Metformin plus chemotherapy versus chemotherapy alone in the first-line treatment of HER2-negative metastatic breast cancer. The MYME randomized, phase 2 clinical trial

O. Nanni[1] · D. Amadori[2] · A. De Censi[3] · A. Rocca[2] · A. Freschi[4] · A. Bologna[5] · L. Gianni[6] · F. Rosetti[7] · L. Amaducci[8] · L. Cavanna[9] · F. Foca[1] · S. Sarti[2] · P. Serra[1] · L. Valmorri[1] · P. Bruzzi[10] · D. Corradengo[3] · A. Gennari[11] on behalf of MYME investigators

Abstract

Purpose To investigate the efficacy of metformin (M) plus chemotherapy versus chemotherapy alone in metastatic breast cancer (MBC).

Methods Non-diabetic women with HER2-negative MBC were randomized to receive non-pegylated liposomal doxorubicin (NPLD) 60 mg/m^2 + cyclophosphamide (C) 600 mg/m^2 × 8 cycles Q21 days plus M 2000 mg/day (arm A) versus NPLD/C (arm B). The primary endpoint was progression-free survival (PFS).

Results One-hundred-twenty-two patients were evaluable for PFS. At a median follow-up of 39.6 months (interquartile range [IQR] 24.6–50.7 months), 112 PFS events and 71 deaths have been registered. Median PFS was 9.4 months (95% CI 7.8–10.4) in arm A and 9.9 (95% CI 7.4–11.5) in arm B ($P = 0.651$). In patients with HOMA index < 2.5, median PFS was 10.4 months (95% CI 9.6–11.7) versus 8.5 (95% CI 5.8–9.7) in those with HOMA index ≥ 2.5 ($P = 0.034$). Grade 3/4 neutropenia was the most common toxicity, occurring in 54.4% of arm A patients and 72.3% of the arm B group ($P = 0.019$). M induced diarrhea (G2) was observed in 8.8% of patients in Arm A. The effect of M was similar in patients with HOMA index < 2.5 and ≥ 2.5, for PFS and OS.

Conclusions The MYME trial failed to provide evidence in support of an anticancer activity of M in combination with first line CT in MBC. A significantly shorter PFS was observed in insulin-resistant patients (HOMA ≥ 2.5). Noteworthy, M had a significant effect on CT induced severe neutropenia. Further development of M in combination with CT in the setting of MBC is not warranted.

Keywords Metformin · Insulin resistance · Advanced breast cancer · HOMA index

Introduction

There is increasing evidence that the insulin pathway is involved in the development and prognosis of a variety of human neoplasms, including breast cancer (BC) [1]. This association is biologically plausible as hyperinsulinemia induces proliferative tissue abnormalities due to the strong anabolic effect of insulin, resulting in the enhancement of DNA synthesis and cell proliferation [2]. This effect may also be attributable to the cross-activation of the insulin-like growth factor (IGF) receptor family. Insulin-like growth factors (IGFs) are endocrine mediators of growth hormones that also act in a paracrine and autocrine manner to regulate cell growth, differentiation, apoptosis, and transformation in numerous tissues including the breast [3]. The downstream pathway of the insulin/IGF system is well defined: IGF-I and insulin activate the tyrosine kinase growth receptor pathway, i.e., insulin, IGF-I, and hybrid IGF-I/insulin receptors, all of which are overexpressed in breast cancer cells. Activation of these receptors results in the upregulation of the insulin receptor-substrate-2 (IRS2), leading to the downstream activation of the MAPKinase and PI3K-Akt pathways [4]. It has also been shown that stimulation of the insulin receptor by insulin or IGFs enhances

The members of the MYME investigators study group are listed in the acknowledgments.

✉ O. Nanni
oriana.nanni@irst.emr.it

Extended author information available on the last page of the article

cancer cell proliferation. These findings suggest that the insulin/IGF pathway may be involved in tumor development and progression, and might thus represent a novel therapeutic target [5]. Furthermore, in patients with BC, higher circulating insulin levels have been found to be associated with adverse outcome, while IGF1 levels do not appear to have such an impact [6, 7] .

Within this context, it has been suggested that metformin (M), the most widely prescribed anti-diabetic drug for the treatment of hyperglycaemia and hyperinsulinemia [8], may improve prognosis in BC patients [9]. M is an oral biguanide that inhibits hepatic gluconeogenesis and sensitizes insulin action at the peripheral level. It is also widely prescribed for the treatment of type 2 diabetes [10] because of its good tolerability, and is approved by FDA for the prevention of diabetes in healthy at-risk subjects [11]. Pre-clinical data have shown that the key mechanism of action of M is the through activation of the AMPK pathway, resulting in a regulation of cellular energy homeostasis and an improvement in insulin sensitivity [12]. Epidemiological studies on diabetic patients indicate an association between the use of M and reduced BC incidence and mortality with respect to other antidiabetic drugs, especially in overweight/insulin-resistant women [13]. It can therefore be hypothesized that the potential antineoplastic effect of M in vivo is related either to its direct effect on cancer cell metabolism or to its indirect effect through the reduction of systemic insulin levels and hyperglycaemia, especially in insulin-resistant patients.

There are little clinical data on the effect of M as an anticancer agent. In a large observational study of BC patients treated with pre-operative chemotherapy, the proportion of M-treated diabetic patients achieving a pathological complete response was significantly higher than that of diabetic patients treated with other antidiabetic drugs and of non-diabetic BC patients [14]. More recently, in a window of opportunity, double-blind, randomized study in early BC patients, the administration of M for 4 weeks before surgery did not impact tumor proliferation, compared to baseline levels, in the overall patient population. However, a significant effect of M on Ki-67 was seen in insulin-resistant patients [15]. A large adjuvant trial on non-diabetic women with early BC comparing M with matching placebo in terms of disease-free survival (DFS) is currently ongoing [16, 17]. The present clinical trial evaluated the anticancer effect of M used in association with first-line chemotherapy in MBC.

