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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 (pts) with hormone-receptor (HR)[+]/human epidermal growth factor receptor 2 (HER2)[–] advanced breast cancer (ABC) in the absence of visceral crisis. In the last few years, the combination of non-steroidal aromatase inhibitor (AI) with a cyclin-dependent kinase (CDK)4/6 agent –palbociclib, ribociclib, and abemaciclib– achieved impressive increments in median progression-free survival (PFS) from 14.5–16.0 to 25.3–28.2 months, with hazard ratios (HRs) ranging between 0.54 and 0.58.[1–3]
- Around 40% of pts with luminal breast cancers harbor PI3K catalytic subunits p110α (*PIK3CA*) mutations[4]. Alpelisib is an α-specific PI3K inhibitor, that has shown to significantly increase the median PFS when combined with fulvestrant in pts with *PIK3CA*-mutated, HR[+]/HER2[–] ABC who had failed on an aromatase inhibitor regimen.[5]
- Hyperglycemia (HG) is an on-target effect of the PI3K inhibition, being the most frequent adverse event (AE) of grade (G)3–4 and the most common AE leading to discontinuation of alpelisib in the randomized, phase 3 SOLAR-1 study.[6] Metformin is approved for pts with diabetes mellitus (DM) and represented the preferred option for treating alpelisib-induced HG in the SOLAR-1 study.[6]
- 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

PRIMARY OBJECTIVE

- To assess the rate of pts with G3–4 HG as per CTCAE v4.03 over the first 2 cycles of treatment with alpelisib plus fulvestrant, and metformin in pts with HR[+]/HER2[-], *PIK3CA*-mutated ABC, with either normal fasting glycemia and HbA1c (cohort A), or with high-risk criteria (cohort B).

SECONDARY OBJECTIVES

Efficacy

- To evaluate the clinical efficacy as per RECIST v1.1 –in terms of progression-free survival, overall response rate, time to progression, clinical benefit rate– of combining alpelisib, fulvestrant, and metformin in pts of both cohorts.

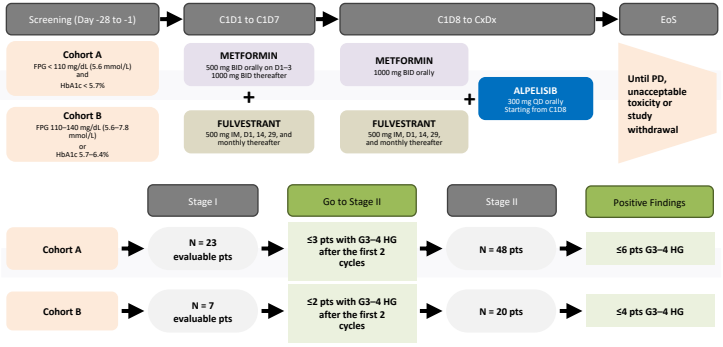
Safety

- To define the rate of pts with G3–4 AEs according to CTCAE v4.03.
- To evaluate the safety and tolerability of the combination of alpelisib, fulvestrant, and metformin.

TRIAL DESIGN

- This is a prospective, multicenter, open-label, two-cohort, Simon's two-stage design, phase II trial.
- The cohort A will recruit *PIK3CA*-mutated, HR[+]/HER2[–] ABC pts with fasting plasma glucose (FPG) < 110 mg/dL (5.6 mmol/L) and glycosylated hemoglobin (HbA1c) < 5.7%.
- The cohort B will recruit *PIK3CA*-mutated, HR[+]/HER2[–] ABC pts with FPG 110–140 mg/dL (5.6–7.8 mmol/L) or HbA1c 5.7–6.4%.
- Pts will receive the combination of metformin, fulvestrant, and alpelisib (BYL719) 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 (BYL719) (on Cycle 1 Day 8).
- Luteinizing hormone-releasing hormone (LHRH) analogue therapy for men and premenopausal women will be given at least one week prior to start treatment.

METALLICA Study Design



Abbreviations

BID: Twice a day; C: Cycle; D: Day; EoS: End of study; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; HG: Hyperglycemia; IM: intramuscular injection; PD: Progressive disease; Pts: Patients; QD: One a day.

Major Inclusion Criteria

- Male or female pts ≥ 18 years of age.
- ER[+] and/or progesterone receptor PgR[+] and HER2[–] ABC not amenable to curative treatment.
- *PIK3CA* mutation on tissue or circulating tumor DNA (ctDNA).
- ≥1 prior line of endocrine therapy for ABC, or progression on, or ≤12 months from completion of a (neo)adjuvant AI-based regimen.
- ≤1 prior chemotherapy-containing regimen for ABC.

Major Exclusion Criteria

- Prior treatment with a PI3K, mTOR, AKT inhibitor or metformin (prior treatment with a CDK4/6 inhibitor is allowed).
- Established diagnosis of type I or II DM requiring anti-diabetic drugs. Patients eligible in the cohort B if no anti-diabetic drug were received in the last 14 days.
- Clinically significant uncontrolled heart disease and/or recent cardiac events.
- Inflammatory breast cancer at screening.

SAMPLE SIZE

Cohort A

- H0 ≥25% and H1 ≤10% rate of pts with G3–4 HG.
- **Futility stop at interim analysis:** >3/20 evaluable pts with G3–4 HG.
- **Positive finding at final analysis:** ≤6/43 evaluable pts with G3–4 HG.
- A sample size of 48 pts is needed to attain 80% power at nominal level of one-sided alpha of 5%.

Cohort B

- H0 ≥40% and H1 ≤15% rate of pts with G3–4 HG.
- **Futility stop at interim analysis:** >2/7 pts with G3–4 HG.
- **Positive finding at final analysis:** ≤4/20 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.

TRIAL ENROLLMENT

- The METALLICA study is open and currently recruiting in 18 institutions around Spain.
- A total of 16 pts have already been recruited: of them, 9 and 7 pts in the cohort A and B, respectively.

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