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CLINICAL TRIAL

VicTORia: a randomised phase II study to compare vinorelbine in combination with the mTOR inhibitor everolimus versus vinorelbine monotherapy for second-line chemotherapy in advanced HER2-negative breast cancer

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Abstract

Purpose Improving the outcome of patients with HER2-negative metastatic breast cancer experiencing tumour progression following first-line chemotherapy remains an urgent medical need. The purpose of the VicTORia trial was to show superiority of everolimus in combination with vinorelbine versus vinorelbine monotherapy as second-line chemotherapy for patients with advanced HER2 negative breast cancer.

Methods In this randomised phase II trial, 133 patients were recruited in 32 centres in Germany. Patients were randomised 1:1 to second-line chemotherapy either with vinorelbine plus everolimus (arm1) or vinorelbine alone (arm2). Primary endpoint was progression-free survival (PFS). Secondary endpoints were PFS rate at 6 months, overall survival (OS), overall response rate (ORR) and safety. Baseline PI3 K mutational status was determined in plasma samples.

Results Median progression-free survival was not different between arms (arm1 vs. arm2: 4.01 months, 95% CI 2.40–6.09 vs. 4.08, 95% CI 2.80–5.33). PFS rate at 6 months (arm1 vs. arm2: 39.4%, 95% CI 27.6–50.9% vs. 36.6%, 95% CI 24.6–48.6%), median OS (arm1 vs. arm2: 16.3 months, 95% CI 11.4–19.0 vs. 13.8 months, 95% CI 10.2–19.1) and ORR were not different between arms. Most frequent grade 3/4 adverse events were neutropenia (50% vs. 40%), gastrointestinal toxicities (19.1% vs. 6.1%), and infections (19.1% vs. 7.7%). PI3 K mutational status was neither associated with PFS nor with OS.

Conclusion Although well tolerated, the efficacy of everolimus and vinorelbine combination therapy was not superior to vinorelbine monotherapy. There was no correlation between PI3 K mutational status and efficacy.
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Keywords Metastatic breast cancer · HER2 negative · Second-line treatment · Everolimus · Vinorelbine

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Introduction

Breast cancer is the most common malignancy in women and the second leading cause of cancer-related deaths in women worldwide [1]. Although the majority of patients with early breast cancer can be cured with modern treatment modalities, metastatic breast cancer is a chronic disease with heterogeneous biology and variable outcome with a 5 years relative survival rate of < 30% in most patients receiving several palliative treatment lines [2]. Considerable progress has been made in patients with HER2-positive disease [3] and in improving endocrine treatment strategies [4], but when it comes to the application of chemotherapy, sequential usage of single agents is still the therapy of choice because of the increased toxicities in combination regimens [5].

The choice of the first-line agent depends on various factors including previous adjuvant treatment, the need to induce a remission and patient preference regarding possible side effects. Taxans or anthracyclines are considered to be standard of care, but a variety of other agents are frequently given because of toxicity or pretreatment issues [6]. Disease control can be achieved in the majority of patients although the duration of benefit is limited. Second-line chemotherapeutic options for patients pretreated with anthracyclines and taxanes include vinorelbine, eribulin and capecitabine [5]. However, response rates are low with an overall survival being < 18 months. Attempts to improve these results by using chemotherapy combinations or adding targeted drugs have been disappointing [7, 8].

Everolimus is a selective inhibitor of mammalian target of Rapamycin (mTOR), which is an important component of the phosphotidyl-inositol 3 kinase (PI3 K) pathway. The PI3 K/AKT/mTOR pathway is dysregulated in a variety of human cancers including HER2-positive, triple-negative, and hormonreceptor (HR)-positive, HER2-negative breast cancer [9, 10].

Combination therapy of everolimus and ultitane has resulted in a clinically meaningful improvement in progression-free survival (PFS) in patients with HR-positive, HER2-negative breast cancer experiencing progressive disease following treatment with aromatase inhibitors [11]. Results in HER2-positive breast cancer were less impressive, although PFS improvements were observed in HR-negative patients in the first-line setting and in trastuzumab-resistant patients [12, 13].

Preclinical research has demonstrated that mTOR is implicated in the chemotherapy resistance against a variety of drugs including antimicrotubuli agents [14]. Accordingly, mTOR inhibition has been shown to potentiate the cytotoxicity of chemotherapeutic agents [15]. Clinical trials exploring the combination of everolimus and chemotherapy are ongoing. Promising early data have been published demonstrating safety and encouraging results in small cohorts of patients [16, 17].

