Metformin in the Prevention of Hyperglycemia in Patients with PIK3CA-mutated, Hormone Receptor (HR)[+]/HER2[–] Advanced Breast Cancer Treated with Alpelisib plus Fulvestrant: METALLICA Study


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BACKGROUND

Endocrine therapy is the gold standard approach for patients with hormone-receptor [+] breast cancer (ABC) in the absence of metastatic disease. In the last few years, the combination of non steroidal aromatase inhibitor (AI) with a cyclin-dependent kinase (CDK) 4/6 inhibitor –palbociclib, ribociclib, and abemaciclib– achieved significant improvements in median progression-free survival (PFS) from 14.5–16.5 to 21.3–28.2 months, with hazard ratios (HR) ranging between 0.48 and 0.51.1

Alpelisib (DCS) is an allosteric, ATP-competitive specific AKT inhibitor that has shown to increase the response of endocrine therapies when combined with endocrine-naive and metformin in pts with PIK3CA-mutated, HR(+/–)-HER2[–] ABC who had failed on an aromatase inhibitor regimen.2

Hyperglycemia (HG) is an on-target effect of the PIK3CA inhibition, being the most frequent adverse event (AE) of grade 3/4–5 the most common. All leading to discontinuation of alpelisib in the randomized, phase 3 SALES study.3 Alpelisib is approved to treat ABC in pts with diabetes mellitus (DM) and represented the preferred option for alpelisib-induced HG in the study 4 for treatment.

METALLICA study is evaluating the effect of metformin in the prevention of HG in pts with PIK3CA-mutated, HR[+/–]-HER2[–] ABC under treatment with alpelisib plus fulvestrant.

OBJECTIVES

SECONDARY OBJECTIVES

Efficacy

• To evaluate the clinical efficacy per RECIST v1.1—v treatment of progression-free survival, response rate (RR), disease control rate (DCR), overall response rate (ORR), clinical benefit rate of combining alpelisib, fulvestrant, and metformin in pts of both cohorts.
• To define the rate of pts with G3–4 AEs according to CTCAE v4.0
• To evaluate the safety and tolerability of the combination of alpelisib, fulvestrant, and metformin.

Safely

• To assess the rate of pts with G3–4 HG as per CTCAE v4.0 over the first 2 cycles of treatment with alpelisib plus fulvestrant, and metformin in pts with HR(+/–) ABC; PIK3CA-mutated ABC, with either normal fasting glycaemia and HbA1c (cohorts A or B), or with high-risk criteria (cohorts B).

TRIAL DESIGN

• This is a prospective, multicenter, open-label, two-cohort, Simon’s two-stage design, phase II trial

• The cohort A will receive PIK3CA-mutated, HR(+/–)-HER2[–] ABC pts with fasting plasma glucose (FPG) ≥110 mg/dL (5.6 mmol/L) and glycosylated hemoglobin (HbA1c) ≥5.7% in the SALES study.

• The cohort B will receive PIK3CA-mutated, HR(+/–)-HER2[–] ABC pts with FPG 110–160 mg/dL (5.6–7.8 mmol/L) or HbA1c 5.7–6.4%.

• Pts will receive the combination of metformin, fulvestrant, and alpelisib (FVS) until progression of disease, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

• Patients should be started on metformin plus fulvestrant within 7 days (on Cycle 1 Day 1) prior to start on alpelisib (FVS) (on Cycle 1 Day 8).

• Lavenderising hormone-releasing hormone [LHRH] analogue therapy for men and premenopausal women will be given 1 week prior to one week start of treatment.

• Major Exclusion Criteria

• Prior to male pts in >10 years of age.
• E[2] and/or progestosterone receptor [E[2] and HER2[–] ABC not amenable to curative treatment.
• PIK3CA mutation on tissue or circulating tumor DNA (ctDNA).
• ≤3 prior line of endocrine therapy for ABC, or progression on, or ≥6 months from completion of a [progressively Advanced] regimen.
• ≤3 prior chemotherapy-containing regimen for ABC.

• Major Inclusion Criteria

• Prior to male pts in >10 years of age.
• E[2] and/or progestosterone receptor [E[2] and HER2[–] ABC not amenable to curative treatment.
• Established diagnosis of type 1 or 2 DM requiring anti-diabetic regimen. Patients eligible in the cohort B if anti-diabetic drugs were received in the last 180 days.

• Clinically significant uncontrolled heart disease and/or recent cardiac events.
• Inflammatory breast cancer at screening.

• Fulvestrant (FVS) study.

• Urol OD, unacceptable toxicity or study withdrawal

BIBLIOGRAPHY

TO TRIAL ENROLLMENT

• The METALLICA study is open and currently recruiting in 18 institutions in Spain.
• A total of 16 pts have already been recruited: of them, 3 and 7 pts in the cohort A and B, respectively.

SAMPLE SIZE

• HD ≥25% and HS ≥15% rate of pts with G3–4 HG.
• Futility stop at interim analysis: ≤1/2 evaluable pts with G3–4 HG.
• Positive finding at final analysis: ≤4/5 evaluable pts with G3–4 HG.
• A sample size of 20 pts is needed to attain 80% power at nominal level of one-sided alpha of 0.05.

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TO TRIAL ENROLLMENT


ACKNOWLEDGEMENTS

The METALLICA trial is extremely grateful to all the pts and their families. We gratefully acknowledge all the staff of the participating sites, the trial unit staff at MEDSIR, and Novartis Farmafarmacia S.A...