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CLINICAL TRIAL

Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomised, open-label superiority phase 3 CARIN trial

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Abstract The study was designed to evaluate efficacy and superiority of capecitabine/bevacizumab + vinorelbine (CAP/BEV/VIN) compared to CAP/BEV alone. Main purpose was to introduce a taxane-/anthracycline-free first-line treatment in advanced breast cancer (ABC), in order to avoid long-term toxicities. In this open-label, superiority, phase 3 trial, patients with HER2-negative ABC were randomized 1:1 to receive either oral CAP at 1000 mg/m^2 [twice daily, days 1–14, q3w] plus intravenous BEV at 15 mg/kg [day 1, q3w] (arm A) or in addition to this protocol intravenous VIN at 25 mg/m^2 [days 1 + 8, q3w] (arm B) until disease progression, unacceptable toxicity or withdrawal of consent. Between 26 February 2009 and 26 October 2012, we randomised 600 patients (arm A $N = 300$; arm B $N = 300$) from 57 German outpatient-centres and 2 university hospitals. Median progression-free survival (PFS) (primary endpoint) was not improved with VIN (CAP/BEV, 8.8 months; CAP/BEV/VIN, 9.6 months; HR 0.84 [95 % CI 0.70–1.01], $P = 0.058$). Median overall survival (OS) (secondary endpoint) was 25.1 and 27.2 months for CAP/BEV and CAP/BEV/VIN, respectively, average HR 0.85 [95 % CI 0.70–1.03], $P = 0.104$). The 1- and 2-year OS rates appeared to be similar (78.0 and 77.0 %; 53.0 and 54.0 %). Toxicity profiles were generally mild and manageable. Adverse events occurred more frequently in arm B. Regarding the balance between clinical efficacy (PFS, OS) and toxicity, the CAP/BEV combination provides a favourable treatment option in first-line ABC avoiding taxane- and/or anthracycline-induced long-term toxicity. Superiority of CAP/BEV/VIN was not met, and side effects were even enhanced. Nevertheless, no safety issues occurred.

Keywords Taxane-free regimen · Capecitabine · Bevacizumab · Vinorelbine · First line · Advanced breast cancer

Key message

The CARIN trial is a large randomized phase 3 trial evaluating capecitabine/bevacizumab with or without vinorelbine in first-line treatment of ABC. PFS and OS are encouraging in both arms. Since the triple combination did not meet superiority, we suggest capecitabine/bevacizumab is favourable and recommendable, as OS is encouraging and taxane-/anthracycline-induced long-term toxicities can be avoided.

On behalf of the Breast Cancer Working Group of AIO (Arbeitsgemeinschaft Internistische Onkologie).

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Introduction

Despite many new treatment options, advanced breast cancer (ABC) remains essentially incurable. Taxanes, especially paclitaxel (PAC), and anthracyclines represent standard agents in first-line chemotherapy [1, 2]. Unfortunately, taxanes and anthracyclines are associated with substantial side effects, including peripheral neuropathy, myelosuppression, cardiotoxicity, and hair loss [3, 4] that heavily impair patients' performance and quality of life [5, 6]. Prolonged taxane and anthracycline exposure is not feasible because of cumulative toxic effects [7]. Therefore, capecitabine (CAP)-based combinations provide an effective and less toxic alternative for patients without rapidly progressive disease [8].

The addition of bevacizumab (BEV) to first-line chemotherapy in the E2100, AVADO, and RIBBON-1 trials resulted in prolongation of progression-free survival (PFS) and improved overall response rates (ORR) as compared to chemotherapy alone [9–11]. The placebo-controlled RIBBON-1 trial [11] was the first study demonstrating significantly improved ORR and PFS by adding BEV to first-line chemotherapy with either taxane-/anthracycline or CAP -based treatment. The TURANDOT trial [12, 13], a randomised phase 3 non-inferiority head-to-head study, assessed efficacy of BEV in combination with either PAC or CAP in first-line treatment for HER2-negative ABC.

Recently presented final OS data indicated non-inferiority of CAP/BEV (demonstrated in the stratified per-protocol analysis, supported by the stratified intent-to-treat analysis but not in the unstratified analysis). The OS curves seemed much the same, both in the per-protocol or the intent-to-treat analysis [13]. Although both, the TURANDOT and RIBBON-1 trial, demonstrated improved PFS for taxanes in combination with BEV, this did not translate into survival benefit.

Vinorelbine (VIN) monotherapy, evaluated in several clinical trials after failure of taxane-/anthracycline-based first-line metastatic treatment, yielded ORRs of about 29 % [14, 15]. VIN in combination with CAP revealed promising clinical activity and good tolerability in the neoadjuvant as well as in the metastatic setting [16–18]. Overlapping toxicities of both substances were rare.

CARIN was developed to improve efficacy through combination of VIN with CAP/BEV, thus offering an effective taxane-/anthracycline-free treatment option in first-line therapy of ABC. Primary objective was to demonstrate clinical superiority of CAP/BEV/VIN compared to CAP/BEV in terms of PFS. Secondary objectives included ORR, safety, and OS.

