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Impact of time to progression on CDK4/6 inhibitor therapy on progression-free survival in HR+/HER2-/*PIK3CA*-mutated advanced breast cancer patients treated with alpelisib plus endocrine therapy:An exploratory analysis of the METALLICA trial

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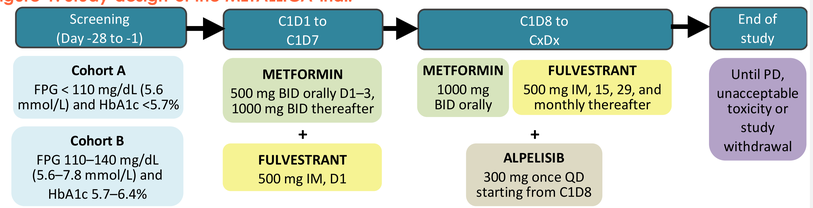
BACKGROUND

- Alpelisib (ALP) is an α-specific PI3K (PIK3CA) inhibitor that was approved in combination with fulvestrant for postmenopausal patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-)/*PIK3CA*-mutated advanced breast cancer (ABC) who have progressed following treatment with an endocrine therapy (ET)-based regimen **[1]**.
- Hyperglycemia is an on-target effect of the PI3K inhibition, being the most frequent adverse event of grade 3/4 and the most common adverse event leading to ALP discontinuation in the SOLAR-1 study **[2,3]**. Metformin is a glucose-lowering agent used to prevent or delay diabetes **[4]**.
- The METALLICA trial showed that prophylactic metformin reduced the incidence and severity of grade 3-4 ALP-induced hyperglycemia in HR+/HER2-/*PIK3CA*-mutated ABC treated with ALP+ET **[5]**.
- The BYLieve study showed that the benefit and safety of ALP+ET was similar in HR+/HER2-/*PIK3CA*-mutated ABC patients who achieved shorter duration of disease control with prior CDK4/6 inhibitor (CDK4/6i)-based therapy and those with longer duration of disease control **[6]**. However, the EMERALD study identified early progressions (<12 months) on prior CDK4/6i for ABC as a strong predictor of resistance to subsequent ET-based treatments **[7]**.
- Here, we retrospectively examined the impact that time to progression on the prior CDK4/6i-based regimen had on the efficacy of ALP+ET.

STUDY DESIGN

- METALLICA was a prospective, multicenter, open-label, two-cohort, phase II trial that evaluated the effectiveness of prophylactic metformin to prevent ALP-induced hyperglycemia in patients with HR+/HER2-/*PIK3CA*-mutated ABC treated with ALP plus ET (Figure 1).

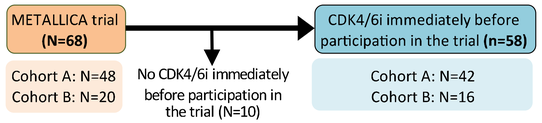
Figure 1. Study design of the METALLICA trial.



BID: Twice a day, **CDK4/6i**: CDK4/6 inhibitors, **CxDx**: Cycle X and Day X, **FPG**: Fasting plasma glucose, **HbA1c**: Glycosylated hemoglobin, **IM**: intramuscular injection, **PD**: Progression of disease, **QD**: once a day.

- This is an exploratory analysis of the METALLICA trial which specifically included patients who received a CDK4/6i-based therapy for ABC immediately before participating in the trial (Figure 2).

Figure 2. Patient population of the METALLICA exploratory analysis (blue box).



PATIENTS AND METHODS

- Female and male adult patients with HR+/HER2-/*PIK3CA*-mutated ABC who progressed on an aromatase inhibitor-containing regimen and were treated with ≤2 prior lines of ET and ≤1 of prior chemotherapy for ABC were eligible.
- ALP (oral, 300 mg QD) was administered together with ET (fulvestrant, letrozole, or exemestane according to investigator's criteria) in 28-day cycles. Metformin 500 mg was administered on days 1 and 3 (oral, BID) and 1000 mg thereafter.
- This analysis evaluated progression-free survival and 1-year overall survival rates according to time to progression on the prior CDK4/6i-based regimen (<12 vs. ≥12 months).
- Survival estimates were analyzed using the Kaplan-Meier method and 95% confidence intervals (CIs). Cox regression model was adjusted by age, ECOG performance status, number and location of metastatic disease, number of prior lines for ABC, and type of CDK4/6i-based therapy.

RESULTS

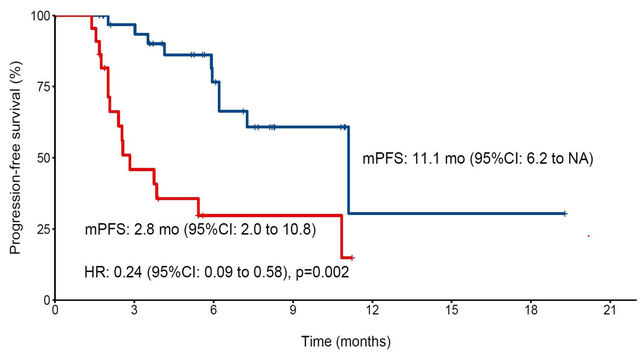
- Between 30 August 2020 and 10 March 2022, a total of 68 patients with HR+/HER2-/*PIK3CA*-mutated ABC were enrolled. Median follow-up was 7.8 months (range, 1.4-19.6).
- A total of 58 patients (85.3%) were previously treated with a CDK4/6i-based therapy for ABC immediately before participating in the METALLICA trial.
- Out of 58 patients, 35 (60.4%) had a time to progression on previous CDK4/6i-based regimen ≥12 months, and 23 (39.6%) had a time to progression on previous CDK4/6i-based regimen <12 months.
- Median progression-free survival was 7.3 months (95% CI, 5.9-not achieved) for all CDK4/6i-treated patients.

Progression-free survival rate (Figure 3):
Among patients with prior exposure to CDK4/6i ≥12 months, ALP plus ET achieved a median progression-free survival of 11.1 months vs. 2.8 months from patients with a time to progression on previous CDK4/6i therapy <12 months (HR=0.24; 95%CI: 0.09-0.58, p=0.002).

1-year overall survival rate (Figure 4):
Among patients with prior exposure to CDK4/6i ≥12 months, ALP plus ET achieved a 1-year OS rate of 96.7% vs. 59.4% from patients with a time to progression on previous CDK4/6i therapy <12 months (HR=0.10; 95%CI: 0.01-0.90, p=0.040).

RESULTS

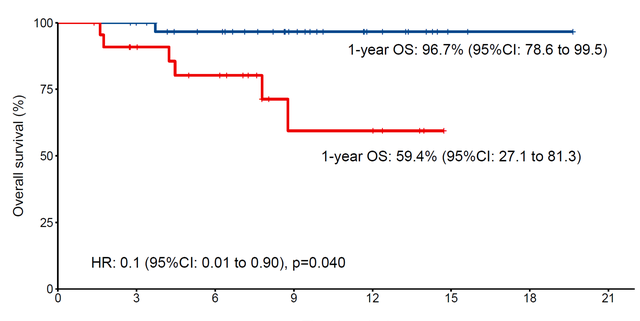
Figure 3. Progression-free survival rate in HR+/HER2-/*PIK3CA*-mutated ABC patients treated with ALP+ET by duration of prior CDK4/6i.



Patients at risk, n(%)

≥12 mo 35 (100)	29 (83)	16 (46)	5 (14)	1 (3)	1 (3)	1 (3)	0 (0)
<12 mo 23 (100)	9 (39)	2 (9)	2 (9)	0 (0)	0 (0)	0 (0)	0 (0)

Figure 4. 1-year overall survival rate in HR+/HER2-/*PIK3CA*-mutated ABC patients treated with ALP+ET by duration of prior CDK4/6i.



Patients at risk, n(%)

≥12 mo 35 (100)	32 (91)	26 (74)	17 (49)	9 (26)	2 (6)	1 (3)	0 (0)
<12 mo 23 (100)	18 (78)	14 (61)	5 (22)	5 (22)	0 (0)	0 (0)	0 (0)

CONCLUSIONS

- The results suggest that duration of prior CDK4/6i exposure may be associated with progression-free survival and overall survival in patients with HR+/HER2-/*PIK3CA*-mutated ABC treated with ALP plus ET.
- Progression within the first year of prior CDK4/6i-based regimen seems to be prognostic of less favorable outcomes.

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Advisory role: Lilly, Roche, Pfizer, Novartis.
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