CLINICAL STUDY PROTOCOL

Capecitabine in combination with Bendamustine in women with pretreated locally advanced or metastatic Her2-negative breast cancer, a Phase II Trial

AGMT MBC-6

Principal and Coordinating Investigator:
Prim. Univ. Prof. Dr. Richard Greil

EudraCT number: 2012-005593-64

An academic clinical trial sponsored by

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I have thoroughly read and reviewed the study protocol “Capecitabine in combination with Bendamustine in women with pretreated locally advanced or metastatic Her2-negative breast cancer, a Phase II Trial – AGMT MBC-6, Version 1, 09.04.2013”. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the international good clinical practice principles and regulatory authority requirements.
I understand that changes to the protocol must be made in form of an official amendment.
I agree to report all serious adverse events, whether considered treatment-related or not within 24 hours.

____________________________
Investigator Name

____________________________  ___________
Investigator Signature  Date
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# 1 STUDY SUMMARY

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<th>AGMT MBC-6</th>
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<tr>
<td>EudraCT number:</td>
<td>2012-005593-64</td>
</tr>
<tr>
<td>Date of protocol:</td>
<td>09.04.2013</td>
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<tr>
<td>Protocol title:</td>
<td><strong>Capecitabine in combination with Bendamustine in women with pretreated locally advanced or metastatic Her2-negative breast cancer, a Phase II Trial</strong></td>
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<td>Protocol Version:</td>
<td>1</td>
</tr>
<tr>
<td>Coordinating Investigator:</td>
<td>Prim. Univ. Prof. Dr. R. Greil</td>
</tr>
<tr>
<td>Sponsor::</td>
<td>AGMT – Arbeitsgemeinschaft medikamentöse Tumortherapie gemeinnützige GmbH</td>
</tr>
<tr>
<td>Project Phase:</td>
<td>II</td>
</tr>
<tr>
<td>Indication:</td>
<td>Progression of an advanced (locally advanced or metastatic) Her2-negative breast cancer after anthracycline and/or taxane pretreatment</td>
</tr>
<tr>
<td>Treatment line</td>
<td>First- or second line (after anthracycline and/or taxane pretreatment in the palliative or adjuvant setting)</td>
</tr>
</tbody>
</table>

### Objectives:

**Primary objective:**
The efficacy of a capecitabine plus bendamustine combination regimen in the treatment of Her2-negative advanced metastatic breast cancer.

**Secondary objectives:**
- To determine the safety profile of a combination with capecitabine and bendamustine in terms of qualitative and quantitative toxicities from first study treatment dose until completion of study treatment due to progression or for any other reason.
- To evaluate the study population with respect to the following: clinical benefit (CR, PR or stable disease for at least 24 weeks), progression free survival (from treatment start until progression or death from any cause) and explorative the overall survival (from treatment start until death from any cause).
- To evaluate Quality of Life (QoL) status within the study population is captured using the EORTC QLQ-C30 standard questionnaire
- Predefined subgroup analysis of triple-negative patients and hormone receptor positive patients in terms of response

### Study design:
This is a non-randomized, multicenter, open-label, single-
arm Phase II study in pretreated patients with Her2-negative advanced breast cancer. Prior therapies must include anthracyclines and/or taxans in the adjuvant or metastatic setting. Following a two-stage design efficacy and safety of bendamustine and capecitabine will be evaluated following recruitment of the first 20 patients. Upon favorable results a further 20 patients will be recruited to reach the target population of 40 evaluable patients.

Eligible patients will receive capecitabine in combination with bendamustine for a maximum of eight cycles and afterwards capecitabine mono will be continued until disease progression or unacceptable toxic effects. **Capecitabine** will be dosed at 1000mg/m² twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).

**Bendamustine** 80mg/m² will be administered on day 1 and 8 of a three week cycle (for a maximum of eight cycles).

Safety assessments will be conducted in 3-weekly intervals; efficacy assessments will be conducted every 9 weeks.

<table>
<thead>
<tr>
<th>Planned sample size:</th>
<th>40 patients</th>
</tr>
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| Inclusion Criteria (selected): | • Signed informed consent  
• Female patients, age ≥ 18 years. Women of childbearing potential must have a negative pregnancy test at screening and must use effective contraception  
• Advanced or metastatic Her2-negative breast cancer, histologically confirmed  
• At least one measurable lesion according to RECIST criteria (patients with bone-only lesions are not eligible for study entry)  
• Documented disease progression  
• Patients with progression after anthracycline and/or taxane treatment (palliative or adjuvant)  
• Life expectancy of at least 12 weeks  
• Performance status 0-2 |
| Duration of the Study: | Start Q2 2013  
Recruitment: 2 years  
Expected end of study: Q3 2016 |
2 BACKGROUND AND RATIONALE

2.1 Background

Breast cancer is the most common cancer diagnosed in women worldwide. In Austria 5,000 new cases are diagnosed each year (Statistics Austria, 2009). 5 to 10% have been diagnosed with metastasis, while up to 30% of node-negative and up to 70% node-positive tumors relapse at a later time. Metastatic breast cancer is largely incurable and with 1,600 deaths per year in Austria 2009 breast cancer is the most common cause of cancer related deaths in women. [1, 2]

The primary goal of metastatic breast cancer treatment is symptom control and preservation of quality of life in addition to a prolongation of life. By now, 17 cytotoxic agents and targeted therapies have been approved for the treatment of the advanced disease. Anthracyclines and taxanes show the highest response rates and so these agents are preferred in combination or as single agents in the first line setting. In the second line or after adjuvant anthracycline and/or taxane pretreatment capecitabine is well established. Bendamustine is also a well-tolerated agent, which has already shown anticancer activity in breast cancer.