Methods

Patients

Eligible patients had HER2/-negative measurable or non-measurable disease, inoperable locally recurrent or ABC, no previous chemotherapy for advanced disease, and ECOG performance status $\leq$2; were aged $\geq$18 years; and had no sign of brain metastases. Adjuvant chemotherapy with either CAP or BEV or VIN was allowed if completed at least 12 months before randomisation. Further inclusion criteria comprised adequate liver, renal, cardiac, and haematological function; no uncontrolled hypertension; or proteinuria. All patients provided written informed consent. Independent ethics committees at all participating sites approved the protocol and all modifications.

Study design

CARIN was an open-label, randomised phase 3 trial. 600 patients were randomly assigned (1:1) to receive either CAP/BEV (arm A) or CAP/BEV/VIN (arm B). Randomisation was stratified by prior (neo)adjuvant therapy with taxanes or anthracyclines (yes/no) and hormone receptor status (±).

In both arms, CAP was administered orally at 1000 mg/m^2 (twice daily, days 1–14, q3w), combined with intravenous BEV at 15 mg/kg (day 1, q3w). In arm B, intravenous VIN was added to CAP/BEV at 25 mg/m^2 (days 1 + 8, q3w). Treatment was continued until progression of disease (PD), unacceptable toxicity, or withdrawal of consent. If any drug was discontinued for reasons of toxicity, treatment continued on the reduced regimen at allocated dosages. No BEV dose reduction was permitted, but treatment could be delayed. Beyond progression, all patients were offered standard-of-care treatment.

Efficacy and safety assessments

Tumour assessments according to RECIST 1.0 were performed at baseline, thereafter every 9 weeks until PD. After PD, patients were followed up for survival every 3 months over up to 3 years after last patient in.

Safety and tolerability assessments in terms of routine laboratory parameters, urinalysis, and vital signs were performed on a regular basis every cycle. Adverse events (AEs) were reported systematically throughout the study, including a 30-day safety follow-up period after treatment discontinuation. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, v3.0 and classified according to MedDRA v17.0 coding.

Statistical analysis

PFS as the primary objective was calculated from the date of randomisation to the date of first signs of tumour progression or death from any cause. Patients not experiencing PD or death were censored at the date of either last visit or start of new antineoplastic treatment. Calculating a drop-out rate of 10 %, a total of 600 patients ($\alpha = 0.05$, two-sided, power = 80 %) were to be enrolled. At study data cut-off for analysis, less events than expected were observed, reducing the power to detect the initially calculated PFS difference between treatment arms (8.0 vs. 10.3; HR = 0.78) to 75 %. Secondary endpoints included ORR, OS, and safety.

Treatment effects on PFS were calculated and compared between treatment arms and within subgroups using the Kaplan–Meier and Cox regression method. Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated by Cox proportional hazards analysis. Subgroup analyses were considered exploratory, no alpha adjustment for multiple testing was applied to the eight comparisons of subgroups: 'age (<65 vs. ≥65 years)', 'number of metastatic sites (<3 vs. ≥3 sites)', 'prior taxane/anthracycline (yes/no)', 'visceral disease (involved/not involved)', 'triple negative breast cancer (TNBC yes/no)', 'ECOG performance status (0 vs. 1/2)', 'prior palliative endocrine therapy (yes/no)', and 'bone metastases (yes/no)'.

Since the OS curves for treatment comparison appeared non-proportional, average hazard ratios were determined by weighted Cox regression method [19]. For OS subgroup analyses, the Cox proportional hazards were estimated.

For objective response evaluation, treatment groups were compared using Cochran Mantel–Haenszel test. Patients were considered evaluable for response if they had measurable disease at baseline.

Demographic and clinical characteristics were evaluated descriptively. All statistical analyses were performed using Statistica v10.0 and R v3.2.0.

Results

Patients

Between 26 February 2009 and 26 October 2012, 600 patients with locally advanced disease or ABC from 59 German outpatient centres and university hospitals were randomised, and 592 were eligible for efficacy and safety analysis (arm A, $N = 297$; arm B, $N = 295$). Eight patients did not receive the allocated treatment. The main reason for treatment discontinuation was PD (arm A, 179 [60.3 %]; arm B, 137 [46.4 %]). Treatment was permanently discontinued due to AE in 48 (16.1 %) and in 75 (25.4 %) patients in arms A and B, respectively (Fig. 1, [trial profile]).

Patient demographic and clinical baseline characteristics were generally well balanced between both arms (Table 1). Notably, the full analysis population was characterized by a considerable portion of patients older than 65 years (arm A: 105 [35.4 %]; arm B 132 [44.7 %]). The majority of patients was heavily pre-treated with (neo)adjuvant chemotherapy (arm A: 193 [65.0 %]; arm B: 195 [66.1 %]), including 114 (38.4 %) and 95 (32.2 %) patients with prior (neo)adjuvant taxane treatment in arm A and arm B, respectively. The proportion of patients with TNBC was identical in both arms (arm A: 61 [20.5 %]; arm B: 61 [20.7 %]).

