**Capecitabine in combination with bendamustine in pretreated women with HER2-negative metastatic breast cancer: results of a phase II trial (AGMT MBC-6)**

Supplementary information

Table S1: Inclusion and Exclusion criteria

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| **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 neoadjuvant or adjuvant)
* Life expectancy of at least 12 weeks
* Performance status 0-2
* Adequate hematology, liver and renal function:
	+ **Hematologic:**
		- ANC (absolute neutrophil count) ≥ 1.5 x 109/L
		- Hemoglobin ≥ 9 g/dL
		- Platelets ≥ 100 x 109/L
	+ **Liver Function:**
		- Albumin ≥ 2.5 g/dL
		- Serum bilirubin ≤ 2 mg/dL
		- AST and ALT ≤ 3 x ULN without liver metastases≤ 5 x ULN if documented liver metastases
	+ **Renal Function:**
		- Serum Creatinine ≤ 1.5 mg/dL OR Calculated Creatinine Clearance ≥ 40 mL/min
 |
| **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
* 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 derivates e.g. brivudin (Mevir©) within the last 4 weeks before and during study treatment with capecitabine
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Table S2: Drug exposure, Number of Cycles, and Dose intensity

|  |  |
| --- | --- |
| **Patient exposure** | **N=40** |
| Median number of treatment cycles (range) | 8 (1-57) |
| Number of patients with dose reduction, n (%) | 20 (50%) |
| **Bendamustine/capecitabine combination therapy** | **N=40** |
| Median number of cycles (range) | 8 (1-10\*) |
| Median bendamustine dose intensity (IQR) | 98% (78%-100%) |
| Median capecitabine dose intensity (IQR) | 97% (81%-100%) |
| Number of patients with bendamustine dose reduction, n (%) | 20 (50%) |
| Number of patients with capecitabine dose reduction, n (%) | 18 (45%) |
| **Capecitabine mono therapy** | **n=18** |
| Median number of cycles (range) | 7 (1-49) |
| Median capecitabine dose intensity (IQR) | 92% (71%-97%) |
| Number of patients with capecitabine dose reduction, n (%) | 7 (39%) |

\* Protocol deviation in one patient: 10 bendamustine cycles were administered by mistake.

Table S3: Adverse events starting during bendamustine plus capecitabine combination treatment

|  |  |  |
| --- | --- | --- |
| **N=40** |  | **Number of patients with maximal grading** |
| **Non haematological adverse events** | **All grades** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Fatigue | 29 (73%) | 13 (33%) | 4 (10%) | - | - |
| Nausea | 19 (48%) | 9 (23%) | < 5% | - | - |
| Hand-Foot syndrome\* | 16 (40%) | 4 (10%) | < 5% | - | - |
| Diarrhoea\* | 12 (30%) | 6 (15%) | < 5% | - | - |
| Musculoskeletal pain\* | 10 (25%) | < 10% | < 5% | - | - |
| Abdominal pain\* | 8 (20%) | 5 (13%) | - | - | - |
| Dyspnoea\* | 7 (18%) | 3 (8%) | < 5% | - | - |
| Headache\* | 7 (18%) | 4 (10%) | - | - | - |
| Constipation | 6 (15%) | 5 (13%) | - | - | - |
| Pulmonary embolism\* | 4 (10%) | < 10% | 3 (8%) | - | - |
| Vomiting | 5 (13%) | < 10% | 2 (5%) | - | - |
| Upper respiratory tract infection\* | 3 (8%) | < 10% | 2 (5%) | - | - |
| Device related infection | 2 (5%) | - | 2 (5%) | - | - |
| Cardiomyopathy | 1 (3%) | - | - | - | 1 (3%) |
| Hepatic failure | 1 (3%) | - | - | 1 (3%) | - |
| **Haematological adverse events** | **All grades** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Leukopenia | 16 (40%) | 9 (23%) | 4 (10%) | 1 (3%) | - |
| Neutropenia | 16 (40%) | 6 (15%) | 8 (20%) | 1 (3%) | - |
| Anaemia | 10 (25%) | 4 (10%) | - | - | - |
| Lymphocyte count decreased | 2 (5%) | - | 2 (5%) | - | - |

Adverse events starting during bendamustin/capecitabine combination treatment ≥ grade 2 and number of patients with maximum grading per event are listed. “All grades” includes patients with maximum grade 1. Adverse events grade 2 with occurrence in ≥10% of patients, grade 3 in ≥5% of patients and all grade 4/5 adverse events are shown. \*Adverse event terms are summarized MedDRA preferred terms.

Table S4: Adverse events starting during capecitabine mono treatment

|  |  |  |
| --- | --- | --- |
| **N=18** |  | **Number of patients with maximal grading** |
| **Non haematological adverse events** | **All grades** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Palmar-plantar erythrodysaesthesia syndrome\* | 13 (72%) | 4 (22%) | 5 (28%) |  |  |
| Musculoskeletal pain\* | 6 (33%) | 2 (11%) |  |  |  |
| Diarrhoea\* | 5 (28%) | < 10% | 2 (11%) |  |  |
| Dyspnoea\* | 4 (22%) |  | 2(11%) |  |  |
| Lymphoedema | 3 (17%) | 2 (11%) |  |  |  |
| Polyneuropathy | 3 (17%) |  | 1 (6%) |  |  |
| Dyspepsia | 2 (11%) | 2 (11%) |  |  |  |
| Gastroenteritis | 2 (11%) | < 10% | 1 (6%) |  |  |
| Angina pectoris  | 1 (6%) |  | 1 (6%) |  |  |
| Ascites | 1 (6%) |  | 1 (6%) |  |  |
| Atrial fibrillation | 1 (6%) |  | 1 (6%) |  |  |
| Herpes zoster | 1 (6%) |  | 1 (6%) |  |  |
| Skin fissures | 1 (6%) |  | 1 (6%) |  |  |
| Toothache | 1 (6%) |  | 1 (6%) |  |  |
| Tooth infection | 1 (6%) |  | 1 (6%) |  |  |
| Hand-foot syndrome\* | 13 (72%) | 4 (22%) | 5 (28%) |  |  |
| **Haematological adverse events** | **All grades** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Leukopenia | 3 (17%) | < 10% |  | 1 (6%) |  |
| Neutropenia | 3 (17%) | 2 (11%) |  |  |  |

Adverse events starting during capecitabine mono treatment ≥ grade 2 and number of patients with maximum grading per event are listed. “All grades” includes patients with maximum grade 1. Adverse events grade 2 with occurrence in ≥10% of patients, grade 3 in ≥5% of patients and all grade 4/5 adverse events are shown. \*Adverse event terms are summarized MedDRA preferred terms.

Figure S1: Progression-free survival in TNBC (A) and HR-positive subgroup according to the thymidylate phosphatase expression



HR: hazard ratio, TNBC: triple negative breast cancer, TP: Thymidylate phosphatase.

Figure S2: Overall survival (A) in the overall population, (B) by receptor status and (C) by thymidylate phosphatase expression



HR: hazard ratio, TNBC: triple negative breast cancer, HR hormone-receptor, TP: Thymidylate phosphatase; OS: Until end of follow up 26 patients died, 14 were censored

**Figure S3: Time to deterioration of Global Health status by clinical benefit**

