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

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Abstract

Background: Bendamustine, a medication approved for the treatment of indolent non-Hodgkin lymphoma, has already shown anticancer activity in metastatic breast cancer (MBC). Here, we present the results of a phase II trial of bendamustine in combination with capecitabine in pre-treated patients with MBC.

Patients and methods: AGMT MBC-6 is a multicentre, open-label, single-arm phase II study in HER2-negative MBC. All patients were pre-treated with anthracyclines and/or taxans and had measurable disease. Patients received per os 1000 mg/m^2 capecitabine twice daily on days 1 to 14 in combination with 80 mg/m^2 bendamustine intravenously on days 1 and 8 of a 3-week cycle for a maximum of eight cycles, followed by a capecitabine maintenance therapy. The primary endpoint was overall response rate (ORR).

Results: From September 2013 to May 2015, 40 patients were recruited in eight Austrian centres. The median age was 60 years (range 29–77). Twenty-five per cent of patients had triple-negative breast cancer (TNBC) and 93% showed visceral involvement. With 17 partial and one complete remission, ORR was 46%. Median progression-free survival (PFS) was 7.5 months [95% confidence interval (CI) 6.1–10.7]. The most common non-haematological adverse events (AEs) of grade 3 were hand-foot syndrome (13%), fatigue (10%), nausea (8%), and dyspnoea (8%). One grade 4 non-haematological AE (hepatic failure) and three grade 4 haematological AEs (neutropenia) were observed. One patient died of restrictive cardiomyopathy, in which a relationship to capecitabine cannot be excluded, but seems unlikely.

Conclusion: The combination of capecitabine and bendamustine shows promising efficacy and moderate toxicity. Further evaluation of this drug combination is warranted.

The clinical trial AGMT MBC-6 was registered at ClinicalTrials.gov, (https://clinicaltrials.gov/; identifier: NCT01891227).

Keywords: advanced breast cancer, chemotherapy, combination therapy

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Introduction

By the introduction of novel endocrine agents and targeted drugs, substantial progress has been made especially in hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC). Recently, the approval of immunotherapy for triple-negative MBC has aroused considerable attention.[1] However,

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chemotherapy remains a mainstay of MBC treatment, as several new agents are combined with chemotherapy and resistance might either exist primarily or develop during therapy.

Anthracycline or taxane-based chemotherapy regimens are the preferred agents in the first-line chemotherapy setting in HER2-negative MBC patients.[2] In second line, or in case of early relapse after adjuvant anthracycline and/or taxane pretreatment, capecitabine is well established.[2] Bendamustine is also a well-tolerated agent that has already shown anticancer activity in breast cancer.[3]

Bendamustine is a hybrid cytotoxic drug because of its structural similarity to alkylating agents and purine analogues. Like other alkylating agents, bendamustine causes DNA breaks by DNA cross-linking. It is currently approved by the US Food and Drug Administration (FDA) as well as the European Medicine Agency (EMA) for the treatment of chronic lymphocytic leukaemia (CLL) and indolent B-cell non-Hodgkin's lymphoma (NHL). The evidence of bendamustine in the treatment of MBC has previously been reviewed by Pirvulescu *et al.*[3] published in *Breast Care* in 2008. As monotherapy for pre-treated patients (one pilot trial[4] and three phase II trials),[5–7] bendamustine revealed an overall response rate (ORR) ranging from 20% up to 48%, accompanied by a moderate toxicity profile. In a first-line phase III trial in MBC, a combination of bendamustine, methotrexate and 5-fluorouracil (5-FU) (BMF) was compared to cyclophosphamide, methotrexate and 5-FU (CMF).[8] ORRs of 44% (BMF) and 40% (CMF) were similar in both groups, but myelotoxicities were more frequent in the BMF group (leukopenia 62.7 *versus* 40%). A significantly longer time to progression (TTP), 8.2 *versus* 6.7 months, was seen in the BMF group.