Treatment exposure

Median duration of treatment was comparable between both arms (arm A: 27.9 weeks; arm B: 29.0 weeks). Median dose intensities for CAP were 84 and 79 % and for BEV 98 and 94 % in arms A and B, respectively. VIN dose intensity was 85 % (data not shown).

Efficacy

The addition of VIN slightly increased median PFS compared to CAP/BEV alone (8.8 vs. 9.6 months; HR 0.84 [95 % CI 0.70–1.01], log-rank $P = 0.058$), and therefore, the criteria for superiority of CAP/BEV/VIN were not met (Fig. 2, [patient characteristics]).

Hence, potential PFS differences between treatments were observed. When exploring subgroups according to clinical characteristics, significantly improved PFS among patients aged <65 years (8.2 vs. 10.2 months, HR 0.73 [95 % CI 0.58–0.93], $P = 0.009$), with <3 metastatic sites (8.8 vs. 10.7 months, HR 0.74 [95 % CI 0.59–0.93], $P = 0.009$), with (neo)adjuvant taxane/anthracycline pre-treatment (7.2 vs. 9.6 months, HR 0.71 [95 % CI 0.56–0.90], $P = 0.004$), with non-visceral disease (9.2 vs. 12.0 months, HR 0.63 [95 % CI 0.42–0.93], $P = 0.020$), with TNBC (4.2 vs. 7.0 months, HR 0.57 [95 % CI 0.39–0.84], $P = 0.004$), and with bone-only metastases (12.6 vs. 15.4 months, HR 0.46 [95 % CI 0.24–0.88], $P = 0.017$) was observed (Fig. 3, [subgroup analysis of progression-free survival]).

Confirmed ORRs were significantly lower in arm A compared to arm B (36.3 vs. 47.5 %, $P = 0.047$). Among responders, median duration of response was fairly comparable between arm A and arm B (8.8 vs. 9.6 months, HR 0.99 [95 % CI 0.67–1.45], $P = 0.944$) (data not shown).

At a median follow-up of 22.2 and 23.6 months in arm A and arm B, respectively, in total, 418 (70.6 %) patients had died (arm A: 218 [73.4 %]; arm B: 200

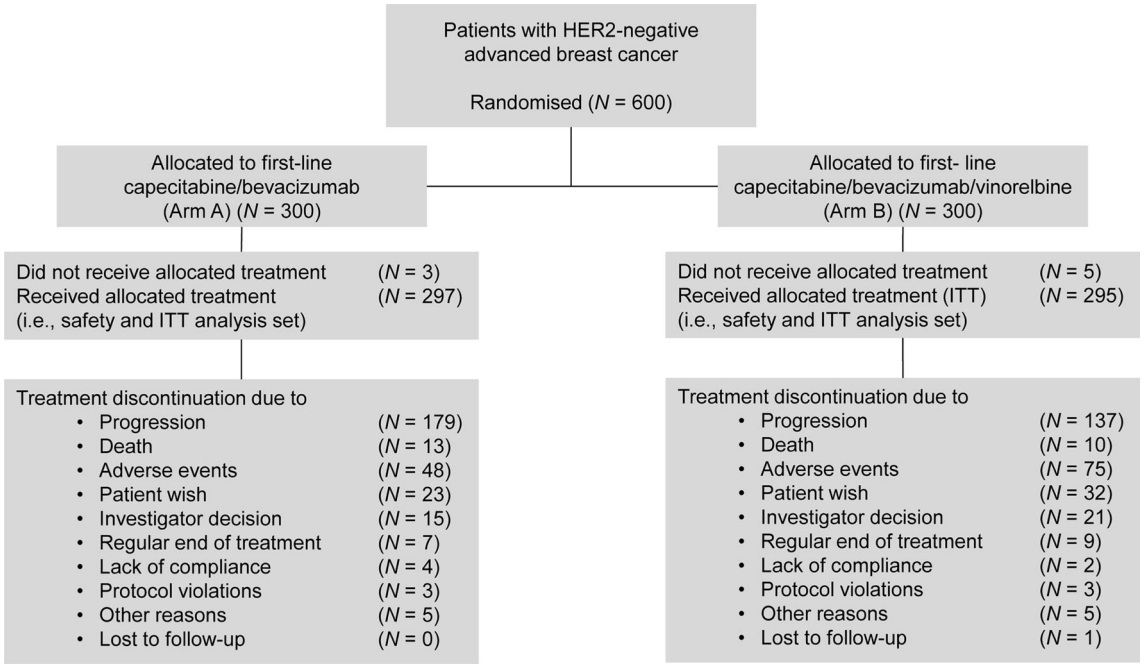

Fig. 1 Trial profile

[67.8 %]) (Fig. 4). The 1- and 2-year OS rates were quite similar between both treatment arms (arm A: 77.6 and 53.3 %; arm B: 76.6 and 54.4 %) (data not shown). Also, median OS appeared comparable in arm A and arm B, respectively (25.1 vs. 27.2 months; Average HR 0.85 [95 % CI 0.70–1.03], $P = 0.104$). Nevertheless, treatment effects on OS became obvious comparing arm A versus arm B, respectively, within subgroups with taxane/anthracycline pre-treatment (21.5 vs. 25.2 months, HR 0.70 [95 % CI 0.54–0.90], $P = 0.0048$), and with non-visceral disease (29.3 vs. 42.4 months; HR 0.64 [95 % CI 0.51–0.98], $P = 0.040$) (Fig. 4, [Kaplan–Meier estimate for overall survival]).

