Preventing alpelisib-related hyperglycaemia in HR+/HER2−/*PIK3CA*-mutated advanced breast cancer using metformin (METALLICA): a multicentre, open-label, single-arm, phase 2 trial

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Summary

Background Hyperglycaemia is an early and frequent adverse event during alpelisib treatment. METALLICA aimed to evaluate prophylactic metformin to prevent or reduce hyperglycaemia occurrence in patients with HR+/HER2−/*PIK3CA*-mutated advanced breast cancer (ABC).

Methods Between August 13th, 2020 and March 23rd, 2022, this 2-cohort, phase 2, multicentre, single-arm trial (NCT04300790) enrolled patients with HR+/HER2−/PIK3CA-mutated ABC: cohort A, normal glycaemia (fasting plasma glucose <100 mg/dL [<5.6 mmol/L] and HbA1c <5.7%), and cohort B, prediabetes (fasting plasma glucose 100–140 mg/dL [5.6–7.8 mmol/L] and/or haemoglobin A1C [HbA1c] 5.7–6.4%). Participants were at least 18 years old, with Eastern Cooperative Oncology Group performance status of 0–1, and up to two prior lines of endocrine therapy (ET) for ABC. Alpelisib plus ET were administered in 28-day cycles after initiation of prophylactic metformin plus ET. Primary endpoint was the incidence of grade 3–4 hyperglycaemia over the first 8 weeks. Secondary endpoints included safety, progression-free survival (PFS), objective response rate (ORR), and clinical

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benefit rate (CBR). The primary objective for cohort A and B is met with ≤7 (14.6%) and ≤4 (20%) patients with grade 3–4 hyperglycaemia over the first 8 weeks, respectively.

Findings 233 patients were screened, and 68 (20.2%) patients were enrolled in cohorts A (n = 48) and B (n = 20). Median follow-up was 7.8 months (IQR 1.4–19.6). Over the first 8 weeks, one (2.1%) of 48 patients in cohort A (95% CI: 0.5–11.1; $P < 0.0001$), and three (15.0%) of 20 patients in cohort B (95% CI: 5.6–37.8; $P = 0.016$) had grade 3–4 hyperglycaemia. Serious treatment-related adverse events occurred in seven patients (10.3%). The most common were rash (two [2.9%]), vomiting (two [2.9%]), and diarrhoea (two [2.9%]). Discontinuation of alpelisib caused by AEs was reported in nine patients (13.2%), none caused by hyperglycaemia. At data cutoff (15 June, 2022), no treatment-related deaths were observed. In the full analysis set, median PFS was 7.3 months (95% CI: 5.9–not reached), ORR was 20.6% (95% CI: 11.7–32.1%), and CBR was 52.9% (95% CI: 40.4–65.2).

Interpretation In HR+/HER2–/*PIK3CA*-mutated ABC, prophylactic metformin before alpelisib plus endocrine treatment has low incidence and severity of alpelicib-induced hyperglycaemia.

Funding Novartis Pharmaceuticals.

Keywords: Alpelisib; Hyperglycaemia; Prophylactic metformin; HR+/HER2–/*PIK3CA*-mutated advanced breast cancer

Research in context

Evidence before this study

Hyperglycaemia was one of the most frequent adverse events reported in previous studies (SOLAR-1 and BYLieve) using alpelisib plus endocrine therapy (ET) to treat hormone receptor-positive (HR+)/HER2–/PIK3CA-mutated advanced breast cancer (ABC). Grade 3–4 hyperglycaemia occurred in approximately a third of patients in the previous trials and frequently led to treatment discontinuation or dose modifications, which could negatively impact the potential clinical benefit for the patients.

Added value of this study

In METALLICA, the addition of prophylactic metformin to alpelisib plus ET significantly reduced the incidence rate of hyperglycaemia in HR+/HER2–/PIK3CA-mutated ABC patients, both with normal glycaemia or prediabetes status at baseline. No patient discontinued treatment because of hyperglycaemia events. The incidence of diarrhoea was higher in this study (any-grade and grade ≥3) than in SOLAR-1 and BYLieve; however, this was not unexpected, given that metformin is associated with this adverse event.

Implications of all the available evidence

Our findings support the use of prophylactic metformin in HR+/HER2– ABC patients with PIK3CA-mutation who receive alpelisib plus ET, especially in those with prediabetes, to prevent or minimise hyperglycaemia occurrence and, thus, sustain treatment continuation.

Introduction

Breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer deaths among them.[1] Most breast cancer diagnosis are of the hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) type.[2] The treatment landscape for patients with HR+/HER2– advanced breast cancer (ABC) changed with the introduction of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), which significantly improved progression-free survival (PFS) and provided consistent overall survival (OS) benefit when combined with endocrine therapy (ET).[3,4] Accordingly, CDK4/6i plus ET is currently the first-line standard of care.[5–7] However, patients often develop resistance to therapy through various mechanisms, including hyperactivation of the phosphatidylinositol 3-kinase (PI3K) pathway, caused frequently by mutations in *PIK3CA*,[3,8] which occur in approximately a third of patients with HR+/HER2– breast cancer.[9–11]

Patients with HR+/HER2–/*PIK3CA*-mutated ABC can be treated with alpelisib plus fulvestrant after progression on ET.[5–7] Alpelisib is a specific small-molecule inhibitor of the protein PI3K-α, encoded by the gene *PIK3CA*.[12,13] It led to a statistically significant and clinically meaningful PFS benefit when combined with fulvestrant to treat patients with HR+/HER2–/*PIK3CA*-mutated ABC in the pivotal phase 3 SOLAR-1 trial.[14,15] In SOLAR-1, few patients had been previously treated with CDK4/6i, as this was not the standard of care at the time of study recruitment; the phase 2 BYLieve trial demonstrated treatment benefit of alpelisib plus ET in patients who had progressed on or after CDK4/6i-based therapy.[16]