The fluoropyrimidine 5-FU has been used for over 40 years as monotherapy or in combination with other cytostatic drugs in breast cancer treatment. The optimal administration mode of 5-FU for the treatment of MBC has not been defined yet. As reviewed by Cameron *et al.*,[9] continuous 5-FU in combination with leucovorin seems to be more effective than 5-FU bolus administration, but prospective data on that topic are missing. Based on promising efficacy rates of continuous 5-FU in numerous tumour entities but with the inconvenience of intravenous access devices, several oral formulations of 5-FU have been developed.[10] Capecitabine is an orally administered prodrug of 5-FU with confirmed efficacy as monotherapy in MBC in three phase III trials.[11–13] In contrast to colorectal cancer in which capecitabine has been shown to be as effective as continuous 5-FU, a head-to-head comparison in MBC is missing. One of the enzymes involved in the conversion of capecitabine to 5-FU is thymidine phosphorylase (TP), which plays an important role in pyrimidine metabolism.[14,15] TP expression has been linked to capecitabine sensitivity.[16]

Based on these findings, we investigated the combination of bendamustine plus capecitabin in pretreated MBC patients within the MBC-6 trial of the Austrian Group Medical Tumour Therapy (AGMT).

Patients and methods

Study design and participants

The AGMT MBC-6 trial is a non-randomised, multicentre, open-label, single-arm phase II study in pre-treated patients with HER2-negative advanced breast cancer. Eight centres in Austria recruited 40 patients following a two-stage design. Efficacy and safety of bendamustine and capecitabine was evaluated after recruitment of the first 20 patients. On favourable results, a further 20 patients were recruited to reach the target population of 40 evaluable patients.

HER2 negativity was defined as immunohistochemically (IHC) 0–1, or IHC 2+ and HER2 gene amplification measured by *in-situ* hybridisation (ISH) ratio of <2.0 between HER2 gene copy number and centromere of chromosome 17 or a copy number of 4 or less. Hormone receptor positivity was defined as positive staining for estrogen receptor (IHC $\geqslant 1\%$) and/or progesterone receptor (IHC $\geqslant 1\%$). Receptor status assessment was performed by local pathology, without central confirmation. If available, assessment had to performed from biopsies of metastatic sites, otherwise tissue from primary tumour was analysed.

Patient selection

Patients with metastatic histologically confirmed HER2-negative adenocarcinoma of the breast with documented disease progression after an anthracycline and/or taxane treatment (neoadjuvant, adjuvant or palliative) with at least one measurable lesion according to response

evaluation criteria in solid tumours (RECIST) version 1.1 were eligible for participation (for detailed inclusion and exclusion criteria see Supplemental Table 1).

Dosage selection

Bendamustine has been investigated in different dosages and schedules: in monotherapy regimes bendamustine 120 mg/m^2 or 150 mg/m^2 was given on days 1 and 2 of a 3 or 4-week cycle.[7] In another phase II trial, bendamustine monotherapy was evaluated in a weekly schedule with 60 mg/m^2 on days 1, 8 and 15, followed by a week of rest, showing the same efficacy but less toxicity.[4] Furthermore, bendamustine was investigated in combination with methotrexate plus 5-FU (BMF *versus* CMF), anthracyclines,[17,18] vincristine,[17] or paclitaxel.[19] In the latter trial, bendamustine 70 mg/m^2 was given in combination with paclitaxel 90 mg/m^2, both administrated on days 1, 8 and 15 of a 4-week cycle, showing a remarkable efficacy. In accordance with that dose intensity, we selected bendamustine 80 mg/m^2 on days 1 and 8 of a 3-week cycle to be investigated in the MBC-6 trial.

Capecitabine is taken orally twice daily (BID) on days 1 to 14 of a 3-week cycle. The recommended start dosages are 1250 mg/m^2 BID as a single agent.[11–13] In pretreated MBC patients capecitabine has been investigated with dosages between 825 mg/m^2 BID and 1250 mg/m^2 BID in combination with other cytotoxic drugs.[20] It has been demonstrated that the capecitabine dosage can be reduced, either in mono or in combination therapy, to minimise adverse events without compromising efficacy in terms of TTP or overall survival (OS). Results of retrospective analyses support a starting dose of capecitabine 1000 mg/m^2 BID.[21] Therefore, in our trial capecitabine 1000 mg/m^2 was be administered for 2 weeks of a 3-week cycle.