Safety

Common grade 3/4 events were (*N* patients [%], arm A vs. B) as follows: Nausea/vomiting (8 [2.7 %] vs. 19 [6.4 %]), Infection (27 [9.1 %] vs. 34 [11.5 %]), Fatigue/malaise (6 [2.0 %] vs. 19 [6.4 %]), Thromboembolic events (12 [4.0 %] vs. 15 [5.1 %]) including pulmonary embolism (4 [1.3 %] vs. 14 [4.8 %]), and peripheral neuropathia (1 [0.3 %] vs. 11 [3.7 %]) (Table 2b, [adverse events], separated by grades 3 and 4).

Conversely, grade 3/4 hand-foot syndrome was reported more often in arm A (70 [23.6 %] vs. 43 [14.6 %]), diarrhoea was reported slightly more often (13 [4.3 %] vs. 9 [3.0 %]), and hypertension occurred clearly more frequently in arm A (23 [7.8 %] vs. 9 [3.1 %]). Mucosal inflammation was reported equally (8 [2.7 %]) in both arms. Haematological toxicities as neutropenia (3 [1.0 %] vs. 57 [19.3 %]), leukopenia (1 [0.3 %] vs. 31 [10.5 %]), and febrile neutropenia (2 [0.7 %] vs. 5 [1.7 %]) were considerably more frequently reported in arm B. Overall, AEs of grade 3/4 (173 [58.2 %] vs. 216 [73.2 %]), serious AEs (112 [37.7 %] vs. 146 [49.5 %]), and AEs leading to treatment discontinuation occurred more often in arm B (Table 2a, [Overview of safety results]). In arm A, respectively, 63 (21.2 %) and 65 (21.9 %) patients required BEV and CAP treatment discontinuations due to AEs. In arm B, reflecting the higher incidence of AEs, more patients discontinued BEV (91 [30.8 %]), CAP (89 [30.2 %]), and VIN (100 [33.9 %]) treatment.

Serious AEs, deemed to be treatment-related by the investigator, led to death of three patients in arm A (pancytopenia, thromboembolic event, pulmonary embolism), and of two patients in arm B (pulmonary embolism and leukopenia associated with sepsis) (data not shown).

Discussion

The CARIN trial, a German phase 3 study, aimed to improve efficacy of CAP/BEV by adding VIN to establish a less toxic alternative to taxane-/anthracycline-based first-line treatment. PFS was the primary endpoint assuming a

Table 1 Patient characteristics (intent-to-treat population)

	Arm A CAP/BEV $N = 297$		Arm B CAP/BEV/VIN $N = 295$		Total $N = 592$	
Age						
All patients, *n* median years (range)	297	60.6 (28.9–85.1)	295	62.7 (34.1–88.3)	592	61.8 (28.9–88.3)
<65 years, *n* | %	192	64.6 %	163	55.3 %	355	60.0 %
≥65 years, *n* | %	105	35.4 %	132	44.7 %	237	40.0 %
Clinical characteristics						
Menopausal status						
Postmenopausal	243	81.8 %	241	81.7 %	484	81.8 %
ECOG performance status						
ECOG 0	172	57.9 %	182	61.7 %	354	59.8 %
ECOG 1/2	105	35.4 %	94	31.9 %	199	33.6 %
Disease free interval						
≤12 months	23	7.7 %	18	6.1 %	41	6.9 %
>12 months	216	72.7 %	228	77.3 %	444	75.0 %
Metastatic at primary diagnosis	58	19.5 %	49	16.6 %	107	18.1 %
Measurable disease	179	60.3 %	162	54.9 %	341	57.6 %
<3 metastatic sites	206	69.4 %	202	68.5 %	408	68.9 %
≥3 metastatic sites	91	30.6 %	93	31.5 %	184	31.1 %
Metastatic sites						
Visceral	232	78.1 %	225	76.3 %	457	77.2 %
Liver	142	47.8 %	143	48.5 %	285	48.1 %
Lung	90	30.3 %	89	30.2 %	179	30.2 %
Bone	149	50.2 %	177	60.0 %	326	55.1 %
Bone only	26	8.8 %	34	11.5 %	60	10.1 %
Receptor status						
Hormone receptor positive	236	79.5 %	233	79.0 %	469	79.2 %
HER2-negative	295	99.3 %	293	99.3 %	588	99.3 %
Triple-negative	61	20.5 %	61	20.7 %	122	20.6 %
Prior treatment for primary breast cancer	278	93.6 %	280	94.9 %	558	94.3 %
Hormone therapy	171	57.6 %	169	57.3 %	340	57.4 %
Chemotherapy	193	65.0 %	195	66.1 %	388	65.5 %
Taxanes	114	38.4 %	95	32.2 %	209	35.3 %
Anthracyclines	162	54.6 %	162	55.0 %	324	54.7 %
Prior treatment for locally recurrent or metastatic disease	128	43.1 %	148	50.2 %	276	46.6 %
Radiotherapy	92	31.0 %	96	32.5 %	188	31.8 %
Hormone therapy	109	36.7 %	118	40.0 %	227	38.3 %