We want to evaluate the efficacy and tolerability of the combination of capecitabine and bendamustine in a phase II clinical trial in 40 patients with advanced breast cancer after anthracycline and/or taxane pretreatment.

2.2 Rationale for the use of bendamustine

In 1963 bendamustine was first synthesized in the former East German Democratic Republic with the intention to develop a less toxic but an at least as equivalent acting drug as other alkylating agents [1]. Bendamustine is a hybrid cytotoxic drug because of its structural similarity to alkylating agents and purine analogs and comprises three elements: a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain. Like other alkylating agents bendamustine causes DNA breaks by DNA cross-linking. However, compared to melphalan, cyclophosphamide and carmustine, bendamustine induces more and longer lasting DNA single- and double-strand breaks [2]. Furthermore bendamustine activates the base excision DNA repair mechanism rather than the alkyltransferase DNA pathway in comparison to other alkylating agents. The benzimidazole ring is unique to bendamustine and may contribute to this specific antitumor activity. [3]
In the treatment of haematological malignancy’s, such as multiple myeloma or lymphoma, bendamustine is well established. But also in the treatment of solid tumors like breast, colon and lung cancer promising data are available.

The evidence of bendamustine in the treatment of metastatic breast cancer has been well represented in a review by Pirvulescu et al. from the German Breast Group, published in Breast Care 2008 [4]. In monotherapy trials (one pilot trial [5] and 3 phase II trials [6-8]), all including pretreated patients, overall response rates from 20% up to 48% with a moderate toxicity profile were seen. Bendamustine has also been investigated in combination with other cytotoxic drugs. In two pilot trials in which bendamustine has been combined with anthracyclines (bendamustine/doxorubicin/vincristine [9] and bendamustine/mitoxantrone [10]) overall response rates were 48% to 50%. A pilot trial with bendamustine and gemcitabine [11] had to be cancelled because of severe hematological toxicity. In a firstline phase III trial for metastatic breast cancer a combination of bendamustine, methotrexat and 5-FU (BMF) was compared to cyclophosphamid, methotrexat and 5-FU (CMF) [12]. Overall response rates of 44% (BMF) and 40% (CMF) were similar in both groups but myelotoxicities were more frequent in the BMF group (leukopenia 62.7 vs. 40%). A significant longer time to disease progression (TTP), 8.2 vs. 6.7 months, was seen in the BMF group.

In a recently published phase II trial, including 26 patients, bendamustine was combined with paclitaxel in a weekly schedule [13]. The overall response rate was 43.8% independent of anthracycline pretreatment. Median progression free survival and overall survival were 7.3 and 14.9 months, respectively. The toxicity profile was moderate with 50% grade 3-4 hematological toxicities.

2.3 Rationale for the use of capecitabine

Capecitabine is an orally administered pro-drug of the fluopyrimidine 5-fluorouracil (5-FU). 5-FU has been used for over 40 years as mono-therapy or in combination with other cytostatic drugs in breast cancer treatment. Capecitabine is rapidly and nearly complete absorbed, after oral administration. Subsequently capecitabine is extensively metabolized via hepatic carboxylesterase to 5’-deoxy-5-fluorocytidine (5’-DFCR) and via cytidine deaminase to 5’-deoxy-5-fluorouridine (5’-DFUR) in liver and neoplastic tissue. 5’-DFUR is finally converted to 5-FU via thymidine phosphorylase, which is higher concentrated in
tumor tissue, compared to healthy tissues. Capecitabine biotransformation to 5-FU leads to higher concentration in tumor tissue and is therefore “tumor specific”. [3]

Figure: 2 Structures of capecitabine biotransformation to 5-FU

Five multicenter phase II trials evaluated capecitabine monotherapy in taxane and/or anthracycline pretreated patients with advanced or metastatic breast cancer. Capecitabine 1250mg/1255mg per square administered twice daily, two weeks of a three-week cycle, showed overall objective response rates (ORR) of 20 to 36%. Median time to progression (TTP) was 3.0 to 8.1 months and median overall survival (OS) was 7.6 to 12.8 months [4-8]. In three phase III trials in anthracyline and taxane pretreated patients with metastatic breast cancer capecitabine monotherapy showed similar results to the phase II studies with ORR from 9 to 29 months. TTP and OS were 4.1 to 4.4 months and 14.5 to 15.6 months, respectively [10-12]. In three phase II trials in untreated patients for the advanced disease with metastatic breast cancer, overall response rate were 30 to 37% with median TTP of 3.9 to 4.1 months and OS of 10.0 to 19.6 months, respectively [9, 13]. See table 1.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Regimen cap mg/m2 twice daily</th>
<th>Prior chemotherapy MBC</th>
<th>ORR, %</th>
<th>TTP, mo</th>
<th>OS, mo</th>
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<tbody>
<tr>
<td>Blum et al. [4]</td>
<td>II</td>
<td>1,255 (n=162)</td>
<td>A and paclitaxel</td>
<td>20</td>
<td>8.1</td>
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<td>Blum et al. [5]</td>
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<td>7.6</td>
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<tr>
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<td>T</td>
<td>15</td>
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<tr>
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<td>-</td>
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<tr>
<td>Lechleider R. et al [10]</td>
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<tr>
<td>Bajetta et al. 21 [13]</td>
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<td>1,000 (n=43)</td>
<td>None</td>
<td>35</td>
<td>4.1</td>
<td>16.0</td>
</tr>
</tbody>
</table>