Study treatment

Patients received per os 1000 mg/m^2 capecitabine BID on days 1 to 14 in combination with 80 mg/m^2 bendamustine intravenously on days 1 and 8 of a 3-week cycle. Capecitabine in combination with bendamustine was administered for a maximum of eight cycles. Afterwards, capecitabine maintenance therapy was continued until disease progression or unacceptable toxic effects.

Endpoints

The primary endpoint of the trial was to determine the efficacy of a capecitabine plus bendamustine combination regimen represented by the ORR [complete response (CR) or partial response (PR)]. ORR was determined by radiological evaluation according to RECIST version 1.1.[22] Secondary endpoints included progression-free survival (PFS); time from start of therapy until progression or death from any cause, including follow-up data), clinical benefit rate [CBR; CR, PR or stable disease (SD) for at least 24 weeks], safety, and quality of life (QoL). Adverse events (AEs) were reported according to the common terminology criteria for adverse events (CTCAE) version 4.03.[23] After discontinuation from study treatment, AE assessment was stopped for the corresponding patient. QoL was assessed using the validated European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-BR23 questionnaires.[24,25] Subgroup analyses of patients with triple-negative and HR-positive tumours were pre-planned.

Response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every 9 weeks throughout therapy. A CR or PR had to be certified by a confirmatory scan no less than 4 weeks following the initial assessment. A central review of CT or MRI scans was established for participating sites which could not provide assessments according to RECIST 1.1. Treatment decisions were made according to local CT/MRI reports.

Expression levels of thymidine phosphorylase

Immunohistochemical thymidylate phosphatase expression analysis was performed by an experienced breast cancer pathologist (CHK) on archival formalin-fixed paraffin-embedded (FFPE) breast cancer tissue using the monoclonal antibody TP (clone P-GF.44C; Thermo Fisher) at a final dilution of 1/100. The immunohistochemical staining was automatically performed on a Ventana Benchmark Ultra platform. Scoring was performed according to the method previously described by Tsuda *et al.*[26] TP staining intensities of 2+ or 3+ were defined as positive.

Statistical methods

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 $1\text{-}\beta = 0.85$, was used to allow for early termination in case of unsatisfactory efficacy results. In the first stage of the study, 20 subjects were accrued and treated. The study was predefined to be stopped if there were fewer than four subjects with a complete response or a partial response. If there were at least four responses, an additional 20 subjects were planned be enrolled for a maximum of 40 subjects. The regimen was predefined as effective if 13 or more responses in 40 patients (ORR $\geqslant$32.5%) were observed at the end of the trial. All analyses were based on the safety population, defined as subjects who received at least one dose of the study medication and had at least one post-treatment safety assessment available. Statistical analysis included descriptive statistics together with Kaplan–Meier survival estimates. Calculations and graphs were performed with MedCalc 19.1 and SPSS 24.

Data availability

This academic clinical trial was sponsored, designed, and monitored by the AGMT, which had exclusive rights to the data and their handling. Mundipharma supported the trial financially, but had no input into the statistical analysis, data interpretation, or writing of the report. The corresponding authors RG, GR and SG had full access to all the study data.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics

The study was conducted under the principles of the Declaration of Helsinki and International Conference on Harmonisation E6 Good Clinical Practice guidelines. The trial was approved by the ethics committee of the state of Salzburg on 13 May 2013 (protocol number: 415-E/2067/16-2016), by the ethics committee of each participating centre, and by the Austrian regulatory authority. (ClinicalTrials.gov-identifier NCT01891227, EudraCT-number 2012-005593-64.) All patients gave their written informed consent.

Results

From September 2013 to May 2015, 40 patients with pre-treated HER2-negative MBC were enrolled. Twenty-seven patients were treated until disease progression, 13 patients discontinued prematurely for reasons other than disease progression (Figure 1). In March 2018, the last patient discontinued study treatment. No continuous follow-up was planned in the study protocol, but a final assessment of the survival status was performed in February 2020 for the preplanned exploratory overall survival (OS) analysis.