ECOG Eastern Cooperative Oncology Group; *HER2* human epidermal growth factor receptor 2

Arm A capecitabine/bevacizumab; *Arm B* capecitabine/bevacizumab/vinorelbine

difference of 2.3 months in favour of the CAP/BEV/VIN combination. In the unselected population, superiority of the triple combination was not met. Exploring subgroups, the effect was more pronounced.

Compared to other phase 3 studies, the CARIN median PFS for CAP/BEV (8.8 months) was in the range of that observed in the CAP/BEV cohort of the TURANDOT (8.1 months) [12, 13] and the RIBBON-1 (9.2 months)

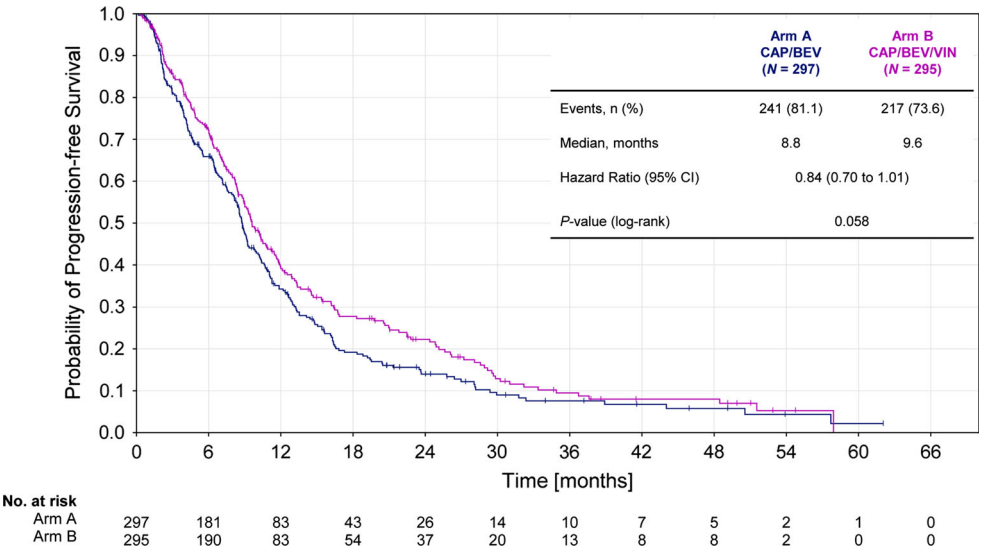

Fig. 2 Kaplan–Meier estimate for progression-free survival (Intent-to-treat population). Arm A: capecitabine/bevacizumab; arm B: capecitabine/bevacizumab/vinorelbine

[11] trials. RIBBON-1 [11] was the first study investigating efficacy and safety of BEV versus placebo combined with different standard chemotherapy backbones to be chosen by investigators before random assignment. This led to a pronounced imbalance between the treatment arms regarding taxane pre-treatment, with 40 % in the CAP/BEV arm and only 15 % in the taxane/anthracycline arm, thus hampering comparability of results. ORR and median PFS were higher in each BEV combination. This effect was most obvious in the CAP/BEV arm. The TURANDOT [12, 13] trial investigated in a randomised fashion whether OS with CAP plus BEV would be non-inferior to PAC plus BEV. Although response rates and PFS were significantly higher for PAC-BEV, results of the final analysis did not point to a survival benefit [13].

The debate regarding the use of taxanes and/or anthracyclines in first-line treatment of ABC on OS is still ongoing. The CARIN trial confirmed the efficacy of the taxane-/anthracycline-free CAP/BEV combination with a median OS of 25.1 months, which is quite comparable to 26.1 months reported from the CAP/BEV arm in the TURANDOT trial. Differences in OS between CARIN and TURANDOT may be explained by a significant discrepancy regarding pre-treatment with adjuvant or neoadjuvant taxanes in TURANDOT and CARIN (20 and 34 %, respectively), pointing to a more favourable prognosis for TURANDOT patients, when compared to the patient population in the CARIN trial. Notably, the 1-year OS rate in the CAP/BEV treatment arms was fairly comparable between CARIN (78 %), TURANDOT (81 %), and RIBBON-1 (81 %) trials, respectively. The taxane-containing PAC-BEV treatment in TURANDOT not only revealed OS of 30.2 months but also enhanced peripheral neuropathy. OS for CAP/BEV/VIN was 27.2 months.

On closer inspection, the CARIN OS estimates showed divergent curve characteristics beyond 33 months. This divergence may represent delayed clinical efficacy of arm B. The divergence may also be due to the differently responding subgroups. Particularly, subgroups with taxane/anthracycline pre-treatment and without visceral involvement obtained clinically meaningful survival benefits in the CAP/BEV/VIN approach, confirming VIN's therapeutic activity. Nonetheless, these subgroup findings require further examination in larger patient cohorts.

Regarding response induction, taxane/anthracycline-based combinations with BEV seem to be more effective than CAP/BEV [8, 9]. Patients presenting with life-threatening metastatic organ involvement may thus benefit from taxane-/anthracycline-based first-line treatment. However, since almost all patients are at risk of developing taxane-induced neurotoxicity [21] that impairs patients' daily life performance and overall quality of life, taxane treatment should be reserved for more advanced stages.

Undoubtedly, vinca alkaloids can also induce characteristic peripheral neurotoxicity [22, 23]. In this aspect, VIN added toxicity to the CAP/BEV combination. Treatment discontinuations due to toxicities occurred more frequently within CAP/BEV/VIN as compared to CAP/BEV alone, suggesting that VIN toxicities are in some way more severe or protracted. However, in the CARIN VIN-containing arm, only 10 of 295 patients developed grade 3 and 1 patient grade 4 polyneuropathy. In general, AEs > -grade 3 were rarely seen. Common side-effects of VIN and main dose limiting toxicities were neutropenia, as observed in other studies [15, 24, 25]. VIN did not cause profound thrombocytopenia. Other toxicities were mild to moderate and generally well manageable.