Abbreviations: A – Anthracycline, T – Taxane

Table 1: Phase II and III trials of capecitabine mono in metastatic breast cancer
Capecitabine is therefore approved in taxane and/or anthracycline pretreated patients with advanced breast cancer or in patients for whom anthracycline therapy is not indicated. This oral fluoropyrimidine is further approved in the combination with docetaxel, bevacizumab and lapatinib for advanced breast cancer.

Capecitabine is well tolerated with uncommon grade 3 and 4 toxicities. The leading side effects are gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal pain and stomatitis), hand-foot syndrome (palmar-plantar erythrodynesthesia), fatigue, asthenia, anorexia, cardiotoxicity, thrombosis/embolism, and increased renal dysfunction in patients with preexisting impaired renal function. Complete hair loss and grade 3 and 4 myelosuppression are rare. [3]

2.4 Rationale for the combination of capecitabine and bendamustine

The combination of bendamustine with a fluoropyrimidine has already been tested in a randomized phase III trial comparing CMF (cyclophosphamid, methotrexat and 5-FU) versus BMF (bendamustine, methotrexat and 5-FU) as already mentioned above [14]. In this trial by Minckwitz et al. published 2005 9,3% complete responses (CR), 35.2 % partial responses (PR) and 48.1% stable diseases (SD) were seen. Time to disease progression (TTP) was significant longer in the bendamustine group (8.2 vs. 6.7 months).

Both capecitabine and bendamustine have a moderate toxicity profile. Thrombopenia and neutropenia are uncommon side effects of capecitabine and so an unmanageable increase of haematological toxicities in the combination with bendamustine is not expected.

3 STUDY DESIGN

This is a non-randomized, multicenter, open-label, single-arm Phase II study in pretreated patients with Her2-negative advanced breast cancer. Prior therapies must include anthracyclines and/or taxans in the adjuvant or metastatic setting. Following a two-stage design efficacy and safety of bendamustine and capecitabine will be evaluated following recruitment of the first 20 patients. Upon favorable results a further 20 patients will be recruited to reach the target population of 40 evaluable patients.

3.1 Study Treatment

Capecitabine will be dosed at 1000mg/m2 twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).
**Bendamustine** 80mg/m² will be administered on day 1 and 8 of a three week cycle (for a maximum of eight cycles).

Eligible patients will receive capecitabine in combination with bendamustine for a maximum of eight cycles and afterwards capecitabine mono will be continued until disease progression or unacceptable toxic effects. Safety assessments will be conducted in 3-weekly intervals; efficacy assessments will be conducted every 9 weeks.

**Figure: 3: Study design**

4 STUDY DURATION

This study is expected to start in Q2 2013. The last patient is expected to enter the study in Q1 2015, following a 24 month recruitment period. Last Subject Last Visit will be at final staging after end of treatment of last patient. Follow-up after Last Subject Last Visit will be conducted according to local standard of care thereafter, and is not part of study procedures.

5 NUMBER OF PATIENTS

40 eligible patients will be enrolled. A two-stage design efficacy and safety of bendamustine and capecitabine will be evaluated following recruitment of the first 20 patients. Upon favorable results a further 20 patients will be recruited to reach the target population of 40 evaluable patients.
6 OBJECTIVES OF THE STUDY

6.1 Primary objective

Primary Endpoint of this study is to determine the efficacy of a capecitabine plus bendamustine combination regimen in the treatment of Her2-negative advanced metastatic breast cancer, in terms of overall response rates (complete or partial response, determined by radiologic evaluation according to Response Evaluation Criteria in Solid Tumors – RECIST Version 1.1) [23].

6.2 Secondary objectives

- To determine the safety profile of a combination with capecitabine and bendamustine in terms of qualitative and quantitative toxicities from first study treatment dose until completion of study treatment due to progression or for any other reason
- To evaluate the study population with respect to the following:
  - clinical benefit (CR, PR or stable disease for at least 24 weeks)
  - progression free survival (from treatment start until progression or death from any cause)
  - overall survival (explorative, from treatment start until death from any cause)
- To evaluate Quality of Life (QoL) status within the study population using the EORTC QLQ-C30 standard questionnaire and the BR23 module (for breast cancer patients)
- Predefined subgroup analysis of triple-negative patients and hormone receptor positive patients in terms of response