Methods

Study design and participants

The MYME (Myocet® - Metformin) trial was a phase II, open-label, multicenter, randomized clinical trial aimed at assessing whether the addition of M to first-line chemotherapy in HER2-negative MBC is associated with a clinical effect, thus warranting further research. The study was approved by the Ethics Committee of each participating center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice norms and local and national regulatory requirements. Written informed consent was obtained from all patients before study entry. The study is registered in Clinicaltrials.gov (NCT01885013) and in European Clinical Trials Database (EudraCT No. 2009-014662-26).

Women were eligible if they met the following criteria: stage IV histologically or cytologically confirmed MBC, HER2-negative disease (determined by immunohistochemistry [IHC] or fluorescence in situ hybridization [FISH]); non endocrine-responsive disease (negative hormonal status or failure of endocrine therapy in metastatic disease); measurable and/or non-measurable disease according to RECIST Criteria (Version 1.1) [18]; availability of HOMA index calculated according to Matthews' formula [19]; prior endocrine therapy was allowed in the adjuvant and/or metastatic setting; prior chemotherapy was allowed in the adjuvant setting providing patients had completed it at least 12 months before study entry; adjuvant anthracyclines were allowed if prior cumulative dose did not exceed 360 mg/m^2 for epirubicin and 280 mg/m^2 for doxorubicin; adjuvant taxanes; age 18 to 75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2; normal organ and bone marrow functions; and left ventricular ejection fraction (LVEF) $> 50\%$. Patients with known diabetes (type 1 or 2) were excluded.

Randomization

Patients were randomly assigned (1:1) with a centralized procedure to one of two treatment groups: first-line chemotherapy alone or chemotherapy plus M. Randomization was performed using a computer-generated list and permuted blocks within strata. Randomization was stratified by center and HOMA index (< 2.5 vs ≥ 2.5). Investigators and patients were not masked to treatment assignment.

Treatment and procedures

Eligible patients were allocated to arm A (non pegylated liposomal doxorubicin (NPLD) 60 mg/m^2 intravenously (i.v.) plus cyclophosphamide (C) 600 mg/m^2 i.v plus M 1000 mg twice daily) or arm B (NPLD 60 mg/m^2 i.v. plus C 600 mg/m^2 i.v.). Chemotherapy cycles were administered every 21 days for a maximum of 8 cycles. M was administered until disease progression. Staging procedures were performed at baseline a maximum of 28 days before randomization and consisted in contrast-enhanced chest and

abdominopelvic CT scan. Other tests for tumor assessment were performed as clinically indicated. Disease status was monitored every 2 cycles (8 weeks) with the same radiological exams used at baseline.

Anthropometric evaluation and biochemical and hematological laboratory tests were performed at baseline (within 14 days before randomization), before each treatment cycle and every 3 months after the end of treatment. Anthropometric evaluation included assessment of height and weight for body mass index (BMI) calculation and the waist-to-hip circumference ratio (WHR) determined by measuring the waist circumference at the narrowest part of the torso and the hip circumference in a horizontal plane at the level of the maximal extension of the buttocks.

After an overnight fast (> 8 h), blood samples were collected to measure glycaemia, lipidaemia, serum free fatty acid levels, triglycerides, total cholesterol, high and low density lipoprotein, hormones (insulin, C-peptide, norepinephrine, cortisol), inflammatory markers, including those independently associated with insulin resistance or cancer, i.e., C-reactive protein, erythrocyte sedimentation rate, tumor necrosis factor alpha, interleukin-6. A HOMA index ≥ 2.5 was chosen as the cut-off value for insulin resistance based on the results from an Italian-based population study [20].

Outcomes

Progression-free survival (PFS) was calculated from the date of randomization to the date of disease progression, death from any cause, or loss to follow-up, whichever came first. PFS of patients with no events who were lost to follow-up were censored on the date of the last tumor evaluation. Similarly, overall survival (OS) was computed from the day of randomization to the date of death from any cause or loss to follow-up. Response and progression were evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Adverse events were recorded and graded according to the National Cancer Institute (NCI-CTC) common toxicity criteria version 3.0 (CTC 3.0) [21].

Statistical analysis

The primary objective of the study was to compare the efficacy of the combination NPLD plus C plus M with NPLD plus C in HER2-negative MBC in terms of PFS. The study size was estimated using a two-sided log rank test with alfa = 10% and power = 80%. To detect a 4-month increase in the median time to progression, from 6 months in the control arm (arm B) to 10 months in the experimental arm (arm A), corresponding to an hazard ratio (HR) of 0.6, 98 events had to be observed. To this aim, the recruitment of 112 patients was planned over a period of 24 months with a further follow-up of 12 months.

The primary analysis was performed on the intention-to-treat (ITT) population, defined as the population of randomized patients who received at least one dose of the assigned study treatment. The safety population was considered as all the patients in the ITT population. The analysis of ORR was only performed in patients with measurable disease.

Continuous variables were presented as median (interquartile range - IQR) and qualitative variables were presented as absolute or relative frequencies. Median follow-up was measured from random treatment assignment to the date of last follow-up or death for patients alive at the time of cut-off for analysis. Time-to-event data (PFS, OS) were described using the Kaplan–Meier curves and compared with the log-rank test. Ninety-five percent confidence intervals (95% CI) were calculated by non-parametric methods. Estimated HRs and their 95% CI were calculated using univariate and multivariate Cox proportional hazard models. The ORR was calculated with an exact 95% CI using standard methods based on binomial distribution. Evaluation of toxicity was assessed with Cochran-Armitage test for trend.