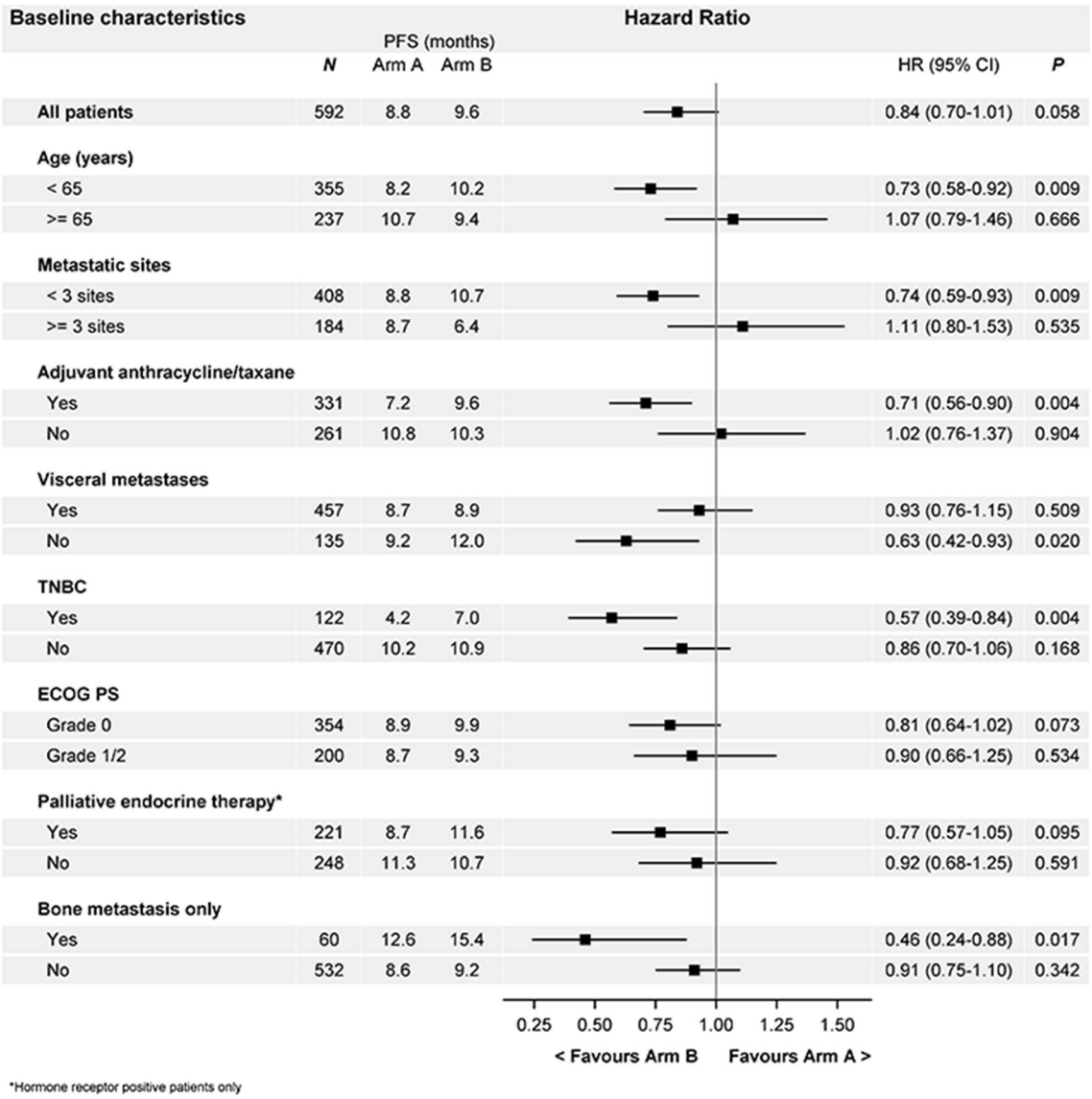

Fig. 3 Subgroup analysis of progression-free survival according to baseline characteristics (intent-to-treat population). HR = hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group performance status; TNBC = triple-negative breast cancer. Arm A: capecitabine/bevacizumab; arm B: capecitabine/bevacizumab/vinorelbine

There was an also manageable increase in adverse events due to hand–foot syndrome. The incidence (all grades) was higher in the CAP/BEV arm than in the CAP/BEV/VIN arm in spite of comparable dose intensities in both arms. In CARIN, hand–foot syndrome was mostly responsible for discontinuations of CAP. However, as compared to the BEV-PAC treatment arm in TURANDOT, the proportion of treatment discontinuations due to toxic effects in our CAP/BEV/VIN arm was somewhat lower (34 and 38 %, respectively).

The safety profile of BEV was consistent with known side effects [26, 27] and did not lead to a significant increase in toxicity. Severe side effects were rare even in patients with long-term treatment.