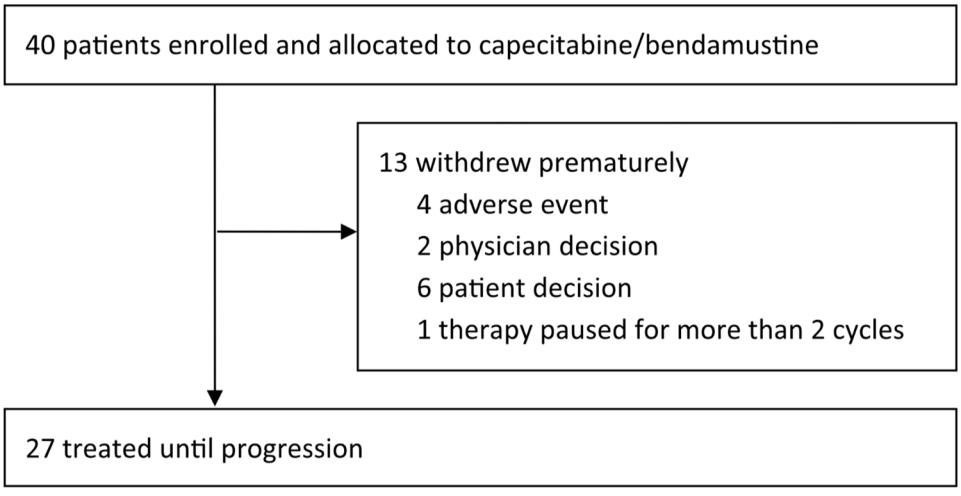

Figure 1. CONSORT diagram.
Response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every 9 weeks throughout therapy. A central review of CT or MRI scans was established for participating sites which could not provide assessments according to response evaluation criteria in solid tumours (RECIST) 1.1. Treatment decisions were made according to local CT/MRI reports.

Baseline characteristics are outlined in Table 1.

The median number of treatment cycles was eight (range 1–57), and eight patients received capecitabine monotherapy after completion of the combination treatment period (Supplemental Table 2).

Adverse events

Eighteen patients (45%) experienced at least one drug-related non-haematological AE grade ⩾3 or a haematological AE grade ⩾4. The most common non-haematological AEs grade ⩾3 were hand-foot syndrome, fatigue, diarrhoea, and dyspnoea. The most common haematological AE grade 4 was leukopenia (Table 2 and Supplemental Tables 3 and 4). Alopecia was uncommon, with only two patients (5%) experiencing grade 1 hair loss.

One patient died as a result of restrictive cardiomyopathy, in which a relationship to capecitabine cannot be fully excluded, but seems unlikely.

Efficacy

With 17 confirmed PR and one confirmed CR, ORR was 45%; 47% (14/30) in HR-positive and 40% (4/10) in TNBC patients, respectively (Table 3). The CBR was 53% (21/40). Median PFS was 7.5 months [95% confidence interval (CI) 6.1–10.7] in the overall population, 8.4 months (95% CI 6.1–12.8) in HR-positive and 4.1 months (95% CI 1.4–8.9) in TNBC patients, respectively (Figure 2). In an unplanned subgroup analysis regarding TP expression, no difference between TP-positive and TP-negative patients was observed [hazard ratio 0.86, 95% CI 0.36 to 2.05; $p = 0.73$; Figure 2(c), Supplemental Figure 1].

The median OS, an exploratory endpoint of this trial, was 19.2 months (95% CI 14.4–34.8; Supplemental Figure 2).

Quality of life

Thirty-two patients where included in the QoL analysis. Three patients were excluded due to missing QLQC30 measurements, and in five patients only a baseline assessment was available.

The median time to 10% deterioration of QLQC30 global health status was 4.6 months (95% CI 0.9–8.1). In patients with a clinical benefit (PR, CR, or SD ⩾24 weeks), the time to 10% deterioration was 8.1 months (95% CI 1.4–14.7), compared to 4.4 months (95% CI 0–9.4) in patients without a clinical benefit (Supplemental Figure 3).