As planned in the original protocol, the prognostic and predictive role of insulin sensitivity was evaluated by comparing PFS in patients with a HOMA index ≥ 2.5 versus < 2.5, and by introducing the HOMA index as a binary covariate in a Cox model, with PFS as the dependent variable and treatment and HOMA index as covariates. The differential effect of M on PFS was evaluated by testing the interaction between treatment arm and HOMA index.

A multivariate model was fitted to further explore the therapeutic role of M in terms of PFS. One-hundred and twenty-two patients were included in multivariate analyses of PFS and the following covariates were fitted in a multivariate model: age, arm, estrogen receptor status, previous adjuvant chemotherapy, and HOMA index. The differential effect of M in strata defined by these factors was explored in a standard subgroup analysis by testing the interaction between treatment assignment and each of these factors.

Results of subgroup analyses were graphically summarized using a forest plot. The significance of all HRs was evaluated by the log-Likelihood ratio test. No interim efficacy analysis was planned and only the safety of the experimental treatment was monitored throughout the study.

P-values were based on two-sided testing and results were deemed to be significant if $P < 0.05$. As an exploratory analysis, the Fisher exact test was used to evaluate modification in insulin sensitivity status. Statistical analyses were carried out using STATA/MP 15.0 for Windows

(Stata Corp LP, USA). No correction for multiple testing was applied.

Results

Between April 7th 2010 and May 29th 2015, 126 patients were randomized from 16 centers. Four (3%) patients (two from each arm) were excluded from the analysis (two withdrew consent, one did not meet eligibility criteria because of prior chemotherapy for MBC, and one was lost to follow up immediately after randomization). The trial profile is represented in Fig. 1. Patient and disease characteristics were well balanced between the two arms (Table 1). Median age at randomization was 60 years (IQR 51–66). ECOG PS was 0 in 77% of patients. One hundred and six patients (87%) had ER-positive BC, 89 patients (73%) had measurable disease and 78 patients (64%) had visceral involvement. Prior adjuvant anthracyclines were administered in 56 (46%) patients.

After a median follow-up of 39.6 months (IQR 24.6–50.7), 112 (92%) PFS events had been observed, 52 (92%) in arm A and 60 (92%) in arm B. Median PFS was 9.4 (95% CI 7.8–10.4) and 9.9 (95% CI 7.4–11.5) months in arms A and B, respectively (HR 1.09, 95% CI 0.75–1.58, $P=0.653$). PFS curves are shown in Fig. 2. Seventy-one patients had died, 30 (53%) in arm A and 41 (63%) in arm B. Median OS was 34.4 (95% CI 19.3–37.2) and 26.8 (95% CI 19.4–37.9) months, respectively (HR 0.81, 95% CI 0.50–1.30, P = 0.382) (Fig. 3). Eighty-nine patients with measurable disease were evaluable for response. ORR was 48% (95% CI 32.0% − 63.5%) in arm A and 49% (95% CI 34.1% − 63.9%) in arm B ($P=0.901$). In the subgroup analysis (Fig. 4), no significant variation in the effect of M in PFS was observed (all P values for interaction > 0.1).

As expected, neutropenia was the most frequently reported toxicity, with grade (G) 3/4 events occurring in 54% of arm A patients and 72% of arm B patients ($P=0.019$). Febrile neutropenia occurred in one patient in arm A compared to six patients in arm B ($P=0.076$). Other toxicities related to M administration included G2 diarrhea observed in 8% of patients in arm A and 0% in arm B. There was no clinical evidence of cardiotoxicity (New York Heart Association Functional Classification G3/4) in either arm. The most frequent adverse events observed during treatment are reported in Table 2.

Overall, 57 of the 122 evaluable patients were insulin-resistant, as measured by HOMA index ≥ 2.5. When patients with HOMA index ≥ 2.5 were compared with those with HOMA index < 2.5, a significant difference in PFS was observed (HR = 1.51, 95% CI 1.03–2.20, P = 0.034) (Fig. 5). Median OS was 30.8 (95%CI 19.4–41.4) and 27.2 months (95%CI 19.3–37.0) in patients with HOMA index < 2.5 and ≥ 2.5 respectively and, no association between HOMA index and OS was observed (HR = 0.97, 95% CI 0.61–1.55, P = 0.900). The effect of M was similar in patients with HOMA < 2.5 and in those HOMA index ≥ 2.5 both for PFS and for OS (p value for interaction 0.997 and 0.942, respectively). Multivariate PFS analysis revealed that older age (> 50 years) (HR = 1.57, 95% CI 0.99–2.49, $P=0.046$), adjuvant chemotherapy (HR = 1.62,