Patients having PIK3CA activating mutations or a hyperactive PI3 K pathway seem to derive the greatest benefit from everolimus [18]. In addition, patients with PIK3CA mutations in circulating-free DNA (cfDNA) have longer progression-free survival when treated with the PI3 K inhibitor Buparlisib as previously reported in a phase III trial [19].

The VicTORia phase II trial was designed with the purpose to show that everolimus in combination with vinorelbine is superior to vinorelbine alone as second-line chemotherapy in patients with locally advanced or metastatic HER2-negative breast cancer.

Patients and methods

Patients

Eligible patients were aged ≥ 18 years diagnosed with HER2-negative locally recurrent (inoperable) or metastatic breast cancer with an indication for second-line chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2. Palliative endocrine treatments did not count as separate treatment lines. Prior treatment with anthracyclines and/or taxanes must have had either failed or not been suitable. Patients were ineligible if previously treated with vinorelbine or a mTOR inhibitor, had known brain metastasis, inadequate bone marrow, liver or kidney function, previous or concurrent cancer, or had a significant risk for major cardiovascular or cerebrovascular events.

Study design

VicTORia (AIO-MAM-0110) was an open-label, randomised (1:1) two-arm prospective multicentre study (ClinicalTrials.gov No. NCT01520103, EudracCT No 2011-001024-38) designed to assess the efficacy and safety of vinorelbine ± everolimus in patients with locally advanced or metastatic breast cancer. The study was conducted in 25 centres in Germany. Patients were randomly assigned to respective treatment arm by using sequential numbers, which were randomly allocated to one of the treatment arms. Randomisation was stratified by the presence or absence of visceral metastases.

Vinorelbine was given at 25 mg/m^2 as a short infusion on day 1,8,15 q3w and everolimus (5 mg) was taken once daily continuously throughout 21-day cycles.

Treatments were administered until tumour progression, unacceptable toxicity, or withdrawal of consent. Specific

dose reduction schedules were recommended for haematological and non-haematological toxicities. Tumour assessments were performed according to RECIST v1.1 based on CT imaging or MRI scans at baseline and every 9 weeks thereafter. The same radiographic assessment used to define measurable disease was used for the individual patients throughout the course of study.

Outcomes

The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary efficacy endpoints included overall survival (OS), 6 months PFS rate and overall response rate (CR + PR).

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v3.0.

Exploratory objectives included analysis of the potential relationship between PI3 K pathway alterations and antitumour activity as well as correlation with treatment response.

PIK3CA genotyping

Plasma samples were prospectively collected to analyse PIK3CA mutations at baseline.

CfDNA was extracted from 2 ml plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany). PIK3CA mutational status was determined by competitive allele-specific TaqMan™ PCR assays (Thermo Fisher Scientific™, Waltham, Massachusetts, USA) for E542 K, E545 K, H1047L, and H1047R.

Statistical analysis

The sample size for this study was determined based on the assumption that the median PFS for patients receiving vinorelbine monotherapy in the second-line setting is approximately 4 months [7]. Prolongation of the PFS by 2.5 months was considered to be clinically significant.

Assuming a recruitment period of 24 months and a follow-up period of a further 12 months, a total sample size of 144 patients (72 in each arm) was required to detect a difference in median PFS of 4.0 versus 6.5 months with 80% power, two-sided log-rank test, $\alpha = 0.05$). To account for a drop-out rate of about 15%, a total of 166 patients were planned to be randomised.

Analysis of efficacy was conducted based on the intent-to-treat (ITT) principle. PFS and OS were estimated using time-to-event analysis by using the Kaplan and Meier method. Kaplan–Meier estimators are presented as survival curves, median PFS and OS times were computed with 95% CIs.

The two treatment arms were compared with respect to PFS and OS using a two-sided log-rank test at a level of significance of $\alpha = 0.05$. The hazard ratio (HR) between the two therapy arms was computed using a univariate Cox proportional hazard model. For the HR, two-sided 95% CIs were presented. A multivariate Cox regression model was used to analyse the influence of treatment adjusted for the covariate "visceral metastases".

All other statistical analyses of the efficacy parameters were descriptive in nature, i.e. the results of comparisons were to be interpreted in an exploratory manner for the generation of hypotheses. Unless specified otherwise, those results were to be reported without giving the significance level.

Results

From December 2011 through October 2016, 154 patients were assessed for eligibility, of whom, 133 patients were randomly assigned to either treatment with vinorelbine and everolimus (68 patients, arm1) or vinorelbine alone (65 patients, arm2; Fig. 1).

Baseline characteristics

The baseline characteristics and demographics of the patients were generally well balanced between treatment arms regarding age, BMI and menopausal status (Table 1). Most patients had an ECOG performance status of 0 or 1 in both treatment arms although the number of patients with ECOG2 was slightly higher in arm2. Visceral disease was present in the majority of patients (89.7% vs. 87.7%) and most patients had two or more metastatic sites in both treatment arms. The proportion of patients with triple-negative disease was slightly higher in patients treated with vinorelbine and everolimus (18 of 68 patients) versus patients treated with vinorelbine alone (12 of 65 patients).

Efficacy

For the analysis of PFS, 118 events were included in the analysis with seven out of 68 patients in arm1 and eight out of 65 in arm2 being censored. Median follow-up duration was 34.5 months (95% CI 31.3–inf months) in the vinorelbine plus everolimus arm and 25 months (95% CI 19.8–43.5 months) in the vinorelbine arm.

Median PFS of patients treated with vinorelbine plus everolimus was 4.08 months (95% CI 2.76–6.32) and 4.21 months (95% CI 3.03–6.35) for patients having received vinorelbine alone, log rank $p = 0.7908$, (HR 1.050 (0.730–1.512), $p = 0.7916$) (Fig. 2a). The PFS rate at 6 months was 39.4% (95% CI 27.57–50.92) for patients assigned to vinorelbine plus everolimus versus 36.58% (95% CI 24.63–48.0) for those assigned to vinorelbine alone. For