7 INCLUSION AND EXCLUSION CRITERIA

7.1 Inclusion criteria

- Signed informed consent
- Female patients, age ≥ 18 years (women of childbearing potential must have a negative pregnancy test at screening and must use effective contraception)
- Advanced or metastatic Her2-negative breast cancer, histologically confirmed
- At least one measurable lesion according to RECIST criteria (Version 1.1)
- Documented disease progression
- Patients with progression after anthracycline and/or taxane treatment (palliative or adjuvant)
- Life expectancy of at least 12 weeks
- Performance status 0-2
• Adequate hematology, liver and renal function:
  o **Hematologic:**
    o ANC (absolute neutrophil count) ≥ 1.5 x 10^9/L
    o Hemoglobin ≥ 9 g/dL
    o Platelets ≥ 100 x 10^9/L
  o **Liver Function:**
    o Albumin ≥ 2.5 g/dL
    o Serum bilirubin ≤ 2 mg/dL
    o AST and ALT ≤ 3 x ULN without liver metastases
    ≤ 5 x ULN if documented liver metastases
  o **Renal Function:**
    o Serum Creatinine ≤ 1.5 mg/dL OR Calculated Creatinine Clearance ≥ 40 mL/min

7.2 *Exclusion criteria*

• Pregnant or lactating women
• Serious medical or psychiatric disorders that would interfere with the patient’s safety or informed consent
• Radiation of the target lesion within the last 4 weeks
• Active bacterial, viral or fungal infection
• Patients with clinically apparent brain metastases
• Known Positivity for HIV
• Positivity for Hepatitis B or C
• History of other malignancy; patients who have been disease-free for 5 years or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.
• Concurrent cancer therapy (chemotherapy, immunotherapy, antihormonal or biologic therapy) or concurrent treatment with an investigational drug
  o Antihormonal therapy must have been discontinued prior to start of treatment (if possible at least 3 weeks before)
• Known hypersensitivity to the study drugs capecitabine and bendamustine or their excipients
• Pretreatment with capecitabine (pretreatment with infusional 5-FU in the adjuvant or neoadjuvant setting is allowed) or bendamustine
• Treatment with sorivudine or derivatives e.g. brivudin (Mevir©) within the last 4 weeks before and during study treatment with capecitabine

7.3 *Subject Withdrawal Criteria*

Study participation/treatment will be stopped in case of
• Patient’s decision
• Investigators decision in best interest of patient
• Progressive disease
• Failure to comply with the requirements of the protocol
• Patients, who missed treatment for more than two cycles (for either bendamustine or capecitabine)

Moreover patients must be withdrawn under the following circumstances:
• Pregnancy or lack of adequate contraception in women of childbearing potential
• Major protocol violation considered to be relevant by the investigator and/or the sponsor

8 ASSESSMENTS

8.1 Baseline

To be performed within 3 weeks before start of therapy (except tumor anamnesis):
• ICF
• Genetic ICF
• Pregnancy test (if applicable)
• Medical history
• Tumor anamnesis (including HER2 status)
• CT (preferred) or MRI (detailed information see 8.8.)
• Physical examination
• Weight, height
• ECOG performance status
• ECG
• Vital signs (blood pressure, HR)
• Complete blood cell count (hemoglobin, platelets, leucocytes, lymphocytes, monocytes and neutrophils)
• Laboratory parameters (ASAT, ALAT, GGT, AP, albumin, total bilirubin, creatinine or creatinine clearance (calculated), Na, Ca, K, Ca15-3, CEA)
• Hepatitis B and C serology
• Questionnaires
  o EORTC QLQ-C30 (including BR 23 module)

8.2 Assessments start of therapy

• Complete blood cell count (hemoglobin, platelets, leucocytes, lymphocytes, monocytes and neutrophils)
• 35ml blood samples for scientific research program
• Pregnancy test (if applicable)
8.3 **Assessments on day 8 (+/- 3 days)**

- 35ml blood samples for scientific research program

8.4 **Assessments every 3 weeks (+/- 3 days)**

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, HR)
- Complete blood cell count (hemoglobin, platelets, leucocytes, lymphocytes, monocytes and neutrophils)
- Laboratory parameters (ASAT, ALAT, GGT, AP, albumin, total bilirubin, creatinine or creatinine clearance (calculated), Na, Ca, K, Ca15-3, CEA)
- Pregnancy test (if applicable) at least every 4 weeks
- History of last cycle including medication compliance
- Adverse Events

8.5 **Additional assessments every 9 weeks (+/- 3 days)**

- CT (preferred) or MRI (detailed information see 8.8.)
- Questionnaires
  - EORTC QLQ-C30 (including BR 23 module)
- 35ml blood samples for scientific research program

8.6 **Follow Up**

(approx. every 3 months from end of treatment until final staging of last patient)

- Documentation of further treatment and response
- Survival

8.7 **Survival Follow up**

After the final visit of the last patient has been completed, patients will be followed according to local standard of care. Survival Follow-up is not counted as a study specific procedure.

8.8 **Assessments at end of study treatment**

(at progression or at premature withdrawal, if possible)

- Physical examination
- Weight
- ECOG performance status
• Vital signs (blood pressure, HR)
• Complete blood cell count (hemoglobin, platelets, leucocytes, lymphocytes, monocytes and neutrophils)
• Laboratory parameters (ASAT, ALAT, GGT, AP, Albumin, total bilirubin, creatinine, creatinine-clearance, Na, Ca, K, Ca15-3, CEA).
• Pregnancy test (if applicable)
• History of last cycle including medication compliance
• Adverse Events
• CT (preferred) or MRI (detailed information see 8.8.)
• Questionnaires
  o EORTC QLQ-C30 (including BR 23 module)
• 35ml blood samples for scientific research program

8.9 Response Assessments

8.9.1 Clinical response assessment
Assessment of response will be performed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [23]. It should include clinical examination, CT or MRI scan of the head (if clinically indicated), chest, abdomen and pelvis.