Linear mixed effects modelling was applied to evaluate whether the two variables (baseline *versus* week 9) and (clinical benefit yes/no) had a significant effect on the different QLQ. For physical function, there was a significant decline from baseline to week 9 ($p = 0.027$). For dyspnoea, average values were higher in the clinical benefit group ($p = 0.013$). Interestingly, for diarrhoea, significant improvements were observed in the clinical benefit group ($p = 0.035$ and interaction week*clinical benefit $p = 0.03$). All other comparisons resulted in (non-significant) p-values >0.05.

Table 1. Baseline characteristics.

Characteristic	Patients *n* (%), *N* = 40
Median age	60 years (range 29–77)
Performance score (%)	
ECOG 0	30 (75)
ECOG 1	10 (25)
HR-positive	30 (75)
TNBC	10 (25)
Previous (neo-)adjuvant chemotherapy	26 (65)
Previous (neo-)adjuvant endocrine treatment in patients HR-positive disease; *n* = 30	30 (100)
Pretreatment chemo-therapy lines for MBC (%)	
0	15 (37)
1	17 (43)
2	6 (15)
3	2 (5)
Visceral disease	37 (93)

ECOG, Eastern Cooperative Oncology Group; HR, hormone-receptor; TNBC, triple negative breast cancer.

Discussion

To our knowledge, the AGMT MBC-6 trial is the only clinical trial investigating a capecitabine plus bendamustine combination treatment of breast

Table 2. Adverse events.

N = 40		Number of patients with maximal grading			
Non-haematological AEs	**All grades (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
Fatigue	29 (73)	13 (33)	4 (10)	–	–
Hand-foot syndrome*	23 (58)	6 (15)	5 (13)	–	–
Nausea	19 (48)	9 (23)	<5	–	–
Musculoskeletal pain*	15 (38)	4 (10)	<5	–	–
Diarrhoea*	14 (35)	6 (15)	3 (8)	–	–
Dyspnoea*	10 (25)	3 (8)	3 (8)	–	–
Abdominal pain*	8 (20)	5 (13)	–	–	–
Headache*	7 (18)	5 (13)	–	–	–
Upper respiratory tract infection*	7 (18)	<10	2 (5)	–	–
Constipation	6 (15)	5 (13)	–	–	–
Vomiting	6 (15)	<10	2 (5)	–	–
Pulmonary embolism*	4 (10)	<10	3 (8)	–	–
Device-related infection	2 (5)	–	2 (5)	–	–
Cardiomyopathy	1 (3)	–	–	–	1 (3)
Hepatic failure	1 (3)	–	–	1 (3)	
Haematological AEs	**All grades (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5**
Leukopenia	17 (43)	10 (25)	4 (10)	2 (5)	–
Neutropenia	17 (43)	6 (15)	9 (23)	1 (3)	–
Anaemia	10 (25)	4 (10)	–	–	–
Lymphopenia	2 (5)	–	2 (5)	–	–

Adverse events (AEs) grade ⩾2 and number of patients with maximum grading per event are listed. 'All grades' includes patients with maximum grade 1. AEs grade ⩾2 with occurrence in ⩾10% of patients, grade 3 in ⩾5% of patients and all grade 4/5 AEs are shown.
*AE terms are summarised MedDRA preferred terms.

cancer patients. According to the prespecified threshold, the regimen was found to be effective seeing as 18 responses were observed in the study, exceeding the efficacy criterion of 13 responses or more in 40 patients. With an ORR of 45% and a median PFS of 7.5 months, this investigational treatment combination seems to be more effective than capecitabine monotherapy.

Five multicentre phase II trials evaluated capecitabine monotherapy in patients with advanced or MBC that were pre-treated with taxane and/or anthracycline. The reported ORRs lay between 20% and 36%.[27–31] The median TTP was 3.0–8.1 months.[27–31] In three phase III trials in patients with MBC that were pre-treated with anthracycline and taxane, capecitabine monotherapy showed similar results to the phase II studies with ORRs from 9% to 29%.[11–13] TTP was 4.1 to 4.4 months.

For the treatment of MBC, the role of combination chemotherapy is still controversial. In a Cochrane Database systemic review, sequential treatment was beneficial in terms of PFS.[32] In contrast, response rates, but also the rate of febrile

Table 3. Response rates in MBC patients following capecitabine and bendamustine combination therapy.