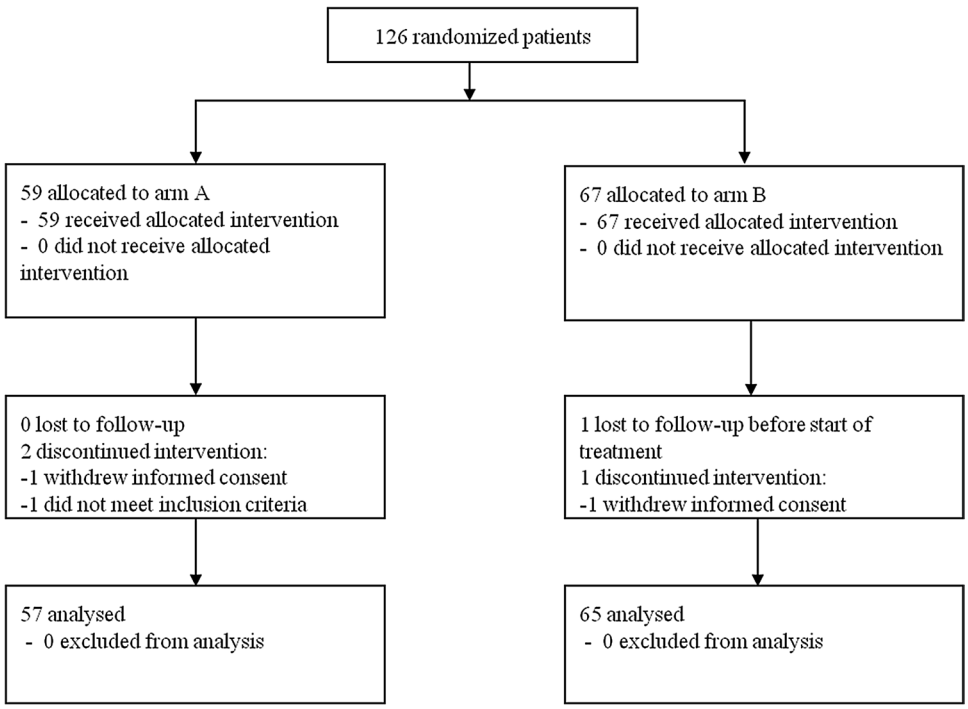

Fig. 1 CONSORT diagram

Table 1 Baseline patient characteristics

	Arm A: NPLD/C/M (*N* = 57) No. (%)	Arm B: NPLD/C (*N* = 65) No. (%)	Overall (*N* = 122) No. (%)
Median age, years (IQR range)	57 (50–68)	61 (54–66)	60 (51–66)
> 50 years	42 (74%)	51 (79%)	93 (76%)
Menopausal status			
Post-menopausal	47 (83%)	53 (82%)	100 (82%)
ER-positive	50 (88%)	56 (86%)	106 (87%)
PgR-positive	44 (77%)	43 (66%)	87 (71%)
ECOG performance status			
0	46 (81%)	48 (74%)	94 (77%)
1	9 (16%)	17 (26%)	26 (21%)
2	2 (4%)	0 (0%)	2 (2%)
Treatment			
Prior adjuvant chemotherapy	38 (67%)	35 (54%)	73 (60%)
Anthracyclines	30 (53%)	26 (40%)	56 (46%)
Prior adjuvant endocrine therapy	39 (68%)	36 (55%)	75 (62%)
Prior endocrine therapy for MBC	17 (30%)	27 (42%)	44 (36%)
Dominant metastatic site			
Bone only	9 (16%)	10 (15%)	19 (16%)
Viscera	37 (65%)	41 (63%)	78 (64%)
Soft tissue	11 (19%)	14 (22%)	25 (21%)
No. of metastatic sites			
1	24 (42%)	15 (23%)	39 (32%)
2	14 (25%)	26 (40%)	40 (33%)
> 2	19 (33%)	24 (37%)	43 (35%)
Measurable disease	42 (74%)	47 (72%)	89 (73%)
Body mass index (BMI)			
< 25	26 (46%)	25 (39%)	51 (42%)
≥ 25 and < 30	17 (30%)	33 (51%)	50 (41%)
> 30	14 (25%)	7 (11%)	21 (17%)
HOMA index			
< 2.5	28 (49%)	37 (57%)	65 (53%)
≥ 2.5	29 (51%)	28 (43%)	57 (47%)

Data are median (IQR) or number of patients (%)

IQR interquartile range, *ER* estrogen receptor, *PgR* progesterone receptor, *ECOG* Eastern Cooperative Oncology Group

95% CI 1.08–2.44, $P = 0.016$), presence of insulin resistance as defined by HOMA index ≥ 2.5 (HR = 1.51, 95% CI 1.02–2.23, $P = 0.037$) and negative estrogen receptor status (HR = 2.56, 95% CI 1.45–4.55, $P = 0.003$), were associated with an increased risk of disease progression.

In an exploratory analysis, the proportion of patients showing a modification in insulin sensitivity during treatment was evaluated in a subset of 100 patients with at least one assessment of the HOMA index after randomization. At baseline there were 23 patients in arm A and 25 in arm B with HOMA index > 2.5. Conversion to insulin sensitivity was observed in 11 (48%) in arm A and in 4 (16%) in arm B ($P = 0.029$). Conversely, 4/22 (18%) patients in arm A and 7/30 (23%) in arm B became insulin-resistant after randomization ($P = 0.741$).

Discussion

This is the first study to evaluate the impact of the addition of M to first-line CT in MBC. Its results indicate that the administration of M did not show any advantage in terms of PFS compared to CT alone. Similarly, no effect was observed in terms of OS. Furthermore, no benefit in PFS was observed in insulin-resistant patients classified by HOMA index ≥ 2.5. This result was unexpected since,