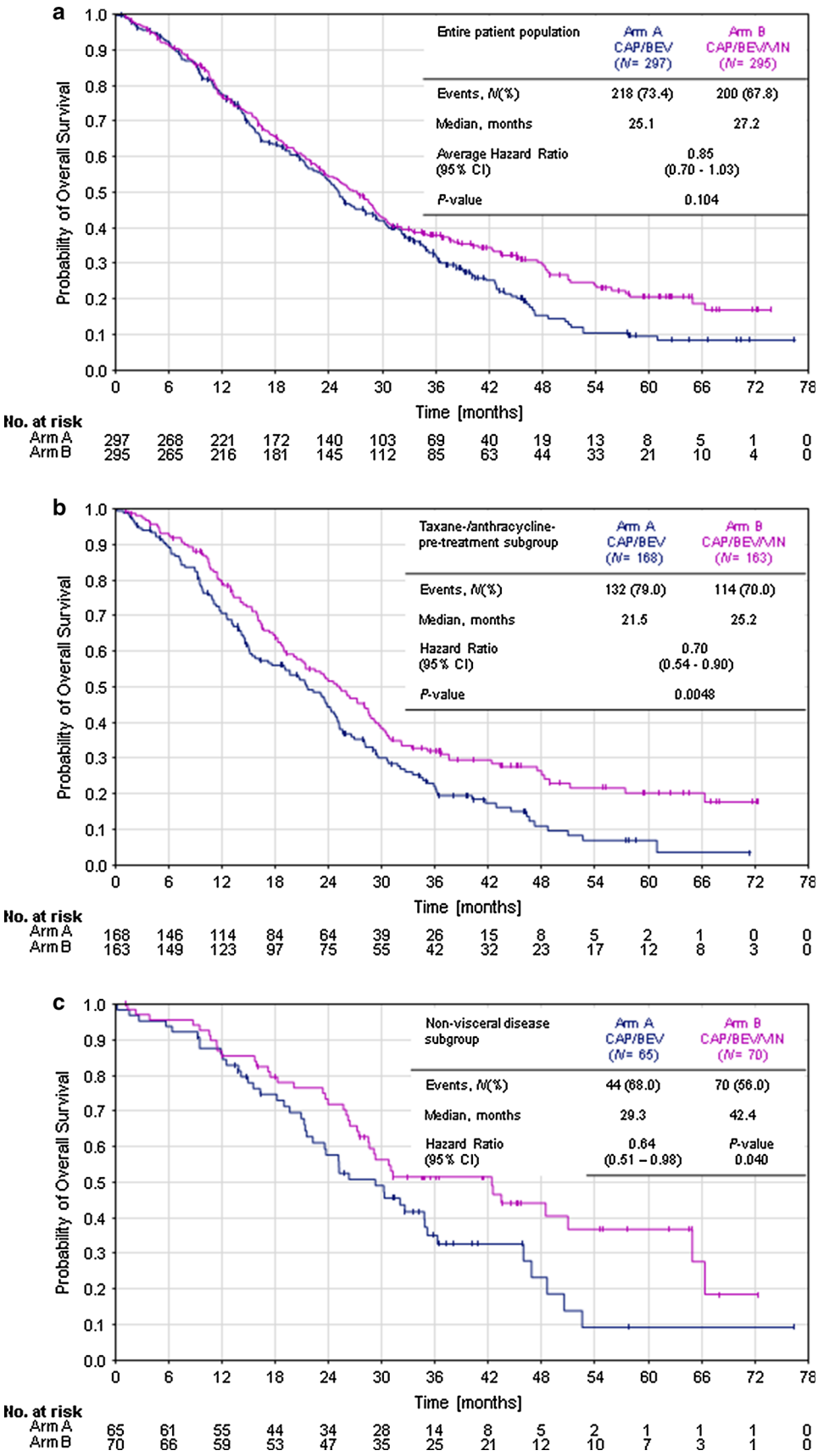

Fig. 4 Kaplan–Meier estimate for overall survival, separated by pre-defined subgroups (intent-to-treat population). **a** Overall population; **b** taxane and/or anthracycline pre-treated subgroup; **c** non-visceral disease subgroup. Arm A: capecitabine/bevacizumab; arm B: capecitabine/bevacizumab/vinorelbine

Table 2 (a) Overview of safety results, (b) adverse events of any grade in ≥10 % of patients, irrespective of relation to study treatment (safety population)

(a)	Arm A CAP/BEV [$N = 297$; n (%)]		Arm B CAP/BEV/VIN [$N = 295$; n (%)]		P value	
	n	%	n	%		
Any AE	286	96.3	288	97.6	0.474	
Related AE (investigator assessment)	279	93.9	286	96.9	0.114	
Any grade 3/4	173	58.2	216	73.2	<0.001	***
Related grade 3/4	125	42.1	189	64.1	<0.001	***
SAE	112	37.7	146	49.5	0.005	**
AE leading to BEV discontinuation	63	21.2	91	30.8	0.009	**
AE leading to CAP discontinuation	65	21.9	89	30.2	0.025	*
AE leading to VIN discontinuation	–	–	100	33.9	–	–

(b)	Arm A CAP/BEV [$N = 297$; n (%)]								Arm B CAP/BEV/VIN [$N = 295$; n (%)]								P value	
	Grade 1/2		Grade 3		Grade 4		Grade 5		Grade 1/2		Grade 3		Grade 4		Grade 5			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Hand-foot syndrome[1]	125	42.1	70	23.6					77	26.1	43	14.6					0.006	**
Nausea/vomiting	100	33.7	8	2.7					127	43.1	18	6.1	1	0.3			0.031	*
Infection	78	26.3	25	8.4	2	0.7			90	30.5	31	10.5	3	1.0	3	1.0	0.347	n.s.
Fatigue/malaise	83	27.9	6	2.0					106	35.9	19	6.4					0.008	**
Diarrhoea	82	27.6	12	4.0	1	0.3	1	0.3	75	25.4	8	2.7	1	0.3	1	0.3	0.516	n.s.
Hypertension	65	21.9	21	7.1	2	0.7			60	20.3	9	3.1					0.017	*
Mucosal inflammation	49	16.5	8	2.7					60	20.3	8	2.7					1.000	n.s.
Peripheral neuropathia	51	17.2	1	0.3					62	21.0	10	3.4	1	0.3			0.003	**
Haemorrhage/bleeding	39	13.1	2	0.7	1	0.3			65	22.0	2	0.7	1	0.3			1.000	n.s.
Dyspnoea	43	14.5	7	2.4					50	16.9	7	2.4			1	0.3	1.000	n.s.
Neutropenia	7	2.4	3	1.0					28	9.5	38	12.9	19	6.4			<0.001	***
Decreased appetite	36	12.1	3	1.0					39	13.2	7	2.4					<0.001	***
Alopecia[2]	20	6.7							59	20.0							0.221	n.s.
Leukopenia	5	1.7	1	0.3					17	5.8	17	5.8	14	4.7	1	0.3	<0.001	***
General physical health deterioration	12	4.0	8	2.7	1	0.3	1	0.3	15	5.1	10	3.4			4	1.4	0.821	n.s.
Proteinuria	20	6.7	3	1.0					18	6.1	1	0.3					0.624	n.s.
Thromboembolic event	1	0.3	12	4.0			1	0.3	10	3.4	15	5.1					0.562	n.s.
Pulmonary embolism					4	1.3	1	0.3	4	1.4	5	1.7	9	3.1	4	1.4	0.017	*
Febrile neutropenia			2	0.7							3	1.0	2	0.7			0.285	n.s.

AE adverse event; *SAE* serious adverse event

Arm A capecitabine/bevacizumab; *Arm B* capecitabine/bevacizumab/vinorelbine

[1] Palmar-plantar erythrodysaesthesia syndrome; [2]Alopecia only grade 1/2, grade 3/4 N/A; significance: * 0.05. ** 0.01; *** 0.001; *n.s.* not significant

Conclusion

The CAP/BEV combination is an effective treatment option in first-line ABC, regarding PFS (8.8 months) and OS (25.1 months). The triple combination CAP/BEV/VIN did not meet superiority criteria and side effects were enhanced. The risk-/benefit-ratio were balanced in CAP/BEV as taxane/anthracycline-induced long-term toxicities can be avoided.

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Compliance with ethical standards

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Informed consent Written informed consent was obtained from all individual participants included in this study.

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