Response will be assessed every 9 weeks throughout therapy, always in comparison with screening status and last staging. Response assessments of Complete Response (CR) or Partial Response (PR) have to be confirmed by a confirmatory scan no less than 4 weeks following the initial assessment. During Follow-Up response assessments should be conducted every 6 months or according to local practice.

8.9.2 Response Assessments During Therapy
CT or MRI are to be performed at any time point if progression is suspected.

8.9.3 Assessments at Screening
CT (preferred) or MRI of chest, abdomen, pelvis and of head (if clinically indicated)

8.9.4 Assessments every 9 weeks
CT (preferred) or MRI of chest, abdomen, pelvis and of head (if clinically indicated)

8.9.5 Assessments at Final Visit / Premature Withdrawal:
CT (preferred) or MRI of chest, abdomen, pelvis and of head (if clinically indicated)

Final assessments should be completed at the last study visit or at premature withdrawal and should use the same imaging modalities as the previous assessments.

8.9.6 Study Continuation According to Response
Patients with CR, PR or SD are eligible to continue study treatment. Patients with PD will discontinue study treatment.

8.10 Flow chart of assessments and procedures
See next page
<table>
<thead>
<tr>
<th>Assessments</th>
<th>Baseline</th>
<th>Assessment therapy start (day 1 of the first cycle)</th>
<th>Assessments therapy (every 3 weeks)</th>
<th>Additional assessments (every 9 weeks)</th>
<th>End of study treatment</th>
<th>Follow Up (every 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic ICF</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor anamnesis (HER2 st.)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT (is preferred) or MRI</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ECOG performance status</td>
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<td>x</td>
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<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Vital signs¹</td>
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<td></td>
<td></td>
<td>x</td>
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<td>x</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples for scientific research program</td>
<td>x</td>
<td>x (if not already drawn at screening)</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>• 2x8 ml whole blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires (EORTC QLQ-30; BR 23)</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test²</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of last cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

¹ Vital signs (blood pressure, HR, weight)
² Complete blood cell count (hemoglobin, platelets, leucocytes, lymphocytes, monocytes and neutrophils)
³ Laboratory parameters (ASAT, ALAT, GGT, AP, Albumin, total bilirubin, creatinine, creatinine-clearance, Na, Ca, K, Ca15-3, CEA).
⁴ Pregnancy Test every 4 weeks
9  STATISTICAL ANALYSIS

A single-arm two-stage Green-Dahlberg design with a total of 40 patients, testing a null proportion of 0.2 versus an alternative proportion of 0.4 with $\alpha = 0.05$ and $1 - \beta = 0.85$ is used to allow for early termination if unsatisfactory efficacy results were observed. In the first stage of the study 20 subjects will be accrued and treated. The study will be stopped if there are fewer than four subjects with an overall response of CR or PR. If there are at least four responses an additional 20 subjects will be enrolled and treated till a maximum of 40 subjects. The regimen is concluded to be effective if 13 or more responses out of 40 are observed at the end of the trial.

All safety analyses will be based on the safety population, defined as subjects who received at least one dose of the study medication and have at least one post-treatment safety assessment available. The safety population will be used for all safety and tolerability analyses including demographic data, vital signs, laboratory data and adverse events.

9.1  Outcome variables

9.1.1  Primary endpoint

- Overall Response Rates (ORR)

Primary outcome variable
Overall tumor response rates (complete response (CR) or partial response (PR), determined by radiologic evaluation according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [23]

9.1.2  Secondary endpoints

- Progression free survival (PFS)
- Clinical benefit (CR, PR or stable disease for at least 24 weeks)
- Safety profile of a combination with capecitabine and bendamustine
- Quality of Life
- Predefined subgroup analysis of triple-negative patients vs hormone receptor positive patients in terms of overall response rates and clinical benefit rate

Secondary outcome variables

- Safety: qualitative and quantitative toxicities
- Overall survival
- Progression free survival
- Change in quality of life (measured with the global scale of the EORTC QLQ-C30, BR 23) from the time of screening up to the time of study end.
9.1.3 Definition

- **Overall survival**
  The overall survival time for each patient is the number of days from treatment start to the earlier of (1) death (from any cause) and (2) the last date of patient contact. If the survival time does not correspond to the patient’s death then it is treated as censored.

  Overall survival will be analyzed according to the Kaplan-Meier method. The median times (with a 95% confidence interval) will be reported.

- **Progression free survival:**
  The progression free survival time is the number of days from treatment start until the first observation of evidence of (1) progression or (2) death from any cause and (3) the last date of patient contact. If the progression free survival time does not correspond to progression or patient’s death then it is treated as censored.

  Progression free survival will be analyzed according to the Kaplan-Meier method. The median times (with a 95% confidence interval) will be reported.

- **Clinical benefit:** CR, PR or stable disease for at least 24 weeks.
  The proportion of patients with CR, with PR, with SD for at least 24 weeks and with CR+PR combined will be provided together with a 95% confidence interval.

- **Change in quality of life** (measured with scales of the EORTC QLQ-C30, BR 23) from the time of screening up to the time of study end.
  To detect differences in quality of life between the test intervals (time of screening to time of study end) parametric paired Student’s t-tests or nonparametric Wilcoxon signed ranks tests will be used, depending on the data distribution. Statistical significance is defined as p<0.05.

9.1.4 Classification of Response

All patients will have their BEST RESPONSE on study classified as outlined below:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- **Partial Response (PR):** at least a 30% decrease in the sum of all target lesions, taking as reference the baseline sum of lesion diameter (LD).

- **Stable Disease (SD):** steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

- **Progressive Disease (PD):** at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started.
Appearance of new lesions will also constitute progressive disease. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

### 10 SCIENTIFIC RESEARCH PROGRAM

Translational biomarker studies of circulating nucleic acids (deoxyribonucleic acid - DNA and ribonucleic acid - RNA) are planned. For that, blood samples will be collected before treatment start, on day 8, at every response assessment time point and at study end. Participation at this translational project is optional.

Blood sample collection, processing, storage and shipment is described in a separate laboratory manual.

Additionally formalin-fixed, paraffin embedded (FFPE) tumor samples (from primum and metastases, if available) will be collected.

### 11 STUDY DRUGS

All drug supplies must be kept in an appropriate locked room which can be accessed only by the pharmacist, the investigator or a duly designated person. Bendamustine will be provided as labeled study drug. Capecitabine will be prescribed.

#### 11.1 Bendamustine dosage

Bendamustine has been investigated in different dosages and schedules: in monotherapy regimes bendamustine 120mg/m² [15] or 150mg/m² [15], was given on day 1 and 2 of a three or four week cycle. In another phase II trial bendamustine mono was evaluated in a weekly schedule with 60mg/m² on day 1, 8 and 15, followed by a week of rest, showing the same efficacy but less toxicity [17]. In combination therapies bendamustine has been used with methotrexate / 5-FU (BMF vs CMF) [14], anthracyclins [18, 19], vincristine [18] or in a previously published trial with paclitaxel [20]. In that trial by the German Breast Group – called RiTa trial – bendamustine 70mg/m² was given in combination with paclitaxel 90mg/m², both administrated on day 1, 8 and 15 of a four week cycle, showing a remarkable efficacy. In accordance with that dose intensity we will administer bendamustine 80mg/m² on day 1 and 8 of a three week cycle.
11.2 Capecitabine dosage

Capecitabine is taken orally twice daily on day 1 to 14 of a three week cycle. The recommended start dosages are 1250mg/m2 BID as a single agent and 1000mg/m2 BID in combination with docetaxel. Capecitabine has also been investigated in combination with vinorelbine in a dosage of 1000mg/m2 BID showing a moderate toxicity profile.

It has been demonstrated that capecitabine dosage can be reduced, either in monotherapy or in combination, to minimize adverse events without compromising efficacy in terms of TTP or OS. Results of retrospective analyses therefore support a starting dose of capecitabine 1000mg/m2 BID. [21]

In our trial capecitabine 1000mg/m2 will be administered for two weeks of a three week cycle.

11.3 Packaging and Labeling

Bendamustine:
Labeling of bendamustine will be in accordance with all local legal requirements and conducted according to Good Manufacturing Practice.

12 SAFETY

12.1 Definition of AEs and SAEs

12.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing conditions should be considered AEs if there is either an increase in severity, frequency or duration of the condition or an association with significantly worse outcomes.
Interventions for pre-existing conditions (e.g. elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered AEs.

Laboratory test value abnormalities should not be recorded in the AE section of the CRF as AEs unless they are considered clinically significant as defined below. Any treatment-emergent abnormal laboratory result that is clinically significant should be recorded as a single diagnosis in the AE section of the CRF. Clinical significance is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Any laboratory abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the CRF.

### 12.1.2 Serious Adverse Event (SAE):

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- resulted in death (was fatal, **NOTE**: death is an outcome, not an event)
- was life-threatening
  
  **NOTE**: The term “life-threatening” refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death if it had been more severe.

- required in-subject hospitalization (at least one night stay) or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, i.e. events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one or other of the outcomes listed above

Events without underlying AE (e.g. hospitalisation due to elective cosmetic surgery, for social reasons or rehabilitation stay) are not considered SAEs. The full requirements of the International Conference on Harmonisation (ICH) Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to.
12.1.3 Events not to be treated as SAEs

Progression of disease (including death due to the underlying malignant disease) is not to be regarded as SAE. Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report Form, i.e.:

- Elective hospitalization and surgery for treatment of disease
- Elective hospitalization to simplify treatment or study procedures

12.2 AE and SAE documentation

All AEs must be documented in the appropriate section of the CRF. Each AE will be evaluated by the investigator for:

- Seriousness
- Severity
- Causal relationship

The Severity will be assessed by the investigator according to the definitions in NCI-CTCAE Version 4.0. AEs not listed in the NCI CTCAE Version 4.0 should be graded according to the following five-point scale:

- Grade 1 Mild (Discomfort noticed but no disruption of normal daily activity)
- Grade 2 Moderate (Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the subject)
- Grade 3 Severe (Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.)
- Grade 4 Life-threatening/disabling (An immediate threat to life or leading to a permanent mental or physical condition that prevents work or the performing normal daily activities; treatment or medical intervention is required in order to maintain survival.)
- Grade 5 Death (AE resulting in death)

The Causal Relationship of any of the study drugs to the AE will be assessed by the Investigator as either YES (related) or NO (unrelated). If there is a reasonable suspected causal relationship to the study medication(s), i.e. there are facts (evidence) or arguments to suggest a causal relationship, the drug-event relationship should be assessed as YES. The criteria for evaluating drug-event relationship must include consideration of potential interactions among treatments in a combination therapy regimen.
The following criteria should be considered in order to assess the relationship as YES:

- Reasonable temporal association with drug administration.
- It may or may not have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- Known response pattern to suspected drug.
- Disappears or decreases on cessation or reduction in dose.
- Reappears on re-challenge.

The following criteria should be considered in order to assess the relationship as NO:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

The reference document for the assessment of the expectedness is the SmPC.

12.3 SAE reporting

Any clinical AE or abnormal laboratory test value that is serious and which occurs during the course of the study (initial and follow up reports) must be reported to AGMT within 24 hours after becoming aware of the event by the Investigator.

Follow-up information on SAEs must also be reported by the Investigator within the same time frame. SAEs will be reported using standard forms provided by AGMT and must be documented in the (Serious) Adverse Event section of the CRF. SAEs must be reported by fax to the number specified on the appropriate form.

In the event of a drug overdose occurring in the course of the present study, this must be reported as a SAE.

12.4 Reporting pregnancies

The Investigator should report all pregnancies (initial and follow up report; female subjects and partner of male subjects) within 24 hours after becoming aware to AGMT using the forms provided by AGMT.

A female subject must be instructed to stop taking the study medications and immediately inform the Investigator if she becomes pregnant during the study. The Investigator should counsel the female subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of
the pregnancy (final follow report). Pregnancies occurring up to 6 months after the last dose of study medications must also be reported to the Investigator.

12.5 Follow up of (S)AEs

All patients having received at least one dose of the study medication must be followed for adverse events for at least 28 days after discontinuing study treatment or completion of study treatment. All (serious) adverse events occurring during study treatment will be collected until 28 days after the end of study treatment.

Follow-up information on the outcome must be recorded on the respective AE page in the CRF. The outcome “unknown” is not acceptable, except if attempts to collect the information have been made and documented. All other information has to be documented in the source documents.

If any SAE persists at study end, the course of the event has to be followed up by the investigator until its resolution or until the SAE is recognized as permanent condition.

Any AE leading to premature withdrawal of the subject from the study has to be followed up. It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

12.6 Reporting to regulatory Authorities and the ethics committees

The sponsor will inform relevant Regulatory Authorities and the Ethics Committee and all participating investigators:

- of all relevant information about serious unexpected adverse events suspected to be related to the study medication that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.
- of all other serious unexpected events suspected to be related to the study medication as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

13 CONCOMITANT MEDICATION

While participating in this study patients should not receive any other anti-cancer therapies (chemotherapy, immunotherapy, antihormonal or biologic therapy) other than study treatment mandated by the protocol.
Only relevant concomitant medication(s) will be reported in the case report form:
- Supportive concomitant medication
- Medication given for AE grade 3/4 or SAE
- Other relevant concomitant medication at the discretion of the physician

14 DOSE MODIFICATIONS FOR TOXICITY

14.1 General Considerations

The dose modifications in this section are recommended but can be modified for the benefit of the patient at the discretion of the physician.

If day 1 with either bendamustine or capecitabine is delayed due to toxicity, administration of the other is also delayed, so both drugs will be started on the same day of each cycle.

14.2 Capecitabine

14.2.1 Non-Hematologic Toxicities

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced. The following are the recommended dose modifications for toxicities:

Table 2: Capecitabine Dose Reduction Schedule

<table>
<thead>
<tr>
<th>Toxicity grades</th>
<th>Dose changes within a treatment cycle</th>
<th>Dose adjustment for next cycle/dose (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
</tr>
<tr>
<td></td>
<td>2nd appearance</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td></td>
<td>3rd appearance</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>4th appearance</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1st appearance</td>
<td>Discontinue treatment permanently</td>
</tr>
<tr>
<td></td>
<td>2nd appearance</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>3rd appearance</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>3rd appearance</td>
<td>Discontinue treatment permanently</td>
</tr>
<tr>
<td></td>
<td>3rd appearance</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
### 14.3 Bendamustine

#### 14.3.1 Hematologic Toxicities

In case of therapy-induced myelosuppression, leukocytes, platelets, hemoglobin, and neutrophils will be monitored at least weekly.

**Dose adjustments for cycle start (day 1):**

<table>
<thead>
<tr>
<th>WBC (x 10⁹/L) on scheduled day 1</th>
<th>ANC (x 10⁹/L) on scheduled day 1</th>
<th>PLT (x 10⁹/L) on scheduled day 1</th>
<th>% Bendamustine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3.0</td>
<td>≥ 1.5</td>
<td>and</td>
<td>≥ 100</td>
</tr>
<tr>
<td>&lt; 3.0</td>
<td>&lt; 1.5</td>
<td>and/or</td>
<td>&lt; 100</td>
</tr>
</tbody>
</table>

*If day 1 has to be delayed for more than one week due to myelosuppression, bendamustine must be restarted at a reduced dose level (see Dose Reduction Scheme for bendamustine).

**Dose adjustments on day 8**

<table>
<thead>
<tr>
<th>ANC (x 10⁹/L) on scheduled day 8</th>
<th>PLT (x 10⁹/L) on scheduled day 8</th>
<th>% Bendamustine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>and</td>
<td>&gt; 75</td>
</tr>
<tr>
<td>1.0 – 1.4</td>
<td>and/or</td>
<td>50 - 74</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>and/or</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>

*If the treatment is delayed for more than one week, bendamustine will be omitted for this cycle.

#### 14.3.2 Non-Hematologic Toxicities

In case of grade 3 or 4 non-hematologic toxicities deemed dose-limiting, the dose may be reduced to the next lower dose level as follows: Dose reduction will be based on the worst CTC grades in the preceding cycle.

If a patient requires a dose modification the individually calculated reduced dose must also be given on day 1 and 8 of the respective treatment cycle.

In case of therapy-induced CTC grade 2 non-hematologic toxicities (except nausea, vomiting, and alopecia), these will be monitored at least weekly, and treatment will not be resumed until symptoms have returned (decreased) to baseline intensity or are < CTC grade 2.
If the next cycle is delayed by more than 1 week patients should be re-started at the next lower dose level, i.e. Dose level -1. If cycles at Dose level -1 lead to a further delay of more than 1 week for the next cycle patients should be re-started at the next lower dose level, i.e. Dose level -2.

### 14.3.3 Dose Reduction Scheme for Bendamustine

**Table 3: Bendamustine Dose Reduction Grid for Non-Hematologic Toxicities**

<table>
<thead>
<tr>
<th>Study Drug Dose to be Administered</th>
<th>Bendamustine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Dose</strong></td>
<td></td>
</tr>
<tr>
<td>Dose level 0</td>
<td>80 mg/m²</td>
</tr>
<tr>
<td>Dose Level -1</td>
<td>65 mg/m²</td>
</tr>
<tr>
<td>Dose Level -2</td>
<td>50 mg/m²</td>
</tr>
</tbody>
</table>

*No further dose reduction*

### 14.4 Pregnancy

Non-childbearing potential includes being surgically sterilized, after hysterectomy or postmenopausal with no menstrual bleeding for at least one year prior study entry. All patients must practice medically accepted contraception throughout the study.

### 15 ADMINISTRATIVE CONSIDERATIONS

#### 15.1 Local regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” and with the applicable local laws and regulations.

#### 15.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The Case Report...
Forms for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

15.3 Independent ethics committees

This protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, will be submitted to an Independent Ethics Committee. Approval from the committee must be obtained before starting the study. Any modifications made to the protocol after receipt of the Independent Ethics Committee approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

15.4 Insurance

All patients and investigators will be covered by an insurance contract existing between the sponsor AGMT gemeinnützige GmbH and HDI Versicherung, according to Austrian regulations.

15.5 Conditions for terminating the study

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, sponsor and investigator will assure that adequate consideration is given to the protection of the patient’s interests.

15.6 Audits and inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from health authority inspectors after appropriate notification. The verification of the Case Report Form data must be by direct inspection of source documents.
15.7 Case report forms

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

15.8 Confidentiality of trial documents and patient records

The investigator must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, patients should not be identified by their names. The investigator should keep a patient enrollment log showing codes and names. The investigator should maintain documents not for submission to sponsor, e.g., patients’ written consent forms, in strict confidence.
16 References

1. Austria Statistics, *Jahrbuch der Gesundheitsstatistik 2010* [German]


17 Appendix 1

ECOG Performance Status

<table>
<thead>
<tr>
<th>Description</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal activity</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic but ambulatory self-care</td>
<td>1</td>
</tr>
<tr>
<td>Ambulatory more than 50% of the time</td>
<td>2</td>
</tr>
<tr>
<td>Ambulatory 50% or less of the time, nursing care needed</td>
<td>3</td>
</tr>
<tr>
<td>Bedridden, may need hospitalization</td>
<td>4</td>
</tr>
</tbody>
</table>

18 Appendix 2

Calculation of creatinine clearance

Cockroft-Gault Formula for females: [22]

Creatinine clearance (mL/min) =

\[
\frac{[(140 – \text{age}) \times \text{weight (in kg)} \times 0.85]}{[72 \times \text{serum creatinine (in mg/dl)}]} \text{ or} \frac{[(140 - \text{age}) \times \text{weight (in kg)} \times 0.85]}{[0.81 \times \text{serum creatinine (in μmol/l)}]}
\]

Cockroft-Gault Formula for males: [22]

Creatinine clearance (mL/min) =

\[
\frac{[(140 – \text{age}) \times \text{weight (in kg)}]}{[72 \times \text{serum creatinine (in mg/dl)}]} \text{ or} \frac{[(140 - \text{age}) \times \text{weight (in kg)}]}{[0.81 \times \text{serum creatinine (in μmol/l)}]}
\]
A. INTRODUCTION
1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement...
should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH
11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   • The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.