The main concerns regarding alpelisib toxicity profile are hyperglycaemia, diarrhoea, and rash, which are on-target effects that may require dose adjustments and sometimes lead to permanent discontinuation of treatment.[12,13] Specifically, grade 3–4 hyperglycaemia was the most common severe adverse event reported in patients treated with alpelisib plus fulvestrant both in SOLAR-1 (36.6%) and BYLieve cohort A (28.3%). It was frequently managed with metformin,[16,17] a glucose-lowering agent used to treat diabetes and prevent or delay it in patients with prediabetes.[18–20] Metformin, like alpelisib, is associated with diarrhoea.[12,13,21]

It has been previously reported that the prophylactic use of drugs in combination with anti-cancer therapy can decrease the incidence and severity of adverse events and, therefore, reduce treatment discontinuation or dose interruption/reduction.[22,23] Consequently, we hypothesised that prophylactic use of metformin might be useful in reducing hyperglycaemia when treating patients with alpelisib plus ET.[21] We evaluated the efficacy and safety of prophylactic metformin to decrease grade 3 and 4 hyperglycaemia when using alpelisib plus ET to treat patients with HR+/HER2–/*PIK3CA*-mutated ABC and normal fasting plasma glucose (FPG) or prediabetes. Here we present the primary endpoint results of the phase 2 METALLICA trial.

Methods

Study design and participants

METALLICA is an ongoing, single-arm, open-label, phase 2 trial conducted following a Simon's two-stage design across 18 sites in Spain. Eligible patients were the following: men or women aged 18 years or older with *PIK3CA*-mutated, histologically confirmed HR+/HER2– ABC (ABC defined as metastatic disease or loco-regionally recurrent disease not amenable to curative therapy)[24]; with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; with up to two prior lines of ET and up to one prior chemotherapy-containing regimen for ABC; and with adequate hematologic and organ function.

The key exclusion criteria were prior treatment with a PI3K, protein kinase B (AKT), or mammalian target of the rapamycin (mTOR) inhibitor; diagnosis of type I or II diabetes mellitus requiring antidiabetic drugs; lung-specific clinically significant illness within three months prior to study initiation; and Child–Pugh score B or C. Full inclusion and exclusion criteria are available in the protocol (Appendix 1 pp 47–51).

Patients were enrolled into two cohorts according to their glycaemic status: cohort A comprised patients with normal glycaemia (FPG <100 mg/dL and haemoglobin A1C [HbA1c] <5.7%); cohort B comprised patients with glycemic criteria of prediabetes (FPG 100–140 mg/dL and/or HbA1c 5.7%–6.4%). Patients will be followed-up for at least 12 months after the last patient initiates treatment.

Ethics

This study was conducted in compliance with the Declaration of Helsinki and was approved an independent ethics committee at Fundacion of Valencian Institute of Oncology, Valencia, Spain (#10–20). The approval for this study was granted by Spanish Agency for Medicines and Health Products, Madrid, Spain. All patients provided written informed consent at enrolment.

Procedures

All patients were treated with alpelisib plus ET and prophylactic metformin. Alpelisib was administered orally at a starting dose of 300 mg once daily in 28-day cycles. ET chosen by the physician was one of the following: fulvestrant (500 mg, intramuscular injection every two weeks during the first month, and every four weeks thereafter); letrozole (2.5 mg, orally, once daily); or exemestane (25 mg, orally, once daily). Treatment with a luteinising hormone-releasing hormone analogue was required at least one week prior to study entry for men and pre- and peri-menopausal women. Metformin was orally administered at an initial dose of 500 mg twice daily; after three days, if no gastrointestinal intolerance occurred, the dose was increased to 1000 mg twice a day. In the first cycle, metformin and ET were administered one week prior to initiating alpelisib. Patients received study treatment (alpelisib plus ET) until disease progression, unacceptable toxicity, elective withdrawal from the study, death, or study completion (Figure S1).

Glycaemia was monitored combining laboratory assessment of FPG (at screening, days 1 and 8 of cycle 1, and day 1 of every subsequent cycle) and capillary self-monitoring blood glucose (SMBG). SMBG was conducted six times per day on day 8 of cycle 1 and day 1 of cycle 2; four times per day on days 9 and 10 of cycle 1 and days 2 and 3 of cycle 2; and once per day (fasting, before breakfast) on days 11–15 and 21 of cycle 1 and days 4–8, 15, and 21 of cycle 2. Patients were instructed to contact the treating physician if fasting blood glucose levels were ≥160 mg/dL. Complete details on glycaemia monitoring are available in the protocol (Appendix 1 pp 54).

Tumour assessments were conducted every 8 weeks from the first dose of study treatment for the first six months and, thereafter, every 12 weeks until the EoS with computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis following Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 until disease progression, elective withdrawal of consent, loss to follow-up, patient decision, or death. Bone scans were conducted at baseline and, if bone lesions were identified, repeated every 24 weeks. Brain MRI was performed in patients with known brain metastases prior to study initiation and repeated every 12 weeks. CT or MRI of other metastatic sites were performed if clinically indicated. Laboratory tests were

performed on days 1 and 14 of the first two cycles after alpelisib start and on day 1 after alpelisib start of subsequent cycles. Vital signs were assessed on day 1 of every cycle. Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 was used to grade toxicity. In the event of treatment discontinuation, safety and survival follow-up were conducted until loss to follow-up, withdrawal of consent, death, or study termination by the sponsor.

Outcomes

The primary endpoint was the incidence rate of patients who had grade 3–4 hyperglycemia per CTCAE v.4.03, reported as an adverse event with an accompanying grade 3–4 FPG or fasting SMBG value, in the first 8 weeks (two cycles) for cohorts A and B.

Secondary safety endpoints reported here are grade 3–4 hyperglycaemia in patients treated with fulvestrant as the ET partner, any-grade and grade 3–4 adverse events (including hyperglycaemia, diarrhoea, and rash) in all patients per CTCAE v.4.03 until data cutoff, and rate of patients with dose reductions, delays, and discontinuations for alpelisib and metformin until data cutoff. The secondary efficacy endpoints reported here were investigator-assessed PFS, objective response rate (ORR) and clinical benefit rate (CBR), without confirmation criteria, and time to progression (TTP) per RECIST v.1.1. Analysis of other secondary endpoints (grade 3–4 hyperglycaemia by endocrine agent received and safety per CTCAE v.5.0, among others) is underway and will be reported separately. The complete list of endpoints is available in the protocol (Appendix 1 pp 36–38).

Statistics

Safety and efficacy were assessed in all participants in cohorts A and B who received at least one dose of study treatment (full analysis set). The study was based on a Simon's two-stage designed to attain an 80% power with 48 patients enrolled in cohort A (admissible design corrected with a 10% dropout rate) and 20 patients in cohort B (minimax design). The one-sided type I error was 0.05 for each cohort. The overall family wise error was 10%. The analyses for cohort A and B were planned to test the null hypotheses that the true rate (r) of patients with grade 3–4 hyperglycaemia was ≥25% and ≥40%, respectively, over the first 8 weeks. These thresholds were selected based on the hyperglycaemia rates observed in SOLAR-1[14] and BYLieve.[16] The alternative hypotheses for cohorts A and B were a true rate for primary endpoint of at most 10% and 15%, respectively. The rate of patients without hyperglycaemia (100-r) was used to calculate the sample size and to estimate the primary endpoint. Interim analyses were planned with 20 patients for cohort A and 7 patients for cohort B. The study would continue to the second stage if ≤3 (15%) and ≤2 (28.6%) patients with grade 3–4 hyperglycaemia were observed in cohorts A and B, respectively. No patient with grade 3–4 hyperglycemia was observed at interim analysis. The analysis of the primary endpoint was conducted in the full analysis set and in patients treated with fulvestrant as the ET partner. We assumed a 10% drop-out rate for cohort A and the expected sample size (n = 43) was increased to 48 patients; the drop-out rate was not applied in cohort B, given their higher risk of hyperglycaemia. The p-values and 95% CI for primary endpoint analysis were calculated following the method developed by Koyama and Chen.[25] The primary objective for cohort A is met with ≤7 (14.6%) patients with grade 3–4 hyperglycaemia among 48 patients. For cohort B, the primary objective is met with ≤4 (20%) patients with grade 3–4 hyperglycaemia among 20 patients. The sample size was calculated with R software (version 4.2.2) using the function "binom.design" from "ph2mult" package version 0.1.1 or "clinfun" package version 1.1.5 (Appendix 2 p 2).

Safety data were summarised with descriptive statistics in the full analysis set. Safety data describes events up to data cutoff, unless otherwise specified. We used the Kaplan–Meier method to estimate the distribution of PFS; corresponding two-sided 95% CI were calculated using the Brookmeyer and Crowley method ("survival" package version 3.5–7). Clopper-Pearson methodology was used to calculate the two-sided 95% CI for ORR and CBR in the full analysis set and in patients with measurable disease at baseline ("DescTools" package version 0.99.50). The p-values and 95% confidence intervals were not adjusted for multiple comparisons and hence cannot be used to infer treatment effects.

This trial is registered with ClinicalTrials.gov, NCT04300790.

Role of funding source

The study was conceived, designed, and conducted by MEDSIR. Novartis Pharmaceuticals funded the study and provided alpelisib. MEDSIR was responsible for data analysis and interpretation and also funded medical writing support. All authors had access to the raw data, and the corresponding author was responsible for the decision to submit for publication.

Results

Patients characteristics

Between 13 August, 2020 and 23 March, 2022, 233 patients were screened, and 68 (29.2%) patients were enrolled in cohorts A (n = 48) and B (n = 20). Median follow-up at the time of this primary analysis was 7.8 months (range, 1.4–19.6) for all patients, 7.3 months (range, 1.4–19.6) for cohort A, and 8.7 months (range, 1.6–15.6) for cohort B. The median duration of exposure to study treatment was 5.5 months (range, 1.2–19.6) for all patients, 4 months (range, 1.2–19.6) for cohort A, and

6.8 months (range, 1.5–13.8) for cohort B. The median relative dose intensity was 95.1% for alpelisib.

Patient baseline characteristics are shown in Table 1. All enrolled patients were female; median age was 55.0 years (range, 29–79). Visceral metastases were present in 40 (58.8%) of the 68 patients; 13 (19.1%) patients had a prior line of chemotherapy for ABC. Sixty-seven (98.5%) patients had received CDK4/6i therapy previously. Sixty-three (92.6%) patients received fulvestrant as endocrine partner. Four (5.9%) patients received exemestane and one (1.5%) patient was treated with letrozole (Table 1 and Table S1).

At data cutoff (15 Jun, 2022), 33 (48.5%) of 68 patients had discontinued the study treatment (alpelisib and ET) because of disease progression, and seven (10.3%) patients had discontinued for other reasons: three (4.4%) patients presented an adverse event related to alpelisib (hypertransaminasaemia, rash, and hypovolaemic shock); three (4.4%) patients were lost of follow-up, and one (1.5%) patient presented deterioration of her health status (Fig. 1).

Primary endpoint

Cohorts A and B met the primary endpoint, with only one grade 3 hyperglycaemia (2.1%) of 48 patients in cohort A (95% CI: 0.5–11.1; $P < 0.0001$) and three patients with grade 3 hyperglycaemia reported (15.0%) of 20 patients in cohort B (95% CI: 5.6–37.8; $P = 0.016$) in the first 8 weeks (Table 2). In particular, among patients treated with fulvestrant as ET, only one (2.2%) of 45 in cohort A and three (16.7%) of 18 in cohort B presented grade 3 hyperglycaemia reported in the first 8 weeks. Any-grade hyperglycaemia was reported in 30 (44.1%) of 68 patients, 16 (33.3% in cohort A and 14 (70.0%) in cohort B. For post-menopausal patients with fulvestrant as ET the any-grade hyperglycaemia was reported in 12 (37.5%) of 32 patients for cohort A (one [3.2%] grade 3) and 11 (68.8%) of 16 patients in cohort B (two [12.5%] grade 3). In addition to metformin, two (4.2%) of 48 patients in cohort A and 5 (25.0%) of 20 patients in cohort B used other treatments to manage hyperglycaemia (Table S2).

Safety and tolerability

Adverse events of any grade were reported for 67 (98.5%) patients (31 [45.6%] grade ≥3) (Table 3). The most common adverse events of any grade were the following: nausea (47 [69.1%] of 68 patients, all grade 1–2; diarrhoea (46 [67.6%] of 68 patients, nine [13.2%] grade ≥3); fatigue (33 [48.5% of 68 patients, three [4.4] grade ≥3); hyperglycaemia (30 [44.1%] of 68 patients, 4 [5.9%] grade ≥3); and rash (28 [41.2%] of 68 patients, 11 [16.2%] grade ≥3) (Tables S3 and S4). Serious treatment-related adverse events were reported in seven (10.3%) of 68 patients; the most common were rash (two [2.9%], all grade 3), vomiting (two [2.9%], one [1.5%] grade 3), and diarrhoea (two [2.9%], all grade <3) (Table S5). Details on adverse events of special interest are available in the Table S6. Ten (14.7%) of 68 patients (9 [18.8%] of 48 in cohort A and one [5.0%] of 20 in cohort B) had diarrhoea during the first week of treatment, when alpelisib had not been initiated.

Permanent discontinuation of alpelisib because of adverse events occurred in nine (13.2%) patients (Table 3), most frequently from diarrhoea (four [5.9%] patients), fatigue (three [4.4%] patients), decreased appetite (three [4.4%] patients), and rash (one [1.5%] patients). No patients discontinued alpelisib because of hyperglycaemia. No treatment-related deaths were observed. Dose interruptions caused by AEs for alpelisib occurred in 32 (47.1%) patients, most frequently from diarrhoea (14 [20.6%] patients), rash (11 [16.2%] patients), and vomiting (5 [7.4%]. Dose reductions for alpelisib occurred in 21 (30.9%) patients. The most frequent adverse events leading to dose reduction were diarrhoea (10 [14.7%]] patients), rash (seven [10.3%] patients), and hyperglycaemia (4 [5.9%]).

Permanent discontinuation of metformin because of adverse events occurred in 8 (11.8%) patients (Table 3), most frequently from diarrhoea (five [7.4%] patients), nausea (two [2.9%] patients), vomiting (one [1.5%] patient), and diabetes mellitus (one [1.5%] patient). Four (50%) of these 8 patients suffered hyperglycemia after metformin discontinuation. All hyperglycemic events after the metformin discontinuation were of grade 1 or 2. Patients did not receive other medication for hyperglycemia and the alpelisib dose was not modified due to hyperglycemic adverse events after metformin discontinuation.

Dose interruptions caused by AEs for metformin occurred in 12 (17.6%) patients, most frequently from diarrhoea (sevent [10.3%] patients) and vomiting (six [8.8%] patients). Dose reductions for metformin occurred in 25 (36.8%) patients. The most frequent adverse events leading to the dose reduction were diarrhoea (15 [22.1%] patients) and vomiting (eight [11.8%] patients).

Other outcome measures

At data cutoff, PFS was still immature owing to the low event rate (42.6%). The median PFS was 7.3 months (95% CI: 5.9–not reached) (Figure S3). The median TTP was 11.0 months (95% CI: 6.2–not reached). ORR was 20.6% (95% CI: 11.7–32.1) in the full analysis set: 16.7% (95% CI: 7.5–30.2) in cohort A, and 30.0% (95% CI: 11.9–54.3) in cohort B (Appendix 2 p 11). CBR was 52.9% (95% CI: 40.4–65.2) in the full analysis set, 41.7% (95% CI: 27.6–56.8) in cohort A and 80% (95% CI: 56.3–94.3) in cohort B. Regarding patients with measurable disease at baseline (41 [60.3%] of 68 patients), ORR was 34.1% (95% CI: 20.0–50.6) and CBR was 48.8% (95% CI: 32.9–64.9) (Table S7).

Discussion

Hyperglycaemia is a key adverse event during treatment with alpelisib, as it can result in early treatment

Baseline characteristics	Cohort A N = 48	Cohort B N = 20	All patients N = 68
Age; median (min; max), years	52 (29; 79)	55 (42; 79)	55 (29; 79)
ECOG Performance status; n (%)			
0	30 (62.5)	10 (50.0)	40 (58.8)
1	18 (37.5)	10 (50.0)	28 (41.2)
Body mass index; n (%)			
<25 kg/m^2	23 (47.9)	7 (35.0)	30 (44.1)
≥25 kg/m^2 to <30 kg/m^2	21 (43.8)	7 (35.0)	28 (41.2)
≥30 kg/m^2	4 (8.3)	6 (30.0)	10 (14.7)
HbA1c; median (min; max), %	5.3 (4.6; 5.6)	5.8 (5.0; 6.4)	5.4 (4.6; 6.4)
FPG, median (min; max), mg/dL	89.5 (65.0; 99.0)	102.0 (79.0; 133.5)	91.0 (65.0; 133.5)
Number of metastatic organ sites; n (%)			
1	15 (31.2)	7 (35.0)	22 (32.4)
2	24 (50.0)	5 (25.0)	29 (42.6)
≥3	9 (18.8)	8 (40.0)	17 (25.0)
Metastatic site; n (%)			
Bone	41 (85.4)	17 (85.0)	58 (85.3)
Liver	24 (45.0)	9 (45.0)	33 (48.5)
Lung	7 (14.6)	5 (25.0)	12 (17.6)
Lymph node	8 (16.7)	5 (25.0)	13 (19.1)
Breast	6 (12.5)	1 (5.0)	7 (10.3)
Skin	2 (4.2)	1 (5.0)	3 (4.4)
Menopausal status; n (%)			
Premenopausal	13 (27.1)	2 (10.0)	15 (22.1)
Postmenopausal	35 (72.9)	18 (90.0)	53 (77.9)
Prior CDK4/6 inhibitors at any time; n (%)			
No	0 (0.0)	1 (5.0)	1 (1.5)
Yes	48 (100)	19 (95.0)	67 (98.5)
Number of previous lines of therapy for ABC; n (%)			
0	0 (0.0)	1 (5.0)	1 (1.5)
1	26 (54.2)	8 (40.0)	34 (50.0)
2	15 (31.2)	9 (45.0)	24 (35.3)
3	7 (14.6)	2 (10.0)	9 (13.2)
Previous systematic therapy for ABC; n (%)			
Endocrine therapy	48 (100)	19 (95)	67 (98.5)
Aromatase inhibitors	43 (89.6)	16 (80.0)	59 (86.8)
LHRH	13 (27.1)	4 (20.0)	17 (25.0)
SERD	7 (14.6)	3 (15.0)	10 (14.7)
Tamoxifen	2 (4.2)	0 (0.0)	2 (2.9)
Chemotherapy	9 (18.8)	4 (20.0)	13 (19.1)
Endocrine therapy received with alpelisib			
Fulvestrant	45 (93.8)	18 (90.0)	63 (92.6)
Exemestane	3 (6.3)	1 (5.0)	4 (5.9)
Letrozole	0 (0.0)	1 (5.0)	1 (1.5)

[a]Negative HER2 status was defined by 0 or 1+ by IHC, or by 2+ IHC and negative ISH.
ABC, advanced breast cancer; FPG, fasting plasma glucose; HbA1c, haemoglobin A1C; HER2, human epidermal growth factor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LHRH, luteinizing hormone-releasing hormone; *PIK3CA*, phosphatidylinotisol-4,5-biphosphate 3-kinase catalytic subunit alpha; SERD, selective oestrogen receptor modulators. Percentages may not total 100% due to rounding.

Table 1: **Baseline characteristics of HR+/HER2-/*PIK3CA*-mutated ABC patients.**[a]

discontinuation and dose adjustments. METALLICA is the first prospective study to evaluate prevention of a key toxicity related to alpelisib. The primary endpoint was met in cohorts A and B, confirming that prophylactic metformin is effective in preventing or reducing the incidence of grade 3–4 hyperglycaemia during the first 8 weeks in patients with HR+/HER2–/*PIK3CA*-mutated ABC treated with alpelisib plus ET (fulvestrant, letrozole, or exemestane). This preventive effect of metformin was also observed in patients specifically receiving

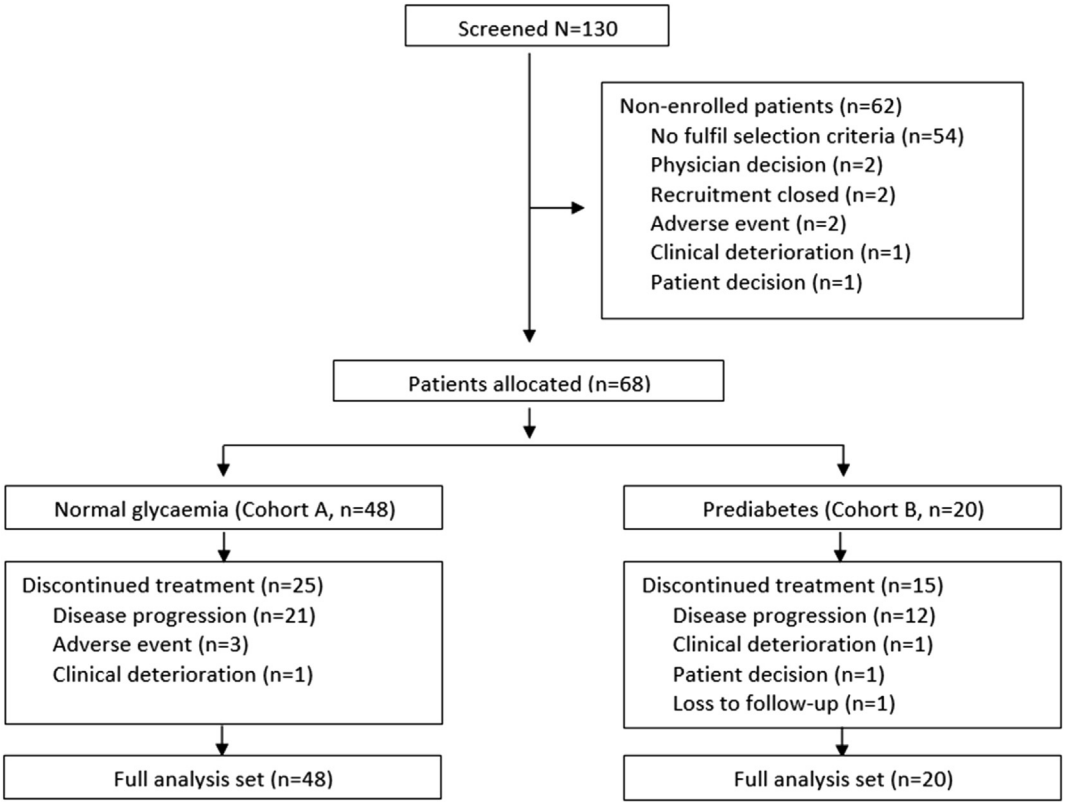

Fig. 1: **Patient enrolment and disposition at data cutoff**. Cohort A: Fasting plasma glucose <100 mg/dL [<5.6 mmol/L] and haemoglobin A1c <5.7%; Cohort B: Fasting plasma glucose 100–140 mg/dL [5.6–7.8 mmol/L] and/or haemoglobin A1c 5.7–6.4%.

fulvestrant (92.6%), which was the sole ET used in both SOLAR-1[14] and BYLieve (cohort A).[16]

SOLAR-1[14] was the first and only phase 3 trial to evaluate alpelisib plus fulvestrant in patients with HR+/HER2–/*PIK3CA*-mutated ABC; since then, BYLieve (cohort A)[16] has explored this combination in patients who have received prior CDK4/6i. The baseline characteristics of patients in METALLICA are similar to those of patients in BYLieve[16] and different from those of SOLAR-1 regarding previous use of CDK4/6i.[14] Patients in METALLICA are more pre-treated and have worse diagnosis compared to SOLAR-1. Hyperglycaemia of grade 3–4 was the most common severe adverse event reported in SOLAR-1 and BYLieve trials. Until data cutoff, the incidence rates of any-grade and grade 3–4 hyperglycaemia in all patients were lower in METALLICA (44.1% and 5.9%, respectively) than in SOLAR-1 (63.7% and 36.6%)[14] and BYLieve (cohort A) (58.3% and 28.3%) trials.[16] In SOLAR-1[17] and BYLieve,[16] patients with normal baseline glycaemic status

Hyperglycaemia	Cohort A n (%) N = 48	Cohort B n (%) N = 20	All patients n (%) N = 68
No hyperglycaemia	35 (72.9)	7 (35.0)	42 (61.8)
Grade 1	10 (20.8)	3 (15.0)	13 (19.1)
Grade 2	2 (4.2)	7 (35.0)	9 (13.2)
Grade 3	1 (2.1)	3 (15.0)	4 (5.9)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Primary endpoint:			
Grade 3-4	1 (2.1)	3 (15.0)	4 (5.9)
95% CI, P-value	(0.5–11.1; P < 0.0001)	(5.6–37.8; P = 0.016)	(2.4–14.4)

At data cutoff, there were no new patients with grade 3-4 hyperglycaemia. Percentages may not total 100% due to rounding. P-values for all patients are not reported, since it was not a predefined primary objective of the protocol. Only the comparison between the study data and historical estimation for cohorts A and B was planned.

Table 2: **Hyperglycaemia over the first 8 weeks of treatment (two cycles).**

Adverse event leading to discontinuation	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
For alpelisib			
Any adverse event, n (%)	4 (5.9)	4 (5.9)	1 (1.5)
Diarrhoea[a]	3 (4.4)	1 (1.5)	0 (0)
Fatigue	2 (2.9)	1 (1.5)	0 (0)
Decreased appetite	1 (1.5)	1 (1.5)	0 (0)
Rash[a]	0 (0.0)	1 (1.5)	0 (0)
Hypovolaemic shock	0 (0.0)	0 (0)	1 (1.5)
Hypertransaminasaemia	0 (0.0)	1 (1.5)	0 (0)
Dysphagia	0 (0.0)	1 (1.5)	0 (0)
Lipase increase	0 (0.0)	1 (1.5)	0 (0)
Odynophagia	0 (0.0)	1 (1.5)	0 (0)
Gastrointestinal pain	1 (1.5)	0 (0)	0 (0)
Pyrexia	1 (1.5)	0 (0)	0 (0)
Stomatitis	1 (1.5)	0 (0)	0 (0)
Vomiting projectile	1 (1.5)	0 (0)	0 (0)
For metformin			
Any adverse event, n (%)	8 (11.8)	0 (0)	0 (0)
Diarrhoea[a]	5 (7.4)	0 (0)	0 (0)
Nausea	2 (2.9)	0 (0)	0 (0)
Vomiting	1 (1.5)	0 (0)	0 (0)
Diabetes mellitus	1 (1.5)	0 (0)	0 (0)

Maximum toxicity grade for each adverse event was reported. Percentages may not total 100% due to rounding. [a]Adverse event of special interest.

Table 3: **Adverse events leading to discontinuation of alpelisib or metformin (N = 68).**

experienced any-grade hyperglycaemia less frequently than prediabetic or well-controlled diabetic patients, especialy grade 3–4 hyperglycaemia. We also observed this distribution pattern in METALLICA between patients with normal glycaemia and those with prediabetes regarding any-grade and grade 3–4 hyperglycaemia. Moreover, no patients discontinued alpelisib owing to hyperglycaemia, whereas 6.3% and 1.6% of patients discontinued alpelisib for this reason in SOLAR-1 and BYLieve, respectively. Our findings support changes in current clinical practice for patients who could benefit from adding prophylactic metformin to alpelisib plus ET to decrease the incidence and severity of alpelisib-related hyperglycaemia, an adverse event that leads to treatment discontinuations and/or dose adjustments.[16]

Diarrhoea is a common adverse event with metformin and alpelisib. In the first week of treatment, when patients were receiving metformin and not yet alpelisib, diarrhoea was reported in 14.7% of patients. Overall, 67.6% of patients experienced any-grade and 11.8% grade 3–4 diarrhoea; these rates are higher than those of 57.7% and 6.7% in SOLAR-1, and 59.8% and 5.5% in BYLieve trials. Discontinuations of alpelisib due to diarrhoea (5.9% of patients) were also more frequent than in SOLAR-1 (2.8%). While all patients in our study were treated with metformin, approximately two-thirds of patients with hyperglycaemia received metformin in the other studies,[14,16] which may explain the higher diarrhoea rates in METALLICA. Considering the potential benefits of prophylactic loperamide, which may include a reduction in the frequency and severity of diarrhoea, it could be worthy to explore its role in improving patient comfort, enhancing treatment regimen adherence and minimizing treatment interruptions. Nevertheless, it's important to note that further clinical evidence is required to substantiate these potential advantages.

Dose interruptions and dose reductions of alpelisib were lower in METALLICA (47.1% and 30.9%, respectively) than in SOLAR-1 (74.0% and 63.9%).[14] A post-hoc analysis revealed that higher doses of alpelisib resulted in numerically longer median PFS,[17] which sheds light on the importance of adverse event management to maximise treatment benefit. In METALLICA, 13.2% of patients experienced adverse events leading to alpelisib treatment discontinuation, a lower rate to that in SOLAR-1[14] (25.0%) and BYLieve (20.6%) trials.[16] Patients with prior CDK4/6i have poorer response and shorter median PFS than patients with no prior CDK4/6i; in our study, median PFS was 7.3 months (95% CI: 5.9–not reached), similar to that found in BYLieve cohort A[16] (7.3 months [95% CI: 5.6–8.3]), where all patients had received prior CDK4/6i plus ET; however, as expected, median PFS was shorter than that found in SOLAR-1[14] (11.0 months [95% CI: 7.5–14.5]), where the majority of patients had not received prior CDK4/6i. Given the similar patient population in METALLICA and BYLieve (cohort A) trials,[16] these results suggest the addition

of metformin improves safety without compromising efficacy of the preferred treatment for patients with HR+/HER2–/*PIK3CA*-mutated ABC.

One limitation of this study is the non-randomised single-arm design; data from SOLAR-1 and BYLieve were used to benchmark the incidence of hyperglycaemia within the first 8 weeks of treatment with alpelisib plus ET. Another limitation is the 8-week timeframe used to evaluate the primary endpoint, which can potentially miss events that occur at a later point; however, hyperglycaemia is an early occurring event, with a median time to onset of grade ≥3 events taking place in the first 15 days in SOLAR-1.[17] The major strength of this study lies in its detailed assessment of adverse events and its inclusion of high risk patients, which are often excluded from breast cancer clinical trials when PI3K signalling pathway inhibitors are explored. Moreover, the negative impact of diarrhoea was palliated by pre-treating patients with metformin and ET for one week before initiating alpelisib to ensure patients were adapted to metformin so as to maximise its prophylactic efficacy. Finally, hyperglycaemia was exhaustively monitored using a number of approaches with multiple timepoints per day on certain days over the first 8 weeks of treatment with alpelisib plus ET; this is a more robust schedule than that used in SOLAR-1 and BYLieve, ensuring no hyperglycaemia events were unaccounted for. On the basis of these data, exploring the role of prophylactic metformin in diabetic patients is warranted.

Management of patients with ABC focuses on prolonging survival while minimising treatment-related adverse events. Here, we provide compelling evidence supporting the addition of metformin to alpelisib plus ET as a practical management strategy to limit hyperglycaemia and minimise treatment discontinuation. This enables patients to receive the optimal treatment dose and, ultimately, maximise clinical benefit. As observed, prophylactic metformin is particularly efficient for patients with high-risk prediabetic status.

Contributors

Conception and design: ALC, JMPG, FGP, JC.
Data analysis: DA, MSC.
DA and MSC have verified the underlying data.
Data interpretation: All authors.
Manuscript writing and review: All authors.
Final approval of manuscript: All authors.
All authors read and approved the final version of the manuscript.

Data sharing statement

Data collected within the METALLICA study will be made available to researchers, upon approval by the METALLICA trial management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes, and the trial protocol, will be provided after completion of a data sharing agreement that will be set up by the study sponsor. The data will be made available two years after publication. Please address requests for data to ALC.

Declaration of interests

ALC reports research support from Roche, Agendia, Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Gilead, and Daichii-Sanyo; a consulting or advisory role with Lilly, Roche, Pfizer, and Novartis. Speakers' bureaus for Lilly, AstraZeneca, Merck Sharp & Dohme; travel support from Roche, Pfizer, AstraZeneca; and stock or other ownership in MEDSIR and Initia-Research.

JMPG reports a consulting or advisory role with Lilly, Roche, Eisai, Daichii Sankyo, AstraZeneca, Seattle Genetics; and employment at MEDSIR.

MRB reports research support and participating in an advisory board of Novartis.

PT reports a consulting or advisory role with AstraZeneca, Daiichi-Sankyo, Novartis and Seagen. Speakers' bureaus for Pfizer, Novartis, Lilly, AstraZeneca, Daiichi-Sankyo and Seagen.

IB reports grants and research support to the Institution: AstraZeneca, Lilly, Pfizer and Roche; honoraria and advisor colaboration: AstraZeneca, Roche, Novartis, Eisai, Celgene, Pfizer, Lilly, Pierre-Fabre, Bristol-Myers Squibb, Daiichi Sankyo, Grünenthal, Seagen and Veracyte and support for attending meetings and/or travel: AstraZeneca, Roche, Novartis, Pfizer, Lilly, Pierre-Fabre, Bristol-Myers Squibb and Daiichi Sankyo.

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AFO reports travel support from Novartis.

CS reports research support, consulting or advisory role from Genentech, AstraZeneca, Aragon Pharmaceuticals, Bayer Pharma, Byondis, Boehringer Ingelheim, Bristol-Myers Squibb, Cytomx Therapeutics, Daiichi Sankyo, F. Hoffmann-La Roche, Eisai, Genomic Health, GlaxoSmithKline, Innoup Farma, Eli Lilly, Macrogenics, Menarini Ricerche, Merck Sharp & Dohme, Merus, Millennium Pharmaceuticals, Novartis, Pfizer, Pierre Fabre, PintPharma, Puma Biotechnology, Sanofi, Seattle Genetics, Zymeworks.

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EG reports honoraria from Roche/Genentech, Pfizer, Novartis, AstraZeneca, Seagen; a consulting or advisory role with AstraZeneca, Seagen, PharmaMar, Gilead Sciences; and speakers' bureaus for Pfizer, Novartis, Roche.

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EC reports consultancy and speakers' bureaus for Novartis, Pfizer, Roche, Lilly, Celgene; and personal fees from Novartis, Pfizer, Roche, Lilly, Celgene, during the conduct of the study.

JFC reports honoraria from Roche, AstraZeneca, Teva, Celgene, Pfizer, GSK, Novartis; and a consulting or advisory role with Roche, AstraZeneca, Pfizer, GSK, Novartis.

MSC reports advisory Board of MEDSIR, Optimapharm; Speaker's Bureau in MEDSIR, Optimapharm; and Funding from MEDSIR, Optimapharm, FGP has taken part in advisory panels for Sanofi and Novo Nordisk; has received research support from Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals and Lilly; and has acted as a speaker for Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Co. and Lilly.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102520.

References

1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72:7–33.
2 *Surveillance epidemiology and end results (SEER) program. Incidence and mortality - SEER research data, 8 registries, Nov 2021 sub (1975-2019)*. 2022.
3 Roberto M, Astone A, Botticelli A, et al. Cdk4/6 inhibitor treatments in patients with hormone receptor positive, her2 negative advanced breast cancer: potential molecular mechanisms, clinical implications and future perspectives. *Cancers (Basel)*. 2021;13:1–20.
4 Nabieva N, Fasching PA. Endocrine treatment for breast cancer patients revisited—history, standard of care, and possibilities of improvement. *Cancers (Basel)*. 2021;13:5643. https://doi.org/10.3390/cancers13225643.
5 Gennari A, André F, Barrios CH, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32:1475–1495.
6 Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31:1623–1649.
7 National Comprehensive Cancer Network. *NCCN guidelines: breast cancer v4 2022*. 2022.
8 Miller TW, Rexer BN, Garrett JT, Arteaga CL. Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. *Breast Cancer Res*. 2011;13:224. https://doi.org/10.1186/bcr3039.
9 Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. *Ann Oncol*. 2020;31(3):377–386. https://doi.org/10.1016/j.annonc.2019.11.006.
10 Koboldt DC, Fulton RS, McLellan MD, et al. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490:61–70.
11 Anderson EJ, Mollon LE, Dean JL, et al. A systematic review of the prevalence and diagnostic workup of PIK3CA mutations in HR+/HER2- metastatic breast cancer. *Int J Breast Cancer*. 2020;2020:3759179. https://doi.org/10.1155/2020/3759179.
12 *PIQRAY® (alpelisib) [package insert]*. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022; 2022.
13 Novartis Europharm Limited. *PIQRAY® (alpelisib) SmPC*; 2020. https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf. Accessed October 14, 2022.
14 André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA -mutated, hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2019;380:1929–1940.
15 André F, Ciruelos EM, Juric D, 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;32:208–217.
16 Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol*. 2021;22:489–498.
17 Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Ann Oncol*. 2020;31:1001–1010.
18 Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetologia*. 2022;65:1925–1966.
19 American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45:S125–S143.
20 American Diabetes Association Professional Practice Committee. 3. Prevention or delay of type 2 diabetes and associated comorbidities: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45:S39–S45.
21 Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. *Diabetologia*. 2017;60:1586–1593.
22 Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol*. 2017;18:654–662.
23 Zhang J, Gao HF, Yang C, et al. Prevention of taxane-associated acute pain syndrome with etoricoxib for patients with breast cancer: a phase II randomised trial. *Eur J Cancer*. 2022;171:150–160.
24 Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014;25:1871–1888.
25 Koyama T, Chen H. Proper inference from Simon's two-stage designs. *Stat Med*. 2008;27:3145–3154.