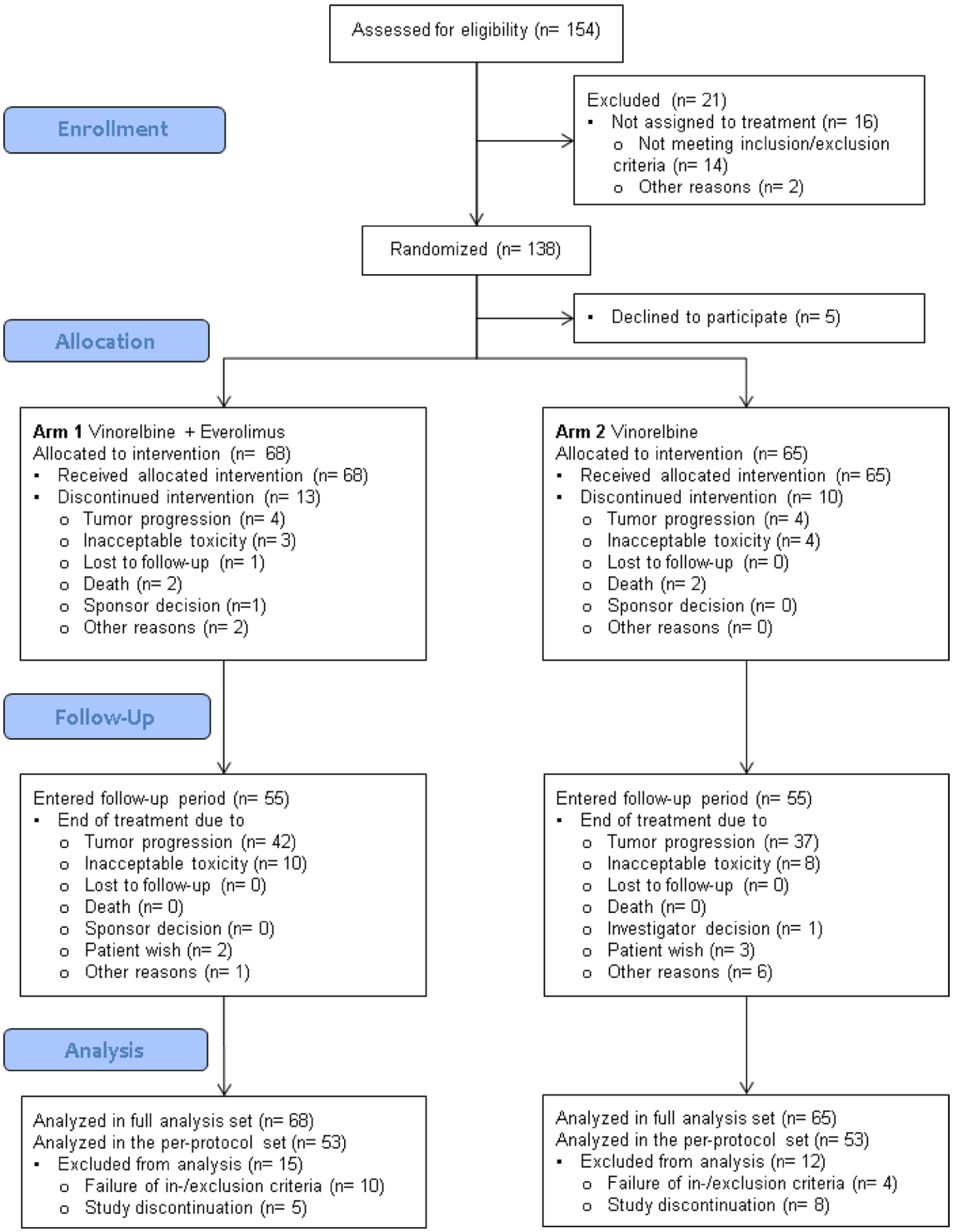

Fig. 1 Consort flow diagram

the OS analysis, 95 events were included in the analysis with 16 out of 68 patients in arm1 and 22 out of 65 patients in arm2 being censored. Median OS was 16.25 months (95% CI 11.38–18.95) for vinorelbine plus everolimus (censored: $n = 16$; 23.5%) and 13.78 months (95% CI 10.23–19.05) for vinorelbine alone (censored: $n = 22$; 33.9%) (Fig. 2b; log rank $p = 0.9361$).

There was no statistical difference between treatment arms for ORR (11.8% arm1, 18.4% arm2). Stable disease (SD) was documented in 26.5% of patients in the vinorelbine

Table 1 Patient characteristics at screening

		Total ($N=133$)	Arm1 ($N=68$)	Arm2 ($N=65$)
Age (years)				
Mean			61.9	60.7
SD			11.9	11.2
BMI (kg/m^2)				
Mean			25.4	27.4
SD			4.7	6.4
ECOG performance status [*n* (%)]				
0		66 (49.6)	34 (50.0)	32 (49.2)
1		60 (45.1)	33 (48.5)	27 (41.5)
2		6 (4.5)	1 (1.5)	5 (7.7)
Menopausal status [*n* (%)]				
Perimenopausal			2 (2.9)	4 (6.2)
Postmenopausal			54 (79.4)	52 (80.0)
Premenopausal			9 (13.2)	7 (10.8)
Unknown			3 (4.4)	2 (3.1)
Metastatic sites[a] [*n* (%)]				
Liver		87 (65.4)	44 (64.7)	43 (66.2)
Bone		58 (43.6)	27 (39.7)	31 (47.7)
Lymph notes		45 (33.8)	23 (33.8)	22 (33.8)
Lung		37 (27.8)	22 (32.4)	15 (23.1)
Visceral versus non-visceral disease [*n* (%)]				
Visceral disease		118 (88.7)	61 (89.7)	57 (87.7)
Non-visceral disease		12 (9.0)	5 (7.4)	7 (10.8)
No. of metastatic sites [*n* (%)]				
1		35 (26.3)	18 (26.5)	17 (26.2)
2		50 (37.6)	28 (41.2)	22 (33.8)
≥ 3		45 (33.8)	20 (29.4)	25 (38.5)
Breast cancer subtype[a] [*n* (%)]				
Oestrogen receptor status	Negative		19 (27.9)	13 (20.0)
	Positive		49 (72.1)	52 (80.0)
Progesterone receptor status	Negative		29 (42.6)	22 (33.8)
	Positive		39 (57.4)	43 (66.2)
Triple-negative		30 (22.6)	18 (26.5)	12 (18.5)

BMI body mass index, *ECOG* eastern cooperative oncology group, *SD* standard deviation

[a]Multiple entries per patient were possible

plus everolimus arm and in 23.1% in the vinorelbine arm (Table 2), respectively. Progressions of disease occurred in 48.5% and 49.2%, respectively. No tumour assessment was reported in 10.3% of patients (arm1) versus 9.2% of patients (arm2), respectively.

The multivariate Cox regression analysis on PFS and OS adjusted for treatment arm and visceral versus non-visceral metastases showed no significant difference between treatment arms neither for PFS [HR 1.671 (0.841–3.319), $p=0.1430$)] nor for OS [HR 2.105 (0.894–4.955), $p=0.0884$]. However, the results should be interpreted with caution due to the low numbers of patients without visceral metastases in both arms. PFS and OS were not different between arms when triple-negative and HR-positive subgroups were analysed separately. As expected, patients with triple-negative disease had worse PFS and OS outcomes compared to patients with HR-positive breast cancer (Fig. 3a, b).

Plasma samples of 92 patients were available for genotyping. PIK3CA activating mutations were detected in 18.5% of patients (2.2, 5.4, 0.0, and 10.9% for E542 K, E545 K, H1047L, and H1047R, respectively). PIK3CA mutational status was neither associated with PFS nor with OS in the total patient cohort, in patients treated with vinorelbine plus everolimus and in patients treated with vinorelbine, respectively (Table 3).

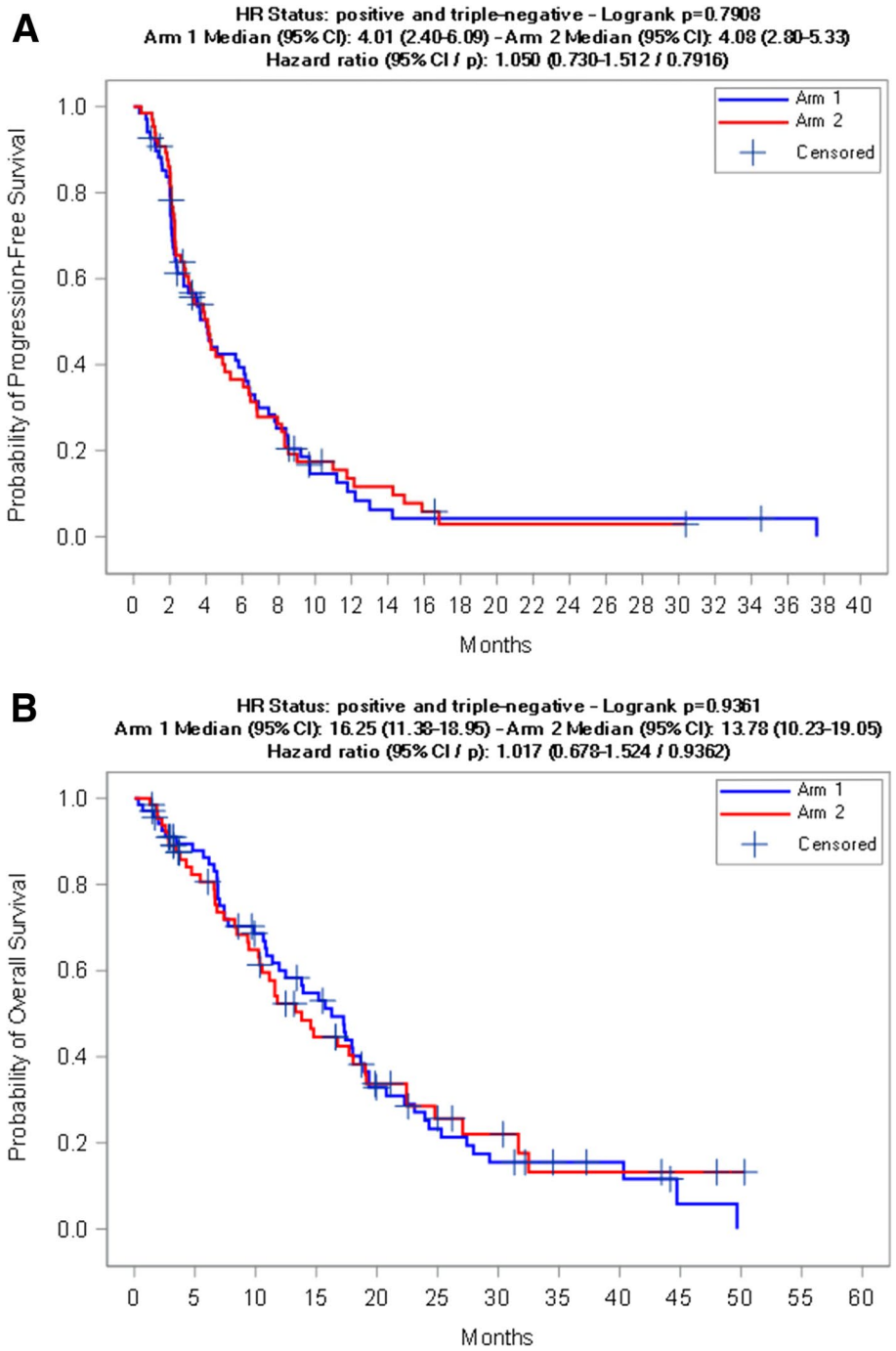

Fig. 2 Kaplan–Meier estimates of progression-free survival (**a**) and overall survival (**b**) in Arm1 (vinorelbine and everolimus) and Arm2 (vinorelbine alone). *HR* Hormone receptor, *CI* confidence interval

Safety

One hundred and thirty-three patients who had received at least one combined dose of either vinorelbine and everolimus ($n=68$, arm1) or vinorelbine alone ($n=65$, arm2) constituted the safety population used in the safety analysis.

The duration of study treatment was equal in both arms (median 9.93 weeks vs. 10.0 weeks) with a mean relative dose intensity of vinorelbine of 96% in arm1 and 97.1% in arm2, respectively. The relative dose intensity of everolimus in arm1 was 92.7%. All patients except one patient in the vinorelbine arm experienced at least one adverse event.

The most common adverse events of any grade in both groups were haematological events, gastrointestinal disorders and fatigue.

The incidence of any grade 3 events was numerically higher in the vinorelbine + everolimus arm (80.9% vs. 66.2%), whereas the incidence of grade 4 events was almost similar (23,.5% vs. 24.6%). Neutropenia of grade 3 or 4 was more frequently reported in the experimental arm (50%) vs.

Table 2 Best overall response

Best overall response *n* (%)	Arm1 (*N* = 68)	Arm2 (*N* = 65)
CR	0	1 (1.5)
PR	8 (11.8)	11 (16.9)
SD	18 (26.5)	15 (23.1)
PD	33 (48.5)	32 (49.2)
Non-CR/non-PD	2 (2.9)	0
NE	1 (1.5)	0
Not evaluated	6 (8.8)	6 (9.2)

CR complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

40% in the vinorelbine arm. The incidence of grade 3 or 4 infections was higher in patients treated with vinorelbine and everolimus (arm1: 19.1%, arm2: 7.7%).

Gastrointestinal toxicities were increased in arm1 (17.6% grade 3) versus arm2 (4.6% grade 3). However, grade 3/4 stomatitis occurred in only 7.4% of patients because of the low everolimus dose of 5 mg/day. AEs leading to dose reduction (8.8%), interruption (32.4%) or permanent discontinuation of everolimus were common (14.7%) in patients treated with vinorelbine and everolimus. In addition, vinorelbine and everolimus were permanently discontinued in 26.5% of patients due to toxicities. Permanent discontinuation of vinorelbine was also common in patients treated with vinorelbine alone (40%).

Table 4 summarises the rates of AEs occurring in ≥ 20% of patients (any grade) and grade 3/4 toxicities reported in ≥ 1 patients.

Discussion

The identification of effective treatment strategies in triple-negative or HR-positive, HER2-negative patients with progressive disease after first-line chemotherapy is currently an unmet clinical need. Adding targeted agents to standard chemotherapies was considered to be a promising strategy to overcome chemotherapy resistance, but a number of drugs have failed to improve patient outcomes in this setting [20–22]. In line with these results, the present trial failed to show that adding everolimus to standard second-line chemotherapy with weekly vinorelbine therapy was able to improve PFS, the primary endpoint of this trial. Secondary endpoints were also not improved. The unfavourable results of the VicTORia trial are in line with other trials evaluating vinorelbine monotherapy in the second-line setting [7, 23].

The dose of everolimus used in this study was 5 mg—lower than that used for established indications—and was chosen on the basis of the results of a dose-escalation trial of everolimus in combination with vinorelbine and trastuzumab [24]. A phase I pharmacokinetic and pharmacodynamic study of everolimus has demonstrated an inhibition of S6 kinase activity in peripheral-blood mononuclear cells at doses ≥ 20 mg/week where 5 mg everolimus was recommended as an appropriate dose for further studies [25].

A large non-interventional trial has shown similar efficacy when everolimus was given at a dose of 5 mg compared to the approved dose of 10 mg in combination with exemestane in breast cancer patients [26]. Therefore, the chosen everolimus dose of 5 mg/day is unlikely to account for the failure of mTOR inhibition to improve treatment efficacy in the present trial. In addition, dose intensity of vinorelbine could be maintained in patients treated with everolimus.

Although mTOR signalling is known to mediate chemotherapy resistance [14], mTOR inhibition with everolimus might result in disruption of the negative feedback loop between S6 K and Akt, resulting in increased activation of the PI3 K/Akt pathway with the increased apoptosis resistance [27].

Vinorelbine is thought to act in the mitotic phase of the cell cycle by inducing polymerisation of microtubule [28]. Therefore, induction of a cell cycle arrest in the G1 phase of the cell cycle by everolimus which is described in several tumour models [29, 30] might inhibit the cytotoxicity of vinorelbine. Antagonism or synergism was observed to be dependent on different dose schedules [31].

In line with the data obtained in the present trial, combination of everolimus with paclitaxel failed to improve response rates in two trials in the neoadjuvant setting, although mTOR signalling was reduced in tumour samples [32, 33]. A modest prolongation of PFS was observed in trastuzumab-resistant HER2-positive disease when vinorelbine was combined with everolimus [34], possibly reflecting the significance of increased PI3 K/AKT signalling in mediating trastuzumab resistance [35].

PIK3 mutations sensitize breast cancer cells to mTOR inhibition [36] and activation of the PI3 K pathway in archival tumour samples was associated with a decreased hazard of progression in patients treated with everolimus in a combined analysis of BOLERO-1 and BOLERO-3 [18]. However, a high occurrence of discrepancy in PIK3CA mutations between primary tumours and metastases has been reported. Microdissection studies have revealed heterogeneity within different sections of the same primary tumour [37]. Therefore, PIK3CA mutational status of archival samples is unlikely to be a reliable biomarker for everolimus treatment.

Detection of PI3 K mutations in circulating-free DNA (cfDNA) is feasible and more accurately reflects the biology of metastatic disease [38]. However, no significant differences in treatment efficacy were detected in the present trial in patients with or without PI3 K mutations in cfDNA. Although PI3 K mutations were predictive for the efficacy of the PI3 K inhibitor Buparlisib in a phase III trial, everolimus

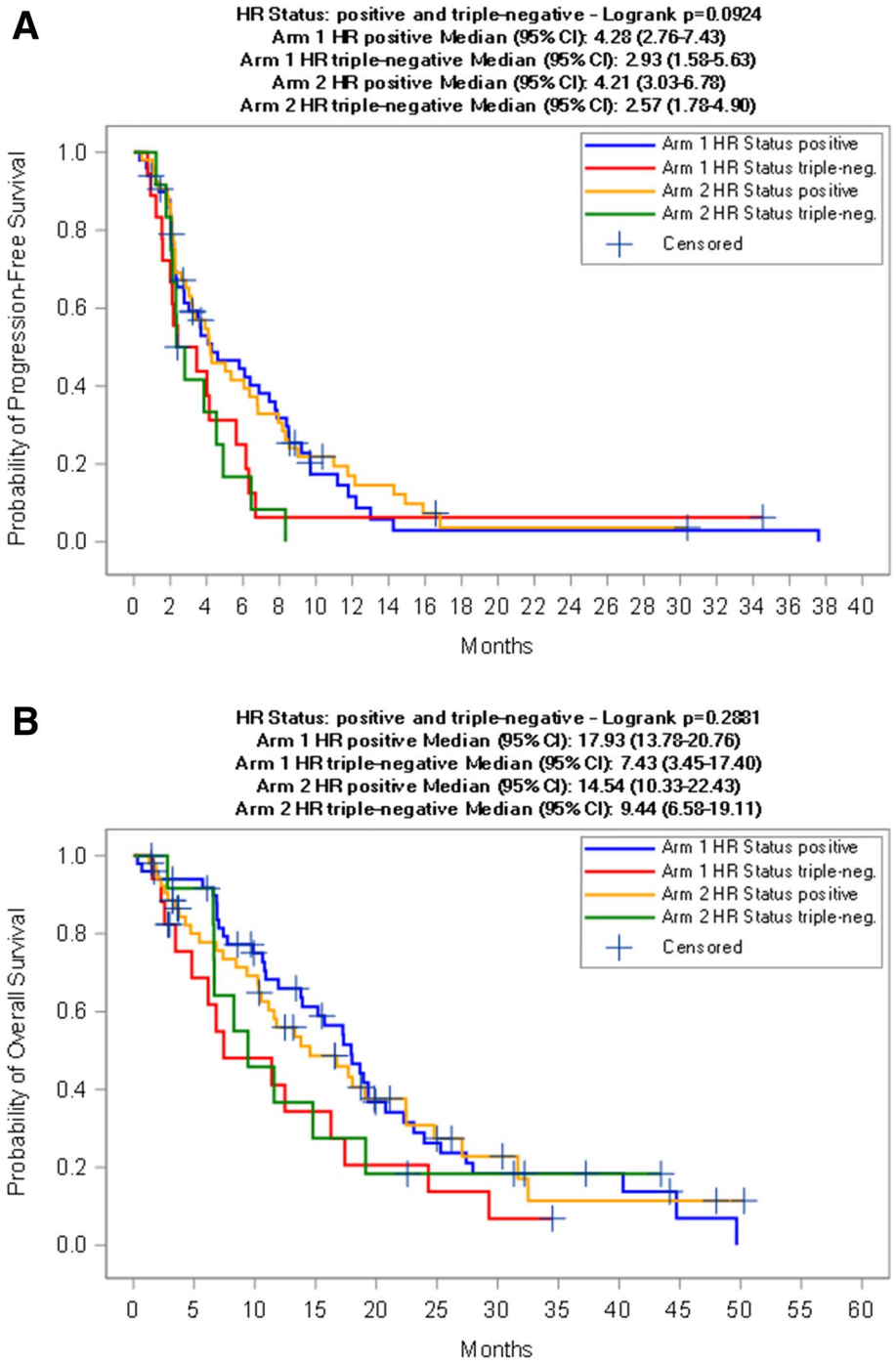

Fig. 3 Kaplan–Meier estimates of progression-free survival (**a**) and overall survival (**b**) in Arm1 (vinorelbine and everolimus) and Arm2 (vinorelbine alone) stratified by HR-positive and triple-negative breast cancer. *HR h*ormone receptor, *CI* confidence interval

efficacy was not increased in patients with PI3 K mutations in cfDNA as reported in the BOLERO-2 trial [39].

A limitation of the present trial is related to study design. For reasons of practicalbility, the study was conducted open label without placebo added to vinorelbine in arm2. Moreover, tumour response was evaluated by the investigators and not additionally by a blinded independent centralised review. However, it is regarded as very unlikely that such design features would have impacted the overall conclusions.

Conclusion

The VicTORia trial is the largest trial of an everolimus/chemotherapy combination in patients with HER2-negative breast cancer reported so far. Although toxicities were manageable, no benefit was observed for patients treated with everolimus and vinorelbine. Other dosing schedules of everolimus and chemotherapy or combination of chemotherapy with drugs targeting different members oft the

Table 3 Association of PIK3CA mutational status with progression-free survival and overall survival

PIK3CA mutational status	PFS, months (median ± IQR)	*p*-Value	OS, months (median ± IQR)	*p*-Value
Total patient cohort				
Negative	3.03 ± 4.31	0.860	9.39 ± 12.70	0.757
Positive	3.14 ± 5.94		10.33 ± 9.61	
Arm1				
Negative	3.03 ± 4.64	0.332	11.41 ± 12.93	0.934
Positive	2.30 ± 2.99		12.35 ± 9.93	
Arm2				
Negative	2.75 ± 3.25	0.221	7.53 ± 8.63	0.606
Positive	4.41 ± 8.38		10.23 ± 12.52	

P-values were calculated by Mann–Whitney-*U*-test

PFS progression-free survival, *OS* overall survival, *IQR* interquartile range

Table 4 Adverse events in ≥ 20% of patients (any grade) and grade 3/4 toxicities in ≥ 1 patients

Event[a], *n* (%) system organ class preferred term	Arm1 (*N* = 68)		Arm2 (*N* = 65)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Blood and lymphatic system disorders				
Anaemia	28 (41.2)	4 (5.9)	22 (33.9)	–
Leukopenia	38 (55.9)	20 (29.4)	27 (41.6)	16 (24.7)
Neutropenia	55 (80.9)	34 (50.0)	39(59.4)	26 (40.0)
Gastrointestinal disorders				
Constipation	13 (19.1)	2 (2.9)	16 (24.6)	–
Diarrhoea	20 (29.4)	3 (4.4)	9 (13.8)	–
Nausea	22 (32.4)	2 (2.9)	24 (36.9)	1 (1.5)
Stomatitis	27 (39.7)	5 (7.4)	6 (9.2)	–
General disorders and administration site conditions				
Fatigue	29 (42.7)	4 (5.9)	28 (43.0)	1 (1.5)
Pyrexia	15 (22.1)	–	9 (13.9)	1 (1.5)

[a]Multiple entries per patient were possible

PI3 K/mTOR pathway might ultimately lead to clinical benefit in this patient group with an urgent need for effective treatment [40].

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Compliance with ethical standards

Conflict of interest TD: Honoraria (advisory board): Novartis and Celgene. NM: Honoraria and travel expenses: Novartis; Employment/leadership position and share ownership: iOMEDICO AG. AW: Advisory boards: Astra Zeneca, Novartis, Roche, Eisal, Pfizer, Amgen, Lilly; Fees: COCS GmbH, iOMEDICO AG, Interplan AG; Funding of scientific program: Novartis; Stocks, other financial relationships: None. VH: Honoraria (travel and meeting expenses): Roche, Amgen, Pfizer, Celgene, BMS, FomF, Janssen Cilag, iOMEDICO AG, Gilead; Consulting role: Roche; Share ownership: BMS, Johnson & Johnson. AM, JR, HS, PJ, KP, CL declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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