European Journal of Cancer 154 (2021) 21–29

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Everolimus plus aromatase inhibitors as maintenance therapy after first-line chemotherapy: Final results of the phase III randomised MAIN-A (MAINtenance Afinitor) trial

Valentina Guarneri [a,b,*], Carlo Alberto Giorgi [b], Saverio Cinieri [c], Carmelo Bengala [d], Gabriella Mariani [e], Giancarlo Bisagni [f], Antonio Frassoldati [g], Claudio Zamagni [h], Costanza De Rossi [i], Vito Amoroso [j], Claudia Andreetta [k], Antonella Ferro [l], Alberto Zambelli [m], Stefania Gori [n], Ornella Garrone [o], Maria Vittoria Dieci [a,b], Laura Orlando [c], Ilaria Pastina [d], Teresa Beninato [e], Gabriella Moretti [f], Elisa Genovesi [a], Margherita Cinefra [c], Roberto Vicini [p], Giovanna Magni [q], Gian L. De Salvo [q], PierFranco Conte [a,b]

[a] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*
[b] *Medical Oncology 2, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy*
[c] *Department of Oncology, Di Summa - Perrino Hospital, Brindisi, Italy*
[d] *Medical Oncology, Ospedale Misericordia, Azienda Toscana Sud-Est, Grosseto, Italy*
[e] *Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[f] *Department of Oncology and Advanced Technologies, Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*
[g] *Clinical Oncology, Department of Morphology, Surgery and Experimental Medicine, S. Anna University Hospital, Ferrara, Italy*
[h] *Medical Oncology Unit, Addarii Institute of Oncology, S. Orsola-Malpighi Hospital, Bologna, Italy*
[i] *Medical Oncology, Ospedale dell'Angelo, AULSS3 Serenissima, Mestre, Italy*
[j] *Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Medical Oncology, University of Brescia at ASST Spedali Civili, Brescia, Italy*
[k] *Department of Oncology, ASUFC Udine University Hospital, Udine, Italy*
[l] *Breast Center, Santa Chiara Hospital, Trento, Italy*
[m] *Unit of Oncology, Ospedale Papa Giovanni XXIII, Bergamo, Italy*
[n] *Medical Oncology, IRCCS Ospedale Sacro Cuore-Don Calabria, Negrar di Valpolicella, Italy*
[o] *Breast Unit, Medical Oncology AO S. Croce and Carle Teaching Hospital, Cuneo, Italy*
[p] *Department of Medical and Surgical Sciences for Children and Adults, Statistics Unit, University Hospital of Modena and Reggio Emilia, Modena, Italy*
[q] *Clinical Trials and Biostatistics Unit, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy*

* *Corresponding author*: Medical Oncology 2, Istituto Oncologico Veneto IOV – IRCCS, via Gattamelata 64, 35128, Padova, Italy.
E-mail address: valentina.guarneri@unipd.it (V. Guarneri).

https://doi.org/10.1016/j.ejca.2021.05.008

Received 15 February 2021; received in revised form 29 April 2021; accepted 5 May 2021
Available online 2 July 2021

KEYWORDS
Metastatic breast cancer;
Maintenance therapy;
Everolimus

Abstract ***Background:*** Despite endocrine therapy being the mainstay of treatment for hormone receptor positive (HR+)/HER2− metastatic breast cancer, patients at risk of visceral crisis or doubt for endocrine sensitivity are still offered first-line chemotherapy. Maintenance hormonal therapy is generally offered at the discontinuation of chemotherapy. The MAINtenance Afinitor study is a randomised, phase III trial comparing maintenance everolimus combined with aromatase inhibitors (AIs) versus AI monotherapy in patients with disease control after first-line chemotherapy.

Methods: Patients with stable disease, partial response or complete response after first-line chemotherapy were randomised to everolimus plus AIs (exemestane or letrozole or anastrozole) or to AIs alone. Primary aim was progression-free survival (PFS). Secondary aims included response rate, safety and overall survival (OS).

Results: In total, 110 patients were randomised to everolimus + AIs (n = 52) or to AIs (n = 58). Median PFS was 11.0 months (95% confidence interval [CI] 8.1−13.8) in the everolimus + AI arm and 7.2 months (95% CI 4.7−10.9) in the AI monotherapy arm (hazard ratio [HR] 0.71, 95% CI 0.47−1.06). Objective response rate was 22.4% in everolimus + AI arm and 19.2% in AI monotherapy arm. A higher proportion of disease progression as best response was reported in the AI monotherapy arm (28.8% versus 14.3%). Median OS was 35.7 months (95% CI 26.0−47.8) in the combination arm versus 33.5 (95% CI 26.4−42.7) in the AI alone arm (HR 1.0, 95% CI 0.61−1.62).

Conclusions: EVE + AIs did not significantly impact on the outcome of metastatic breast cancer patients deemed suitable for first-line chemotherapy. Also taking into account treatment tolerability, maintenance endocrine therapy remains the standard.

Trial registration: EudraCT: 2013-004153-24.

1. Introduction

Breast cancer represents the leading cause of cancer-related death in females [1]. Indeed, despite the implementation of screening programs and the availability of effective strategies in the adjuvant setting, metastatic disease is still incurable. Hormonal therapy is the treatment of choice for hormone receptor positive (HR+)/HER2− advanced breast cancer, even in case of visceral metastases. According to guidelines, upfront chemotherapy should be limited to patients with visceral crisis [2,3]. However, a proportion of patients with HR+/HER2− disease were still offered first-line chemotherapy, in particular before the widespread availability of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors [4−6]. Optimal duration of first-line chemotherapy in this setting has not been established, largely depending on response and side-effects, but as soon as per clinical judgement chemotherapy is discontinued, maintenance endocrine therapy is generally offered. Indeed, even though data from randomised trials are scanty, as recently reviewed by Sutherland *et al.* [7], also in view of the low toxicity, offering endocrine therapy in patients not progressing after chemotherapy to delay disease progression is a reasonable approach.

Everolimus is an oral rapamycin derivative inhibiting the PI3K (lipid kinase phosphoinositide 3-kinase) to mTOR (mammalian target of rapamycin) pathway via allosteric binding to mTOR complex 1 (mTORC1) [8]. In combination with tamoxifen, everolimus was associated with a significantly improved progression-free survival (PFS) and overall survival (OS) relative to tamoxifen alone in patients previously treated with an aromatase inhibitor (AI) [9].

In the phase III breast cancer trials of oral everolimus-2 (BOLERO-2) trial, everolimus− exemestane significantly prolonged PFS compared to placebo−exemestane in patients with recurrence or progression after non-steroidal AIs [10]. The MAINtenance Afinitor (MAIN-A) trial was aimed at evaluating whether the addition of everolimus to an AI as maintenance treatment could improve the outcome of HR+/

HER2− advanced breast cancer patients with disease control after first-line chemotherapy.

2. Methods

MAIN-A is an investigator-driven, phase III randomised study conducted at 16 Italian institutions. The decision for a phase III design with PFS as primary end-point was based on the fact that, despite based on a level of evidence consensus-based, endocrine therapy maintenance at the completion of chemotherapy was considered standard. The trial was approved by local ethical committees of the participating institutions and was conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients provided written informed consent.

2.1. Patients

Patients were eligible if they met the following criteria: HR+/HER2− metastatic breast cancer with disease control (complete response, partial response or stable disease) after standard first-line chemotherapy (minimum 6 cycles), postmenopausal status, Eastern Cooperative Oncology Group performance status (PS) 0–1, normal organ and marrow function, fasting cholesterol <300 mg/dl and triglycerides <2.5 upper limit of normal (ULN) (statins or other lipid lowering drugs permitted) and fasting glucose <1.5 ULN. For premenopausal patients who became amenorrhoeic during chemotherapy, oestradiol level within postmenopausal range at the time of enrolment was required along with pharmacological castration with luteinizing hormone releasing hormone (LHRH) analogue while on study treatment. HR status was locally determined by immunohistochemistry (IHC); positivity was defined as at least 10% of oestrogen receptor (ER) and/or progesterone receptor staining. HER2− status was locally determined by either fluorescence *in situ* hybridisation (FISH) or IHC (IHC 0, 1+, 2+ and/or FISH HER2:centromer enumerator probe 17 (CEP17) ratio <2.0).

2.2. Procedures

After confirmation of eligibility, patients were randomised in a 1:1 ratio to receive everolimus + AIs (Arm A, experimental arm) or AIs (Arm B, control arm) (Supplemental Fig. 1). Randomisation was performed centrally using a web-based system, with restricted access through username and password.

Patients randomised to Arm A were treated with everolimus 10 mg in association with letrozole 2.5 mg or anastrozole 1 mg or exemestane 25 mg continuous daily dosing (CDD). Patients randomised to Arm B were treated with letrozole or anastrozole or exemestane CDD. Concomitant treatment with bone-modifying agents was allowed. The assigned study treatment was continued until disease progression, unacceptable toxicity or consent withdrawal. Dose interruptions and reductions were allowed as required (see Supplemental Appendix 1, online only). Patients who discontinued everolimus because of side-effects were permitted to continue receiving AIs. Tumour assessments (computed tomography or magnetic resonance imaging) were performed at screening, every 12 weeks thereafter until disease progression (including in patients who discontinued treatment for reasons other than progressive disease) and at the end of treatment.

2.3. Study end-points and statistical considerations

The primary objective of the study is to compare the PFS of AIs + everolimus versus AIs. The original sample size was calculated to detect an improvement from 6 months with AIs to 9 months with AIs + everolimus in the median PFS (corresponding to an improvement from 25% to 40% 1-year PFS; hazard ratio = 0.66). A total number of 184 events were required to test the hypothesis with a log-rank test, 5% alpha level (two-sided) and 80% power. The estimated sample size was 115 patients per arm. Due to the low accrual and the changing landscape following the advent of CDK4/6 inhibitors, in 2017 the statistical plan was amended and the sample size recalculated to detect an improvement from 6 months with AIs to 11 months with AIs + everolimus in the median PFS (1-year PFS improvement from 25% to 46.7%; hazard ratio = 0.55). In the new scenario, a total of 88 events were required under the same assumptions. The amended sample size was 54 patients per arm. PFS was defined as the time from randomisation to the first documentation of objective disease progression or death from any cause. Patients without a PFS event at the time of the primary analysis were censored at the date of their last objective tumour assessment. This includes patients lost to follow-up or who have withdrawn consent. Exploratory PFS analyses according to visceral metastases and levels of ER expression were pre-planned. Secondary aims were objective response rate (ORR) for patients with measurable disease at study entry, OS and safety. Response was evaluated according to Response Evaluation Criteria in Solid Tumours criteria version 1.1. OS was calculated as the time from randomisation to death from any cause. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The Kaplan–Meier method was used to estimate survival curves, and the log-rank test was used to compare between groups. Cox proportional regression models were used to calculate hazard ratios and 95% confidence intervals (CIs). Level of significance was $P < 0.05$.

Statistical analyses were performed with SAS software (version 9.4).

3. Results

From July 2014 to January 2019, a total of 110 patients were randomly assigned to AIs + everolimus (Arm A, n = 52) and to AIs (Arm B, n = 58) (Fig. 1). Patient and tumour characteristics were generally balanced between the two arms. Of note, patients randomised to AIs + everolimus presented longer disease-free interval (Table 1).

Two patients, one in each arm, were enrolled having reached amenorrhea during first-line chemotherapy, with ovarian function suppression with LHRH analogue maintained throughout protocol therapy. Eighteen patients presented with lobular histology, n = 10 (17.2%) in the AI arm and n = 8 (15.4%) in the AI + everolimus arm.

Almost a third of the patients have received adjuvant chemotherapy, and approximately half of the patients have received adjuvant hormonal therapy. Overall, 53 patients presented with *de novo* stage IV disease (27 in Arm A and 26 in Arm B).

Thirty-four patients (65%) in Arm A and 35 (60%) in Arm B presented with visceral metastases, respectively. The vast majority of the patients in both arms (92%) had ER expression ≥50%. Bone-only disease was documented in 7 patients (13%) in Arm A and 9 patients (15%) in Arm B, respectively. Twenty-eight patients in Arm A and 26 patients in Arm B underwent metastatic site biopsy for biological re-characterisation of the disease before starting first-line chemotherapy. Median duration of first-line chemotherapy was 5.06 months for patients randomised to AIs (minimum 2.9; maximum 18.9 months) and 5.22 months (minimum 2.3; maximum 12.5 months) for patients randomised to AIs + everolimus. First-line chemotherapy consisted mainly of taxane-based regimens (54% in both arms) and anthracycline-based regimens (35.8% in the AI arm and 37% in the AIs + everolimus arm, respectively).

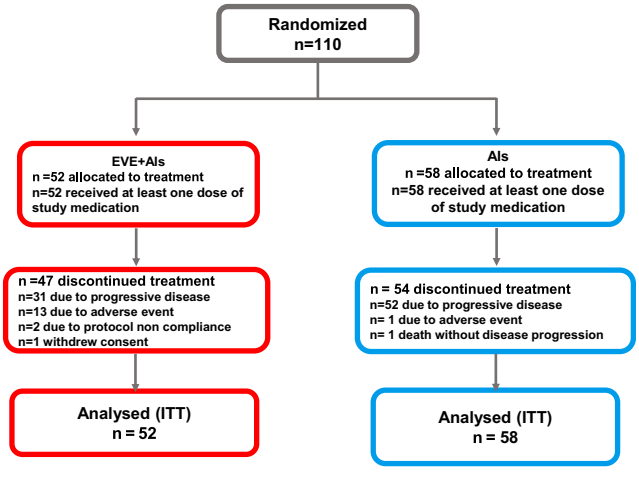

Fig. 1. Consort diagram. AI, aromatase inhibitor; EVE, everolimus.

Table 1
Patient characteristics.

	EVE-AIs (n = 52)	AIs (n = 58)
Median age (minimum–maximum), years	60.7 (29–80)	56.4 (34–81)
ECOG PS 0, n (%)	46 (88)	53 (93)
Prior surgery, n (%)	34 (65.4)	34 (58.3)
Prior adjuvant chemotherapy, n (%)	18 (34.6)	22 (37.9)
Prior adjuvant hormonal therapy, n (%)	24 (46.1)	29 (50.0)
Median DFI (lower quartile; upper quartile), months[a]	98 (67; 194)	78 (61; 127)
Stage IV de novo, n (%)	27(51.9)	26 (44.8)
Metastatic sites		
Visceral, n (%)	34[b] (65)	35 (60.3)
Bone only, n (%)	7 (13.4)	9 (15.5)

AI, aromatase inhibitor; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; EVE, everolimus; PS, performance status; CNS, central nervous system.
[a] Excluding patients presenting with stage IV *de novo*.
[b] Two patients presented with controlled CNS metastases.

Overall, 51 patients (24 in Arm A and 27 in Arm B) were on treatment with bone modifying agents prior to start study therapy.

3.1. Efficacy

At the time of final data cut-off (July 2020), median follow-up was 42.9 months (95% CI 35.3–52.4) and a total of 97 PFS events have been recorded. Median PFS was 11.0 months (95% CI 8.1–13.8) for patients randomised to receive everolimus + AIs and 7.2 months (95% CI 4.7–10.9) for patients randomised to AIs alone (hazard ratio 0.71, 95% CI 0.47–1.06, log-rank $P = 0.0938$) (Fig. 2A). The rates of 12-month PFS were 41.6% (95% CI 28.0–54.6) and 29.3% (95% CI 18.3–41.2), respectively.

Exploratory subgroup analysis according to ER expression (> versus </=50%), and presence of visceral metastases were pre-planned. ER expression (> versus </=0%) was not associated with a different outcome overall (log-rank $P = 0.67$) and by treatment arm (P value for interaction = 0.2983). When looking at the entire cohort of patients, patients presenting with visceral metastases tended to have a shorter PFS compared to patients without visceral metastases (median PFS 7.4, 95% CI 5.5–9.9 versus 13.1, 95% CI 8.3–17.8, log-rank $P = 0.0816$). Among patients with visceral metastases, those treated with AI monotherapy experienced the worst prognosis (median PFS 5.6 months, 95% CI 2.8–9.4). Treatment effect was not significantly different between the two groups (P value for interaction = 0.3377) (Supplemental Fig. 2, online only).

ORR was 22.4% in everolimus + AI arm and 19.2% in AI monotherapy arm. A higher proportion of disease progression as best response was reported in the AI

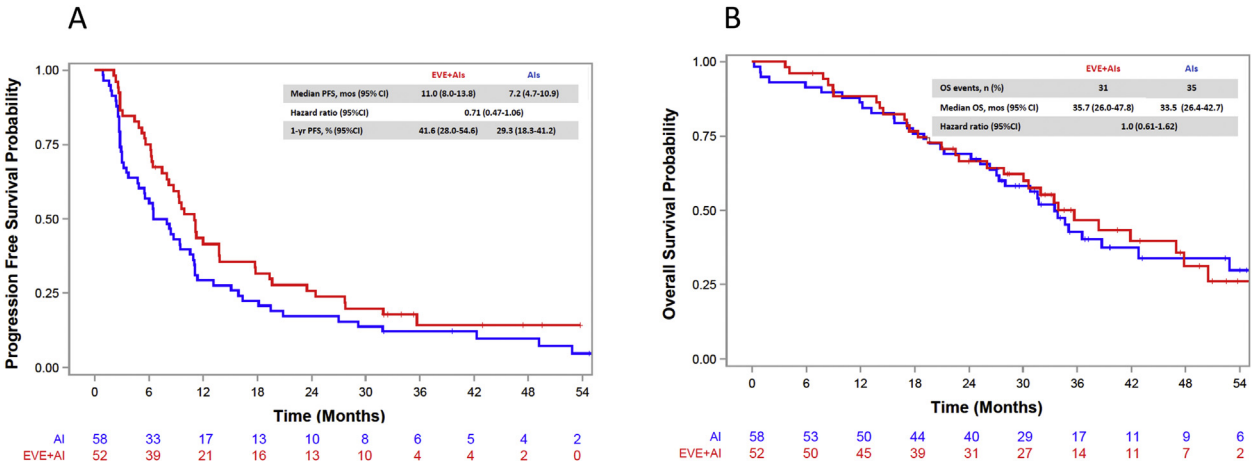

Fig. 2. Kaplan–Meier plot of progression-free (A) and overall survival (B). AI, aromatase inhibitor; CI, confidence interval; EVE, everolimus; OS, overall survival; PFS, progression-free survival.

monotherapy arm (28.8% versus 14.3% in the combination arm).

A total of 66 deaths have been recorded: 31 in the everolimus + AI arm and 35 in the AI-alone arm. Median OS was 35.7 months (95% CI 26.0–47.8) in the combination arm versus 33.5 (95% CI 26.4–42.7) in the AI-alone arm (hazard ratio 1.0, 95% CI 0.61–1.62, log-rank $P = 0.9902$) (Fig. 2B).

3.2. Safety

Grade III–IV AEs occurred in 23% (12) of the patients randomised to everolimus + AIs (stomatitis 13.4%, skin rash, asthenia, hypertriglyceridemia, neutropenia and pneumonitis 1.9% each). Grade I–II pneumonitis was documented in 11 patients. In the AI monotherapy arm, no grade IV AEs were documented, and one patient only reported an episode of grade III dyspnoea. Table 2 summarises grade II–IV toxicity per treatment arm.

Everolimus dose reductions were reported in 55.8% of the patients, and temporary interruptions in 63.4% of the cases. Permanent everolimus discontinuations due to AEs were reported in 30.8% of the cases. In the AI monotherapy arm, one patient only discontinued treatment because of AEs. In the combination arm, median everolimus exposure was 5.8 months (range 0.9–54.5) and median AI exposure was 6.1 months (range 1.2–54.5). In the AI monotherapy arm, median treatment exposure was 6.7 months (range 0.9–56.9).

4. Discussion

To the best of our knowledge, this is the first trial specifically designed to test the combination of everolimus plus endocrine therapy versus endocrine therapy alone as maintenance strategy after chemotherapy. Indeed, chemotherapy is unfortunately still an unavoidable treatment for HR+/HER2– advanced breast cancer, even though its role has been progressively reduced in favour of optimal endocrine therapy including the combination with CDK4/6 inhibitors [11–13]. In the current scenario, upfront chemotherapy is reserved for patients presenting with visceral crisis or with features of low endocrine sensitivity such as early progression while on adjuvant endocrine therapy. Moreover, chemotherapy remains the standard salvage treatment at exhaustion of endocrine therapy. Therefore, the vast majority of advanced breast cancer will receive at some point one or more lines of chemotherapy [14,15]. Optimal duration of chemotherapy in advanced disease has not been established, mainly depending on response, side-effects and patient compliance. In particular, anthracyclines and taxanes are generally administered for 6–8 courses [16,17]. Maintenance hormonal therapy is usually recommended as soon as chemotherapy is discontinued, with the aim of prolonging disease control. In recent years, targeted agents combined with endocrine therapy have produced meaningful clinical results [18–20]. The PI3K–Akt–mTOR is a major intracellular signalling pathway, which responds to the

Table 2
Grade 2–4 treatment-related adverse events (worse toxicity per patient).

Description	Arm A, everolimus + AIs			Arm B, AIs		
	G2	G3	G4	G2	G3	G4
Stomatitis	15.4%	11.5%	1.9%	–	–	–
Skin toxicity	17.3%	1.9%	–	–	–	–
Pneumonia	13.4%	1.9%	–	–	–	–
Asthenia	9.6%	1.9%	–	1.7%	–	–
Neutropenia	7.6%	1.9%	–	–	–	–
Nausea	5.7%	–	–	–	–	–
Hypercholesterolemia	5.7%	–	–	–	–	–

Listed are events that were reported in at least 5% of the patients in any group.
AI, aromatase inhibitor.

availability of nutrients, hormones and growth factor stimulation and play a significant role in tumour cell growth and proliferation. In particular, a close interaction between the mTOR pathway and ER signalling has been described, and the S6 kinase 1, which is a substrate of mTORC1, is responsible for ligand-independent ER activation through phosphorylation of its activation function domain 1 [21,22].

The BOLERO-2 trial demonstrated a significant PFS prolongation for everolimus plus exemestane versus exemestane–placebo, leading to everolimus approval in advanced disease [10]. On these premises, we designed the MAIN-A trial to evaluate the role of everolimus in patients achieving a disease control after first-line chemotherapy. Unfortunately, this trial has failed to achieve the primary end-point. Everolimus + AI was associated with a clinically not negligible 3.8-month median PFS prolongation, which was not statistically significant. It is important to note that the changing scenario following the advent of the CDK4/6 inhibitors resulted in a significant drop in patient accrual, forcing a sample size amendment which rendered more ambitious the expected outcome with the combination The reduced sample size, along with a slight outperformance of the control arm might partly explain our results. The latter observation might be due to the proportion of stage IV *de novo* disease, and therefore potentially endocrine-sensitive disease, enrolled in our trial. We might speculate that this patient composition might have limited the potential benefit of everolimus. However, in the BOLERO-2 trial approximately 20% of the patients were treated as first line, and to be eligible for the study patients have to have failed adjuvant AIs while on or within 12 months after the completion of the adjuvant plan, representing a heterogeneous population in terms of endocrine resistance. When looking at subgroup analyses of the BOLERO-2, there are no suggestions for different treatment effects according to prior therapies [10]. Moreover, in patients naïve to any anticancer therapy, neoadjuvant everolimus plus letrozole was associated with a higher response rate compared to letrozole alone [23]. Anyway, in an exploratory analysis, we found no PFS differences in patients presenting with stage IV versus relapsing disease, overall and per treatment arm (data not shown). Recent data from Vernieri *et al.* [24] have demonstrated an impact of on-treatment glycaemia on everolimus efficacy In our study, very few patients experienced hyperglycaemia, not allowing for statistical analysis.

Although the MAIN-A trial was conducted when everolimus was already widespread used in routine practice and clinicians were well familial with its safety profile, grade III/IV side-effects were reported by 23% of the patients. This is a slightly higher rate of clinically relevant side-effects compared to the pivotal registration trial. In particular, the rate of grade III–IV stomatitis in our trial was 13.4% versus 8% of grade III stomatitis observed in the BOLERO-2 trial [10]. Similar to what was observed for stomatitis, the incidence of pneumonitis was higher in our trial compared to what was reported in the BOLERO-2 trial (any grade: 23% in the MAIN-A and 12% in the BOLERO-2), even though the rates of G3 pneumonitis were similar. However, it is important to note that in the MAIN-A trial everolimus was started in patients with very recent chemotherapy exposure, possibly affecting everolimus tolerability. Moreover, in very recent years the awareness on iatrogenic pneumonitis raised up, leading to an increased attention to radiological findings potentially suspicious for drug-induced lung injury that might partly explain our findings. Indeed, iatrogenic lung diseases are rare but potentially fatal complications of several newly approved anticancer agents, including new antibody-drug conjugate (ADCs), immune check point inhibitors and CDK4/6 inhibitors [25–27]. Nonetheless, being palliation of the goal of treatment of advanced disease, in particular in patients already exposed to the side-effects of chemotherapy, treatment tolerability remains an important criterion for maintenance strategy. Therefore, maintenance endocrine therapy remains the standard, as confirmed by the excellent safety profile of maintenance AI monotherapy in our study. Patients with visceral metastases might deserve particular attention. Indeed, in our study patients with visceral metastases experienced a poor prognosis with only 5.6 months of PFS with AI monotherapy, notwithstanding the disease control achieved with first-line chemotherapy. For this subset of patients, it would be interesting to evaluate the effect of CDK4/6 inhibitors in combination with endocrine therapy.

We observed no differences in terms of OS between the two arms. The median OS of approximately 33 months in our patient population is relatively short for patients with HR+, HER2− metastatic breast cancer, and probably reflects the clinical judgement in the selection of patients with more aggressive disease to be treated with chemotherapy. Indeed, in the mammary oncology assessment of LEE011's [Ribociclib's] efficacy and safety (MONALEESA 7) trial conducted in premenopausal patients, so possibly patients with more aggressive disease, the median OS is 40.9 months for the control arm (endocrine therapy + placebo) and not reached in the endocrine therapy (ET) + ribociclib arm, at a median follow-up of 34.6 months [28,29].

Recent data from the clinical studies of alpelisib in breast cancer 1 (SOLAR 1) study have shown interesting results in terms of OS, even though not formally significant, in the subgroup of patients with visceral metastases treated with the combination of fulvestrant–alpelisib in patients harbouring phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations [30]. In our study, we did not plan routine evaluation of PIK3CA status on the

basis of exploratory analyses of the BOLERO-2 trial, suggesting PFS benefit from everolimus maintained regardless of PIK3CA status [31,32]. However, in future perspective, molecular characterisation of HR+/HER2− patients including PIK3CA status is warranted.

In conclusion, our data do not support the use of everolimus as maintenance strategy in patients with disease control after first-line chemotherapy. However, with a 3.8-month PFS prolongation for the combination arm, although not significant, our data are not closing credits for a potentiated endocrine maintenance strategy, in particular for patients with visceral disease. Newer targeted agents such as CDK4/6 inhibitors, which conjugate efficacy with an excellent safety profile, might be more successful.

Author contributions

Valentina Guarneri helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Carlo Alberto Giorgi helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Saverio Cinieri helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Carmelo Bengala helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Gabriella Mariani helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Giancarlo Bisagni helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Antonio Frassoldati helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Claudio Zamagni helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Costanza De Rossi helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Vito Amoroso helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Claudia Andreetta helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Antonella Ferro helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Alberto Zambelli helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Stefania Gori helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Ornella Garrone helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Maria Vittoria Dieci helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Laura Orlando helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Ilaria Pastina helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Teresa Beninato helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Gabriella Moretti helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources,

software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Elisa Genovesi helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Margherita Cinefra helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Roberto Vicini helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Giovanna Magni helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. Gian Luca De Salvo helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing. PierFranco Conte helped in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing - original draft and writing - review & editing.

Funding

Novartis Pharma provided drug supply and financial support. The study was sponsored by the Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy.

Conflict of interest statement

VG reports personal fees from Roche, Novartis, Eli Lilly and MSD outside the submitted work. CAG reports personal fees from Novartis outside the submitted work. SC reports personal fees from Lilly Oncology outside the submitted work. AF reports personal fees from Roche, Novartis, Pfizer, Lilly, Daiichi and Seagen outside the submitted work. CZ reports grants, personal fees and non-financial support from Roche, Novartis, AstraZeneca and Pfizer; grants and personal fees from Amgen and Tesaro; personal fees from QuintilesIMS; and grants from Eisai, PharmaMar, Pierre Fabre, Istituto Gentili, Takeda, TEVA, Medivation, AbbVie, Array BioPharma, Morphotek, Synthon, Seattle Genetics, Lilly and Celgene outside the submitted work. CDR reports personal fees from BMS and Novartis outside the submitted work. VA reports personal fees from Novartis outside the submitted work. AF reports personal fees from Novartis and Eli Lilly outside the submitted work. AZ reports personal fees from Novartis, Pfizer, Lilly, Roche, AstraZeneca, Merck, Daiichi-Sankyo and Genomic Health outside the submitted work. OG reports grants, personal fees and non-financial support from Novartis, Eisai, MSD, Pfizer, Celgene and Roche outside the submitted work. MVD reports personal fees from Eli Lilly, Genomic Health, Celgene and Novartis outside the submitted work. PC reports personal fees from Novartis, Eli Lilly, AstraZeneca, Tesaro, BMS and Roche outside the submitted work. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.05.008.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021 Feb 4. https://doi.org/10.3322/caac.21660.

[2] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). Ann Oncol 2020;31(12):1623–49.

[3] Rugo HS, Rumble RB, Macrae E, Barton DL, Klein Connolly H, Dickler MN, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069–103.

[4] Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van der Berkmortel F, Smilde TJ, et al. In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium. Ann Oncol 2016;27:256–62.

[5] Jacquet E, Lardy-Cléaud A, Pistilli B, Franck S, Cottu P, Delaloge S, et al. Endocrine therapy or chemotherapy as first-line therapy in hormone receptor-positive HER2-negative metastatic breast cancer patients. Eur J Cancer 2018;95:93–101.

[6] André F, Neven P, Marinsek N, Zhang J, Baladi JF, Degun R, et al. Disease management patterns for postmenopausal women in Europe with hormone-receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer. Curr Med Res Opin 2014;30(6):1007–16.

[7] Sutherland S, Miles D, Makris A. Use of maintenance endocrine therapy after chemotherapy in metastatic breast cancer. Eur J Cancer 2016;69:216–22.

[8] Efeyan A, Sabatini DM. mTOR and cancer: many loops in one pathway. Curr Opin Cell Biol 2010;22(2):169–76.

[9] Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative

metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 2012;30(22):2718–24.
[10] Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366(6):520–9.
[11] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375(18): 1738–48.
[12] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375(20):1925–36.
[13] Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35(32):3638–46.
[14] Guarneri V, Conte P. Metastatic breast cancer: therapeutic options according to molecular subtypes and prior adjuvant therapy. Oncol 2009;14:645–56.
[15] Martin M, Zielinski C, Ruiz-Borrego M, Carrasco E, Turner N, Ciruelos EM, et al. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial-PEARL. Ann Oncol 2020 Dec 29;S0923–7534(20). 43221-1.
[16] Conte PF, Guarneri V, Bruzzi P, Salvadori B, Bolognesi A, Aldrighetti D, et al. Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial. Cancer 2004;101(4):704–12.
[17] Gennari A, Bruzzi P, Orlandini C, Salvadori B, Donati S, Landucci E, et al. Activity of first-line epirubicin and paclitaxel in metastatic breast cancer is independent of type of adjuvant therapy. Br J Cancer 2004;90(5):962–7.
[18] Johnston SR. Clinical efforts to combine endocrine agents with targeted therapies against epidermal growth factor receptor/human epidermal growth factor receptor 2 and mammalian target of rapamycin in breast cancer. Clin Cancer Res 2006;12(3 Pt 2): 1061s–8s.
[19] Schiff R, Massarweh SA, Shou J, Bharwani L, Mohsin SK, Kent Osborne C. Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. Clin Cancer Res 2004;10(1 Pt 2):331S–6S.
[20] Guarneri V, Generali DG, Frassoldati A, Artioli F, Boni C, Cavanna L, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. J Clin Oncol 2014;32(10):1050–7.
[21] Yamnik RL, Holz MK. mTOR/S6K1 and MAPK/RSK signaling pathways coordinately regulate estrogen receptor alpha serine 167 phosphorylation. FEBS Lett 2010;584(1):124–8.
[22] Yamnik RL, Digilova A, Davis DC, Nilly Brodt Z, Murphy CJ, Holz MK. S6 kinase 1 regulates estrogen receptor alpha in control of breast cancer cell proliferation. J Biol Chem 2009;284(10): 6361–9.
[23] Baselga J, Semiglazov V, van Dam P, Manikhas A, Bellet M, Mayordomo J, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 2009;27(16):2630–7.
[24] Vernieri C, Nichetti F, Lalli L, Moscetti L, Giorgi CA, Griguolo G, et al. Impact of baseline and on-treatment glycemia on everolimus-exemestane efficacy in patients with hormone receptor-positive advanced breast cancer (EVERMET). Clin Cancer Res 2021 Mar 30. https://doi.org/10.1158/1078-0432.CCR-20-4928. clincanres.4928.2020 [Online ahead of print].
[25] Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis 2016;10(3):183–93.
[26] Hackshaw MD, Danysh HE, Singh J, Ritchey ME, Ladner A, Taitt C, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat 2020;183(1):23–39.
[27] FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer. FDA Drug Safety Communication; 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammationibrance-kisqali-and-verzenio-breast-cancer. [Accessed 28 June 2020].
[28] Azim Jr HA, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 2012;18(5):1341–51.
[29] Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381(4):307–16.
[30] André F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32(2):208–17.
[31] Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA, Pritchard KI, et al. Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from BOLERO-2. J Clin Oncol 2016;34(5): 419–26.
[32] Moynahan ME, Chen D, He W, Sung P, Samoila A, You D, et al. Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR+, HER2- advanced breast cancer: results from BOLERO-2. Br J Cancer 2017;116(6):726–30.