Best overall response	Overall, *n* (%), *N* = 40	TNBC, *n* (%), *N* = 10	HR-positive, *n* (%), *N* = 30
Complete response* (CR)	1 (3)	1 (10)	0 (0)
Partial response* (PR)	17 (43)	3 (30)	14 (47)
Stable disease (SD)	11 (28)	2 (20)	9 (30)
<24 Weeks**	8 (20)	2 (20)	6 (20)
⩾24 Weeks	3 (8)	0 (0)	3 (10)
Progressive disease (PD)	8 (20)	3 (30)	5 (17)
Not evaluable (NE)	3 (7.5)	1 (10)	2 (6)
Overall response rate (ORR)	18 (45)	4 (40)	14 (47)
Clinical benefit rate (CBR)	21 (53)	4 (40)	17 (57)

*Responses had to be confirmed after ⩾4 weeks.
**Including one not confirmed PR.

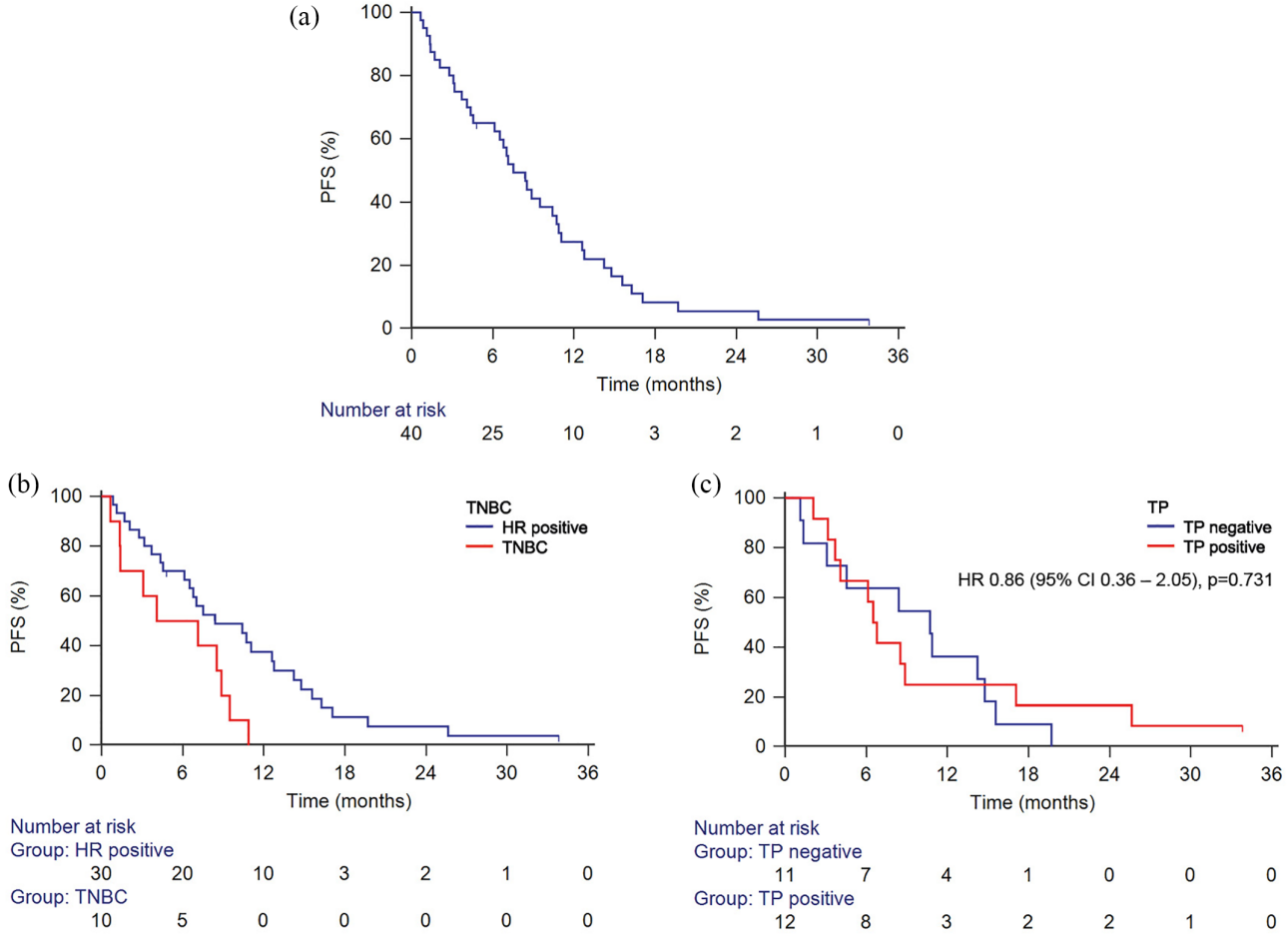

Figure 2. Progression free survival.
Progression free survival (a) in the overall population, (b) by receptor status, (c) and by thymidylate phosphatase expression in patients who received capecitabine and bendamustine combination therapy.
HR, hormone receptor; TNBC, triple negative breast cancer; TP, thymidine phyosphorylase.

neutropenia, were higher with combination regimens. No difference in OS was seen. Therefore, international guidelines recommend sequential treatment as the first option.[2] Combination chemotherapy regimens should be preserved for patients with 'rapid clinical progression, life-threatening visceral metastases, or a need for rapid symptom and/or disease control'.[2] Within the MBC-6 trial, a moderate toxicity profile was observed, with no toxicity-induced worsening of the overall QoL. The median time to 10% deterioration of QLQC30 global health status was longer in patients with a clinical benefit compared to patients who did not benefit from treatment (8.1 *versus* 4.4 months).

A major advantage of this combination regimen is the low incidence of alopecia (grade 1 was observed in two patients =5%). Since chemotherapy-induced alopecia can be psychosocially devasting,[33] this regimen might be preferrable to patients who are frightened by the idea of losing their hair. A further interesting aspect is the fact that both are available as generics, making it a cheap treatment option which could even be applied in low-income countries.

TP expression, a potential biomarker for capecitabine efficacy, had no effect on PFS in our trial. This could imply that the combination of bendamustine plus capecitabine overcomes the intrinsic resistance to the 5-FU pro-drug in case of missing or low expression of TP in the tumour.

In our opinion, further development of the bendamustine–capecitabine combination in a randomised phase III trial, for example in comparison with capecitabine monotherapy, would be justified. The generic availability of both drugs and the resulting lack of financial support from industry, however, make it very difficult for an academic study group to carry out such a large trial.

Conclusion

The combination of capecitabine and bendamustine shows promising efficacy and a moderate toxicity profile. Further evaluation of this drug combination is warranted.

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Authors' contributions

Gabriel Rinnerthaler: Conceptualisation, methodology, writing – original draft, project administration; **Simon Peter Gampenrieder:** Conceptualisation, methodology, writing – original draft; **Andreas Petzer:** Investigation, resources, writing – review and editing; **Michael Hubalek:** Investigation, writing – review and editing; **Edgar Petru:** Investigation, resources, writing – review and editing; **Margit Sandholzer:** Investigation, resources, writing – review and editing; **Johannes Andel:** Investigation, resources, writing –review and editing; **Marija Balic:** Investigation, resources, writing – review and editing; **Thomas Melchardt:** Writing – review and editing; **Cornelia Hauser-Kronberger:** Formal analysis, writing – review and editing; **Clemens A Schmitt:** Resources, writing – review and editing; **Hanno Ulmer:** Data curation, formal analysis, visualisation, writing – review and editing; **Richard Greil:** Conceptualisation, methodology, writing – review and editing, supervision, funding acquisition.

Conflict of interest statement

Conflicts of interest with Mundipharma: Employment or leadership position: none; Consultant or advisory role: Andreas Petzer, Richard Greil; Fees for non-CME services received directly from commercial interest or their agents: none; Contracted research: Richard Greil; Ownership interest: none; Traveler grants: none.

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Supplemental material

Supplemental material for this article is available online.

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