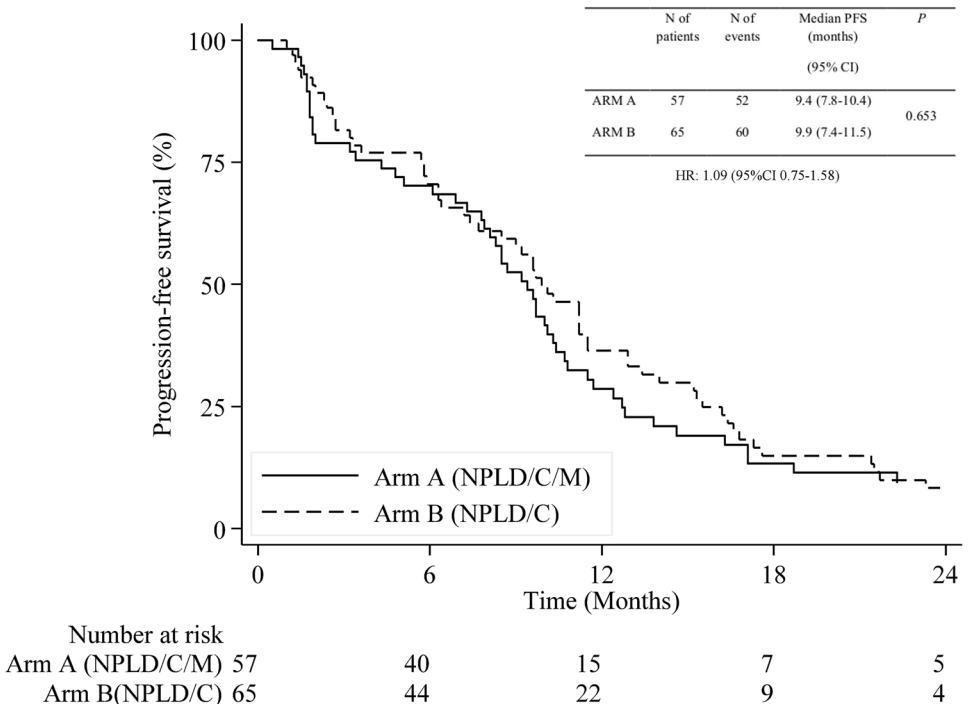

Fig. 2 Kaplan–Meier curves for A progression-free survival by arm

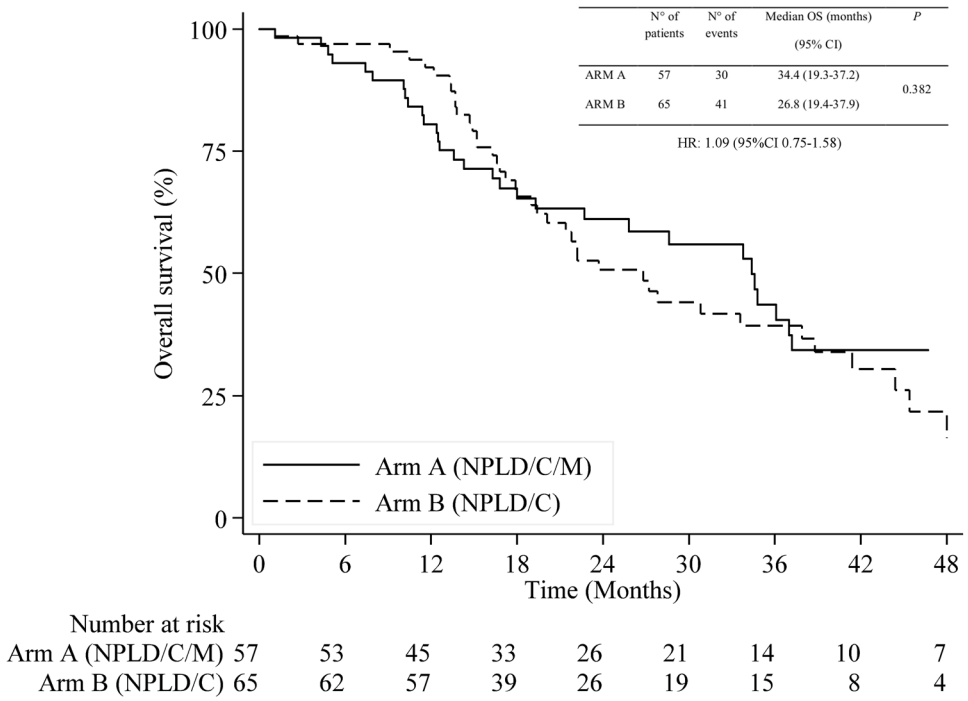

Fig. 3 Kaplan–Meier curves for overall survival by arm

at the time the study was planned, increasing evidence was suggesting that M could retain an anticancer activity either through a direct effect on cancer cell metabolism by AMPK pathway activation or through an indirect effect associated with the host metabolism modulation, especially in insulin-resistant patients.

Of note, this result was consistent with recent findings by our group showing no effect of M on tumor proliferation, measured by Ki-67, in patients with early BC who were candidates for primary surgery [15]. Indeed, a significant interaction between M and HOMA index was detected, especially in luminal B tumors, supporting the hypothesis of an

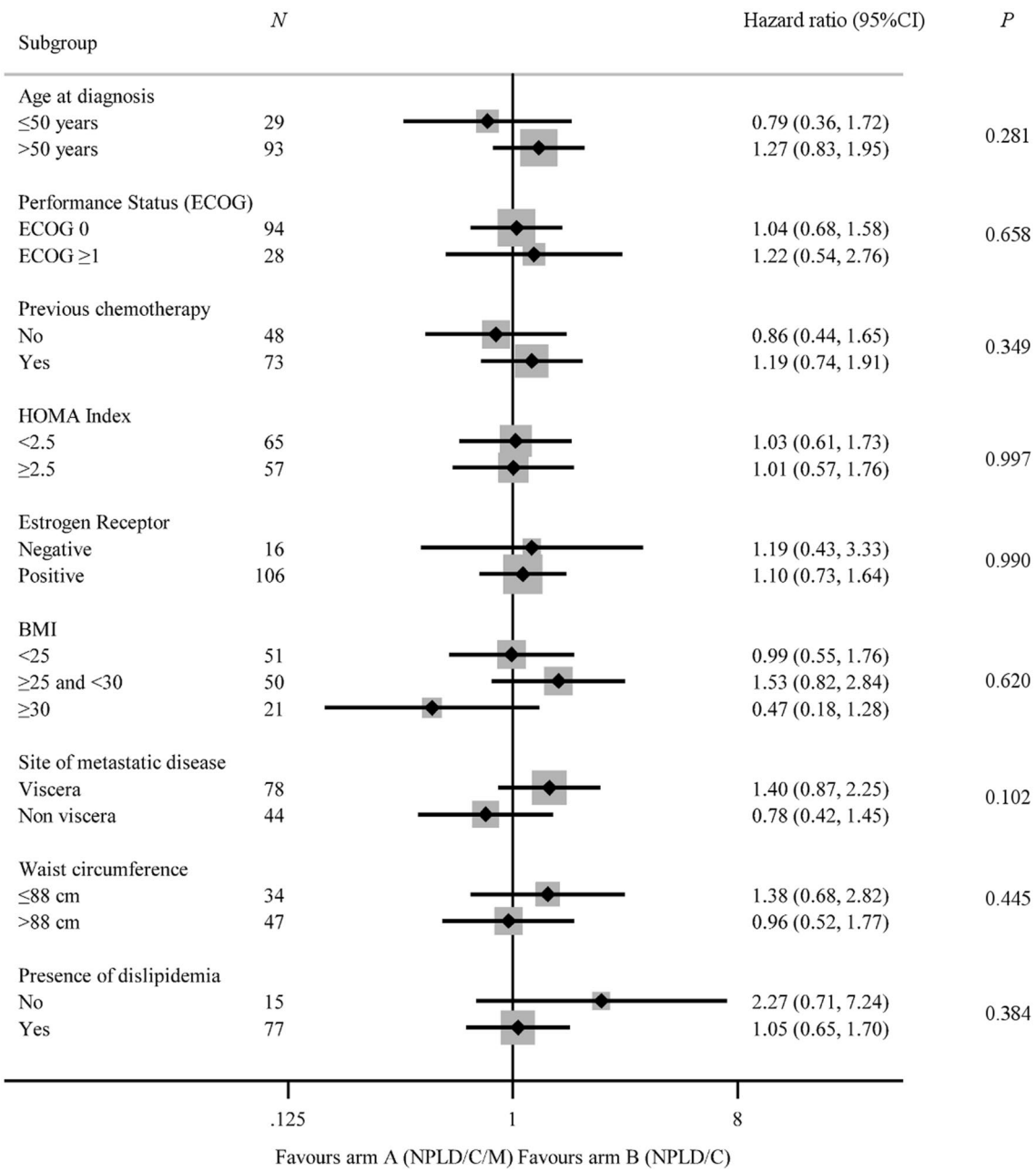

Fig. 4 Subgroup analysis of progression free survival

indirect effect of M in insulin-resistant patients [15]. The present study on advanced BC patients fails to support this hypothesis, suggesting that, in the presence of aggressive tumor load, the potential effect of M on host metabolism is less important in modulating response to chemotherapy.

A strong prognostic effect of insulin sensitivity was observed in our study, with insulin-resistant patients (HOMA index ≥ 2.5) showing a significantly lower PFS compared to non insulin-resistant women, irrespective of the use of M. This association has never been reported before. Several reports suggest a worse prognosis among obese women with ER-positive early BC [22, 23], but the association has not been consistently observed and is not present in early BC patients with rapidly proliferating or triple-negative disease [24–26]. Furthermore, no evidence of an adverse prognostic effect of higher BMI was observed in MBC patients treated with chemotherapy [27]. These findings support the hypothesis that obesity, per se, is not a prognostic factor in BC, whereas evidence linking high plasma insulin levels with adverse BC prognosis suggests that insulin sensitivity may play a key role [6]. In our study, almost one in two M-treated patients with baseline HOMA

Table 2 Adverse events in patients receiving at least one cycle of treatment

	Arm A: NPLD/C/M (*N* = 57) No. (%)			B: NPLD/C (*N* = 65) No. (%)			*P* value
	G0–G1	G2	G3–G4	G0–G1	G2	G3–G4	
Absolute neutrophil count	23 (40%)	3 (5%)	31 (54%)	13 (20%)	5 (8%)	47 (72%)	0.019
Febrile neutropenia	56 (98%)	0 (0%)	1 (2%)	59 (91%)	0 (0%)	6 (9%)	0.076
Anemia	47 (82%)	9 (16%)	1 (2%)	52 (80%)	11 (17%)	2 (3%)	0.654
Thrombocytopenia	51 (89%)	3 (5%)	3 (5%)	60 (92%)	2 (3%)	3 (5%)	0.681
Nausea	38 (67%)	17 (30%)	2 (4%)	51 (78%)	12 (19%)	2 (3%)	0.200
Vomiting	43 (75%)	12 (21%)	2 (4%)	60 (92%)	4 (6%)	1 (2%)	0.019
Fatigue	30 (54%)	22 (39%)	4 (7%)	54 (83%)	7 (11%)	4 (6%)	0.005
Diarrhea	52 (91%)	5 (9%)	0 (0%)	65 (100%)	0 (0%)	0 (0%)	0.014
Mucositis	51 (89%)	5 (9%)	1 (2%)	62 (95%)	3 (5%)	0 (0%)	0.081
Infection	56 (98%)	1 (2%)	0 (0%)	62 (95%)	3 (5%)	0 (0%)	0.376
Alopecia	55 (96%)	1 (2%)	1 (2%)	62 (95%)	2 (3%)	1 (2%)	0.867

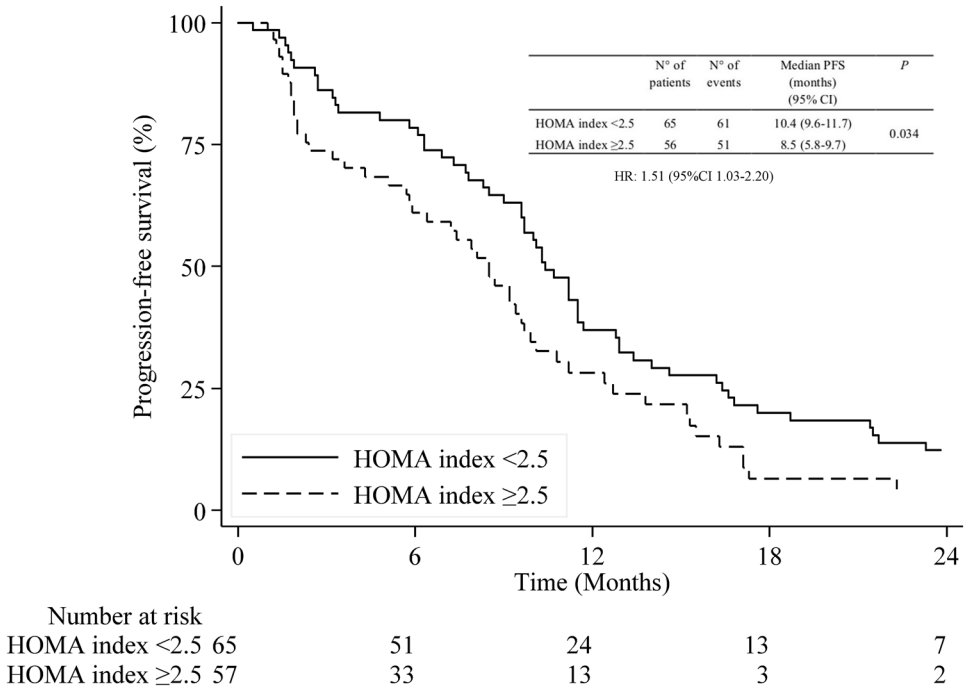

Fig. 5 Kaplan–Meier curves for progression free survival by HOMA index

index ≥ 2.5 became insulin-sensitive compared to one in six in arm B, confirming the strong activity of M on host metabolism, as recently shown in early BC [17]. However, this did not translate into a beneficial effect on PFS or OS in the present study.

An intriguing finding of our study is the significantly decreased incidence of severe neutropenia ($P = 0.019$) and febrile neutropenia ($P = 0.076$) in the M arm. Of note, the incidence of severe neutropenia in the control arm (72%) was in line with that previously reported for the same chemotherapy regimen. The protective effect of M on ^{131}I-induced neutropoenia has also been previously reported in diabetic patients with differentiated thyroid cancer [28]. Thus, confirmation of our finding is needed to evaluate the potential protective properties of M on bone marrow toxicity induced by neutropenic treatments such as chemotherapy and radiotherapy.

Conclusion

In conclusion, the addition of M to first-line chemotherapy in MBC did not provide a meaningful clinical benefit in terms of PFS or OS, but decreased the incidence of severe

neutropenia. Insulin resistance was a strong adverse prognostic factor in MBC and adequate lifestyle interventions should be therefore recommended for patients in both early and advanced disease settings. Randomized trials [17] are ongoing to define whether M-induced changes in insulin sensitivity and host metabolism in early BC are associated with an important clinical benefit.

Acknowledgements We thank all the other investigator involved in the study: Laura Scaltriti (Ospedale di Guastalla), Gianni Michele Turolla (Ospedale Umberto I, Lugo), Claudio Dazzi (Ospedale Civile Santa Maria delle Croci), Laura Cortesi (Arcispedale S. Maria Nuova, Modena), Petros Giovanis (Ospedale S.Martino, Belluno), Silvana Saracchini (Azienda Ospedaliera Santa Maria degli Angeli, Pordenone), Mariangela Ciccarese (Presidio Ospedaliero Vito Fazzi, Lecce), Francesco Carrozza (Azienda Ospedaliera Antonio Cardarelli, Campobasso). We thank all the site personnel, in particular Antonella Spada, Erika Gervasi, Giuliana Drudi, Britt Rudnas, Silvia Coccato, Alessandra Piancastelli and Camilla Di Nunzio.

Author Contributions ON, DA, PB and AG designed and supervised the trial. ADC, AR, AF, AB, LG, FR, LA, LC, SS, PS, LV and DC were responsible for patient recruitment and data collection. FF, ON and PB analyzed the data. The first draft of the manuscript was written by AG, FF PB and ON, and the remaining co-authors subsequently provided valuable input. DA critically reviewed the paper for important intellectual content. All the authors read and approved the final version of the article. The corresponding author assumes responsibility for the completeness and integrity of data, the study fidelity to the protocol, and the statistical analysis. She had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding The MYME study was supported by the Italian Association for Cancer Research (AIRC –IG 2009, Project Number 9239) and TEVA Pharmaceuticals.

Compliance with ethical standards

Conflict of interest AG and DA were consultant for TEVA and DA received a funding from TEVA.

Ethical approval The study was approved by the Ethics Committee of each participating center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice norms and local and national regulatory requirements.

Informed consent Written informed consent was obtained from all patients included in the study.

References

1. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 8(12):915–928
2. Boyd DB (2003) Insulin and cancer. Integr Cancer Ther 2(4):315–329
3. Chitnis MM, Yuen JS, Protheroe AS, Pollak M, Macaulay VM. The type 1 insulin-like growth factor receptor pathway. Clin Cancer Res. 2008 Oct 15; 14(20):6364–6370
4. Belfiore A (2007) The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. Curr Pharm Des 13(7):671–686
5. Pollak M (2008) Targeting insulin and insulin-like growth factor signalling in oncology. Curr Opin Pharmacol 8(4):384–392
6. Goodwin PJ, Ennis M, Pritchard KI et al (2002) Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 20(1):42–51
7. Pollak M, Chapman JW, Sheperd L et al (2006) Insulin resistance, estimated by serum c-peptide level, is associated with reduced event-free survival for postmenopausal women in the NCIC MA14 adjuvant breast cancer trial. J Clin Oncol 24(Suppl.):524
8. Scarpello JH, Howlett HC (2008) Metformin therapy and clinical uses. Diabetes Vasc Dis Res 5(3):157–167
9. Sachdev D, Yee D (2007) Disrupting insulin-like growth factor signaling as a potential cancer therapy. MolCancer Ther 6(1):1–12
10. Nathan DM, Buse JB, Davidson MB et al (2009) Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 52(1):17–30
11. Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346(6):393–403
12. Zakikhani M, Dowling R, Fantus IG et al (2006) Metformin is an AMP kinase dependent growth inhibitor for breast cancer cells. Cancer Res 66(21):10269–10273
13. Gandini S, Puntoni M, Heckman-Stoddard BM et al (2014) Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res 7(9):867–885
14. Gonzalez-Angulo AM, Meric-Bernstam F (2010) Metformin: a therapeutic opportunity in breast cancer. Clin Cancer Res 16(6):1695–1700
15. Bonanni B, Puntoni M, Cazzaniga M et al (2012) Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. J Clin Oncol 30(21):2593–2600
16. Cazzaniga M, Bonanni B, Guerrieri-Gonzaga A et al (2009) Is it time to test metformin in breast cancer clinical trials? Cancer Epidemiol Biomarkers Prev 18(3):701–705
17. Goodwin PJ, Parulekar WR, Gelmon KA et al (2015) Effect of metformin vs placebo on and metabolic factors in NCIC CTG MA.32. J Natl Cancer Inst 107(3):1–8
18. Costelloe CM, Chuang HH, Madewell JE et al (2010) cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. J Cancer 1:80–82
19. Matthews DR, Hosker JP, Rudenski AS et al (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7):412–419
20. Bonora E, Kiechl S, Willeit J et al (1998) Prevalence of insulin resistance in metabolic disorders: The Bruneck Study. Diabetes 47(10):1643–1649
21. Common Terminology Criteria for Adverse Events (CTCAE), version 3.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3. pdf (accessed Jan 5, 2018)
22. Pfeiler G, Königsberg R, Fesl C et al (2011) Impact of body mass index on the efficacy of endocrine therapy in premenopausal patients with breast cancer: an analysis of the prospective ABCSG-12 trial. J Clin Oncol 29(19):2653–2659
23. Sparano JA, Wang M, Zhao F et al (2012) Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer 118:5937–5946
24. Gennari A, Amadori D, Scarpi E et al (2016) Impact of body mass index (BMI) on the prognosis of high-risk early breast cancer

(EBC) patients treated with adjuvant chemotherapy. Breast Cancer Res Treat 159(1):79–86
25. Dawood S, Lei X, Litton JK et al (2012) Impact of body mass index on survival outcome among women with early stage triple-negative breast cancer. Clin Breast Cancer 12(5):364–372
26. Ademuyiwa FO, Groman A, O'Connor T et al (2011) Impact of body mass index on clinical outcomes in triple-negative breast cancer. Cancer 117(18):4132–4140
27. Gennari A, Nanni O, Puntoni M et al (2013) Body mass index and prognosis of metastatic breast cancer patients receiving first-line chemotherapy. Cancer Epidemiol Biomark Prev 22(10):1862–1867
28. Bikas V, Van Nostrand D, Jensen K et al (2016) Metformin attenuates ^{131}I-induced decrease in peripheral blood cells in patients with differentiated thyroid cancer. Thyroid 26(2):280–286

Affiliations

O. Nanni[1] · D. Amadori[2] · A. De Censi[3] · A. Rocca[2] · A. Freschi[4] · A. Bologna[5] · L. Gianni[6] · F. Rosetti[7] · L. Amaducci[8] · L. Cavanna[9] · F. Foca[1] · S. Sarti[2] · P. Serra[1] · L. Valmorri[1] · P. Bruzzi[10] · D. Corradengo[3] · A. Gennari[11] on behalf of MYME investigators

1 Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Piero Maroncelli 40, 47014 Meldola, Italy

2 Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

3 Division of Medical Oncology, EO Ospedali Galliera, Genoa, Italy

4 Department of Medical Oncology, Centro di Riferimento Oncologico (CRO), Aviano, Italy

5 Department of Oncology, Arcispedale S. Maria Nuova IRCCS, Reggio Emilia, Italy

6 Department of Medical Oncology, Ospedale Infermi, Rimini, Italy

7 Department of Medical Oncology, AULSS, n. 13, Mirano, Italy

8 Department of Onco-hematology, Ospedale degli Infermi, Faenza, Italy

9 Department of Oncology, AUSL Piacenza, Piacenza, Italy

10 Azienda Ospedaliera Universitaria San Martino IRCCS, Istituto Nazionale per la Ricerca sul Cancro (IST), Genoa, Italy

11 Division of Oncology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy