure (TTF). Analysis Set = enrolled population (N=9). *Statistics: Median survival time including 95% confidence interval.

d) Overall survival (OS):

Figure 4 shows the Kaplan-Meier curve for time to death (OS). Only 3 deaths occurred, hence median OS could not be estimated.

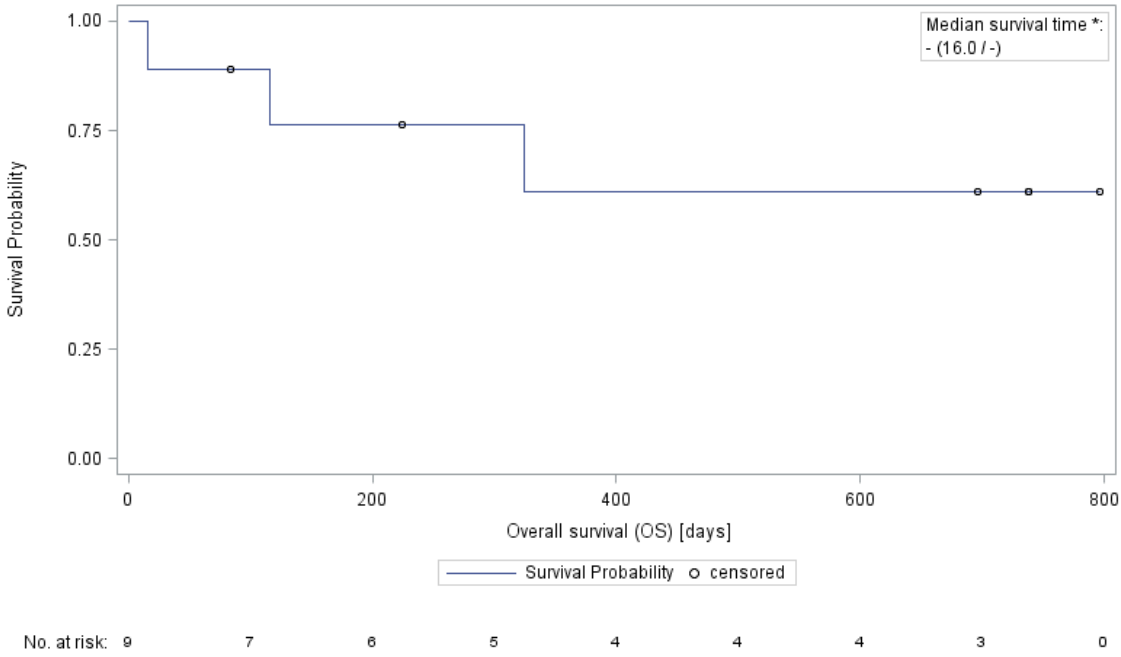

Fig. 4: Kaplan-Meier curve for time to death (OS). Analysis Set = enrolled population (N=9). *Statistics: Median survival time including 95% confidence interval.

e) Overall response rate (ORR):

There was no response achieved after 12 weeks of treatment.

f) Duration of disease control and duration of stable disease (DoDC and DoSD):

Table 2 displays the results of the duration of disease control (DoDC) and the duration of stable disease (DoSD). The results of both analyses are identical, because only stable disease could be achieved. The mean number was 320.5 days. However, the results have to be interpreted with caution, because only 2 patients reached stable disease or disease control.

Table 2: Duration of disease control (A) and duration of stable disease (B).

Variable	**All patients (N=9)**
A) Duration of Disease Control (DoDC) in days	
N	2
Mean (SD*)	320.50 (142.13)
Median	320.50
Range	220.0-421.0
Missing	7
B) Duration of Stable Disease (DoSD) in days	
N	2
Mean (SD*)	320.50 (142.13)
Median	320.50
Range	220.0-421.0
Missing	7

*SD: Standard Deviation

g) Duration of response (DoR):

Not applicable. No response was observed.

IV. Safety results

a) Adverse Events:

All 9 patients enrolled in the clinical trial VinoMetro experienced at least 1 adverse event (AE) related to study treatment. In total, 73 AEs were reported (8.1 per patient). Thereof, 37 AEs were assessed as related to study treatment. 4 (5.5%) of the 73 AEs were documented as serious adverse events (SAE), 2 (22.2%) patients experienced at least 1 SAE. 1 SAE (preferred term (PT): sinus tachycardia) was assessed as unrelated to study treatment. 3 SAEs (included in 1 SAE report) were assessed as related, 1 of them expected (PT: klebsiella sepsis), 2 of them unexpected due to fatal outcome (PT: neutropenic infection and pneumonia) and therefore reported as suspected unexpected serious adverse events (SUSAR). Table 3 displays an overview of the treatment emergent adverse events.

Table 3: Adverse Events (AE) summary table. AEs with missing causality assessments were considered as related adverse events.

Number of patients with...	All patients (N=9)	(nAE=73)
...at least one AE	9 (100.00%)	73 (100.00%)
...at least one AE with causal relationship to vinorelbine	9 (100.00%)	37 (50.68%)
...at least one SAE	2 (22.22%)	4 (5.48%)
...with a fatal AE	1 (11.11%)	3 (4.11%)

The most frequent AEs were gastrointestinal disorders (7 patients, 5 of them suffered from nausea, 3 from diarrhoea) followed by investigations (5 patients, several increased liver enzymes), general disorders and administration site conditions (5 patients, 4 of them with fatigue), musculoskeletal and connective tissue disorders (5 patients) and infections and infestations (4 patients).

b) Laboratory Values:

There were no remarkable laboratory values apparent, apart from abnormal liver values already mentioned in the AEs section.

c) Vital Signs:

Figure 5 shows the patients´ weights during the course of the study. The graph suggests that the patients lost weight during the course of the treatment/disease.

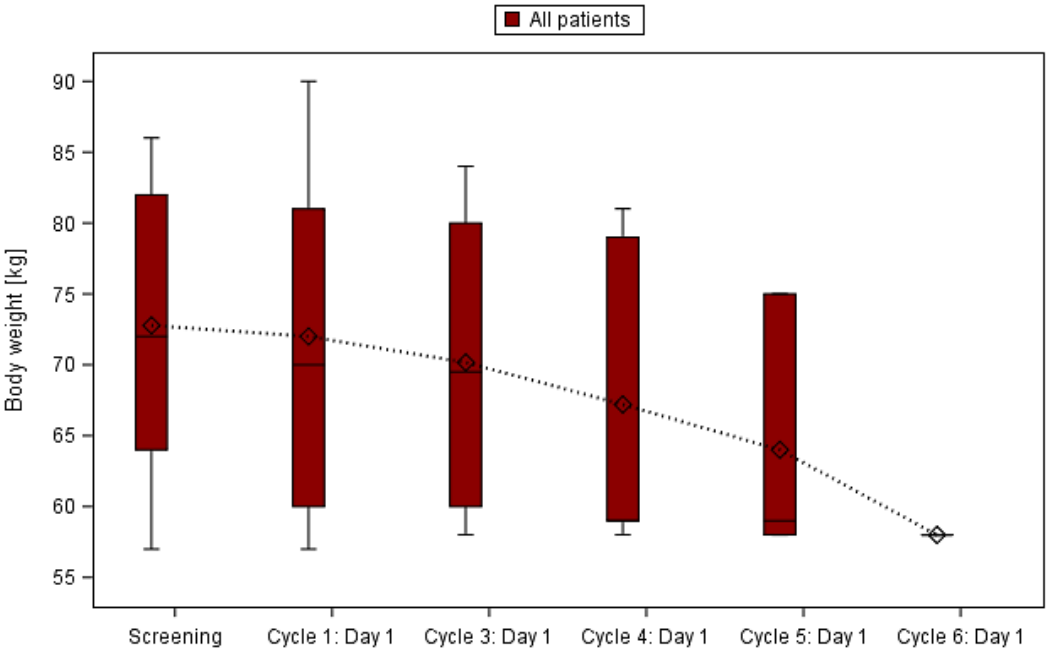

Fig. 5: Patients´ body weights during the course of the study. Analysis set = enrolled population (N=9).

Conclusion:

This phase 2 study had to be terminated early after 9 patients. One patient had a fatal event, only 2 patients showed a disease-contol rate with a median of 320.50 days. These results show only a limited benefit of this treatment regimen in advanced ER+/HER2- breast cancer patients with progressive disease after endocrine therapy.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 06.10.2019

Print Name: Univ.Prof. Dr. med. Marcus Schmidt

Signature: