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Metformin (MET) for the prevention of Alpelisib (ALP)-related Hyperglycemia (HG) in PIK3CA-mutated, Hormone Receptor-Positive (HR[+])/HER2-Negative (HER2[-]) Advanced Breast Cancer (ABC): The METALLICA study

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BACKGROUND

- ALP is an α-specific PI3K-α inhibitor, that has shown to significantly increase the median progression-free survival (PFS) when combined with fulvestrant in patients (pts) with PIK3CA-mutated, HR[+]/HER2[–] ABC who had failed to an aromatase inhibitor (AI) regimen [1].
- 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 ALP in the randomized, phase 3 SOLAR-1 study [2].
- MET is approved for pts with diabetes mellitus (DM) and represented the preferred option for treating ALP-induced HG in the SOLAR-1 study [2].
- METALLICA aims to evaluate the effect of MET in the prevention of HG in PIK3CA-mutated, HR[+]/HER2[–] ABC pts treated with ALP plus fulvestrant.

OBJECTIVE

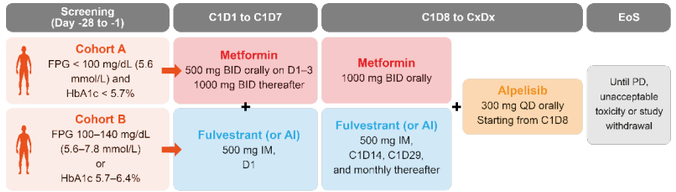
- METALLICA [NCT04300790] is a prospective, multicenter, open-label, two-cohort, Simon's two-stage design, phase II trial of ALP in combination with fulvestrant (or AI) plus MET as a treatment for preventing HG in pts with PIK3CA-mutated, HR[+]/HER2[–] ABC.

METHODS

Main inclusion criteria

- Male or female patients ≥ 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0/1.
- ER[+] and/or progesterone receptor PgR[+] and HER2[–] ABC not amenable to curative treatment.
- Presence of PIK3CA mutation on tissue or circulating tumor ctDNA.
- Measurable or evaluable disease as per RECIST v.1.1.
- ≥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.
- Adequate organ function.

Study design



Primary Endpoint

Incidence rate of G3–4 HG by CTCAE criteria 4.03 over the first two cycles of treatment with ALP (8 weeks).

Secondary Endpoints

Rate of any grade and G3–4 HG, rate of treatment-emergent adverse events (TEAEs) by CTCAE criteria 4.03, rate of treatment discontinuations, objective response rate (ORR), duration of response (DoR) for responders, clinical benefit rate (CBR), and PFS defined per RECIST 1.1.

Statistical considerations

- Sample size for each cohort was based on a Simon's two-stage design, planned to attain an 80% power at nominal level of one-sided α of 0.05.
- **Cohort A (n=48):** H0: ≥25% G3–4 HG pts / HA: ≤10% G3–4 HG pts.
- **Cohort B (n=20):** H0: ≥40% G3–4 HG pts / HA: ≤15% G3–4 HG pts.
- Positive finding in: **Cohort A:** ≤7 among 48 pts with G3–4 HG in the first 2 cycles;
  Cohort B: ≤4 among 20 pts with G3–4 HG in the first 2 cycles.
- The rate of HG between METALLICA and SOLAR-1/BYLieve (Cohort A) trials were compared with a random-effects meta-analysis (Q-test).

PATIENT DISPOSITION

Between August 13, 2020 and March 10, 2022, 68 pts were enrolled at 18 sites (48 cohort A, 20 cohort B).

At data cutoff (May 25, 2022), 28 (41.2%) pts were continuing treatment. The reasons for discontinuation included progression disease (48.5%), TEAEs (4.4%), physical deterioration (2.9%), consent withdrawal (1.5%), and lost of follow-up (1.5%). Median follow-up was 6.8 months (range, 1.4–18.6) for all patients; 5.6 months (range, 1.4–18.6) for cohort A; and 8.0 months (range, 1.6–14.9) for cohort B.

Table 1. Summary of patient characteristics.

Baseline characteristics	Cohort A n (%) N = 48	Cohort B n (%) N = 20	All patients n (%) N = 68
Age; median (min; max), years	52.0 (29; 79)	55.0 (42; 79)	55.0 (29; 79)
Sex, female	48 (100)	20 (100)	68 (100)
ECOG Performance status			
0	30 (62.5)	10 (50.0)	40 (58.8)
1	18 (37.5)	10 (50.0)	28 (41.2)
Body mass index, median (min; max)	25.4 (18.1; 42.1)	25.1 (19.1; 35.0)	26.5 (18.1; 42.1)
Body mass index; n (%)			
< 25 kg/m2	23 (47.9)	7 (35.0)	30 (44.1)
≥25 kg/m2 to <30 kg/m2	4 (8.3)	6 (30.0)	10 (14.7)
≥ 30 kg/m2	21 (43.8)	7 (35.0)	28 (41.2)
FPG mg/dL; median (min; max)	89.5 (65; 99)	102 (79; 133.5)	91 (65; 133.5)
HbA1c (%) median (min; max)	5.3 (4.6; 5.6)	5.8 (5; 6.4)	5.4 (4.6; 6.4)
Measurable disease at baseline	31 (64.6)	10 (50.0)	41 (60.3)
Visceral disease	28 (58.3)	12 (60.0)	40 (58.8)
Number of metastatic organ sites			
1	15 (31.3)	7 (35.0)	22 (32.4)
2	25 (52.1)	5 (25.0)	30 (44.1)
≥3	8 (16.7)	8 (40.0)	16 (23.5)
Menopausal status			
Premenopausal	14 (29.2)	2 (10.0)	16 (23.5)
Postmenopausal	34 (70.8)	18 (90.0)	52 (76.5)
HER2 status by IHC			
0	25 (52.1)	12 (60.0)	37 (54.4)
1+	10 (20.8)	6 (30.0)	16 (23.5)
2+ (FISH-negative)	13 (27.1)	2 (10.0)	15 (22.1)
Prior CDK4/6 inhibitors at any time			
No	0 (0.0)	2 (10.0)	2 (2.9)
Yes	48 (100)	18 (90.0)	66 (97.1)
Number of previous lines of therapy for advanced/metastatic disease			
1	27 (56.3)	9 (45.0)	36 (52.9)
2	16 (33.3)	9 (45.0)	25 (36.8)
3	5 (10.4)	2 (10.0)	7 (10.3)
Previous systematic therapy for advanced/metastatic disease			
Endocrine therapy	48 (100)	20 (100)	68 (100)
Aromatase inhibitors	43 (89.6)	16 (80.0)	59 (86.8)
LHRH	10 (20.8)	4 (20.0)	14 (20.6)
SERD	6 (12.5)	3 (15.0)	9 (13.2)
Tamoxifen	2 (4.2)	0 (0.0)	2 (2.9)
Chemotherapy	10 (20.8)	3 (15.0)	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	1 (5.0%)	1 (1.5)

HbA1c, glycated hemoglobin A1C, FISH: fluorescent in situ hybridization, FPG: fasting plasma glucose, IHC: immunohistochemistry, LHRH: luteinizing hormone-releasing hormone; SERD: selective oestrogen receptor modulators. Percentages may not total 100% due to rounding.

RESULTS

Safety

Primary endpoint: Rate of G3–4 HG over the first two cycles of treatment (8 weeks)

- **Cohort A:** meets the primary endpoint with **2.1% of pts** (1 of 48 pts; 95% CI, 0.5–11.1; p < 0.001) experienced **G3-4 HG over the 2 first cycles**.
- **Cohort B:** meets the primary endpoint with **15% of pts** (3 of 20 pts; 95% CI; 5.6 – 37.8; p = 0.016) experienced **G3-4 HG over the 2 first cycles**.

Table 2. Summary of HG adverse events by grade and cohort over the first two cycles of treatment (8 weeks)

Patients with TEAEs, n (%)	Cohort A n (%) N = 48	Cohort B n (%) N = 20	All patients n (%) N = 68
No HG	38 (79.2)	9 (45)	47 (69.1)
Grade 1 HG	7 (14.6)	3 (15)	10 (14.7)
Grade 2 HG	2 (4.2)	5 (25)	7 (10.3)
Grade 3 HG	1 (2.1)	2 (10)	3 (4.4)
Grade 4 HG	0 (0)	1 (5)	1 (1.5)
Primary endpoint			
Grade ≥3 HG	1 (2.1)	3 (15.0)	4 (5.9)

HG, Hyperglycemia.

Table 3. TEAEs occurring in >10% of patients or grade 4 (N=68)

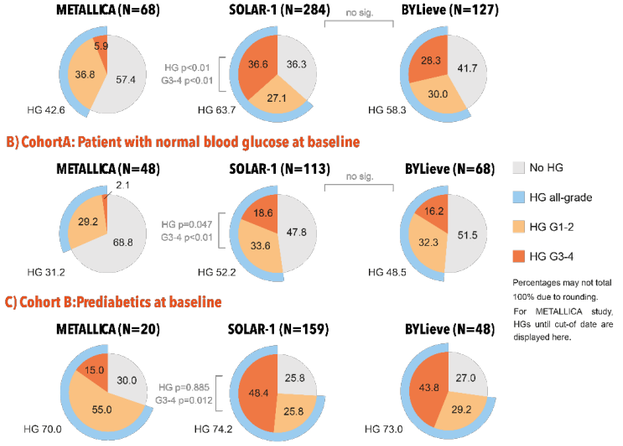
Patients with TEAEs, n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
ANY	67 (98.5)	30 (44.1)	3 (4.4)
HEMATOLOGICAL	8 (11.8)	0 (0)	0 (0)
Anaemia	7 (10.3)	0 (0)	0 (0)
NON-HEMATOLOGICAL	67 (98.5)	30 (44.1)	3 (4.4)
Diarrhoea	46 (67.6)	9 (13.2)	0 (0)
Nausea	46 (67.6)	0 (0)	0 (0)
Fatigue	31 (45.6)	2 (2.9)	0 (0)
Hyperglycemia	**29 (42.6)**	**3 (4.4)**	**1 (1.5)**
Rash	27 (39.7)	12 (17.7)	0 (0)
Vomiting	23 (33.8)	1 (1.5)	0 (0)
Stomatitis	19 (27.9)	1 (1.5)	0 (0)
Decreased appetite	15 (22.1)	1 (1.5)	0 (0)
Increased ALT	9 (13.2)	1 (1.5)	0 (0)
Increased AST	9 (13.2)	1 (1.5)	0 (0)
Pruritus	8 (11.8)	0 (0)	0 (0)
Arthralgia	7 (10.3)	0 (0)	0 (0)
Hypokalaemia	2 (2.9)	0 (0)	1 (1.5)
Hypovolaemic shock	1 (1.5)	0 (0)	1 (1.5)

n (%), number of patients (percentage based on N); N, Number of patients in the FAS population; TEAE: Treatment-emergent adverse event.
TEAEs from pts during all study treatment until cut-of date are reported. Only TEAEs affecting at least 10% of pts or grade 4 are displayed. TEAEs of special interest (AESIs) are shown in bold.

- For pts treated with fulvestrant (N= 63), G3-4 HG rates were 2.2% (1 of 45 pts) and 16.7% (3 of 18 pts) for cohorts A and B.
- TEAEs affecting at least 10% of pts or G4 are summarized in Table 3.
- No study discontinuations were caused by hyperglycemia.
- No treatment-related deaths were reported.

- Rate of reported HG was better than in SOLAR-1 [2] and BYLieve (Cohort A) [3] (Figure 1).

Figure 1. Rate of HG reported in METALLICA, SOLAR-1, and BYLieve (Cohort A) (%)



Percentages may not total 100% due to rounding.
For METALLICA study, HGs until cut-of date are displayed here.

Efficacy

Table 4. Best Overall Response and PFS according to local assessment

Endpoints, n (%)	Cohort A n (%) N = 48	Cohort B n (%) N = 20	All patients n (%) N = 68
ORR, n (%, 95% CI)	8 (16.7, 7.5–30.2)	6 (30.0, 11.9–54.3)	14 (20.6, 11.7–32.1)
DoR in months, median (Range)	2.8 (2–10.7)	5.7 (0.9–11.9)	3.9 (0.9–11.9)
CBR, n (%, 95% CI)	18 (37.5, 24–52.6)	16 (80, 56.3–94.3)	34 (50, 37.6–62.4)
PFS in months, median (95% CI)	7.4 (4.2-NA)	6.9 (5.8-NA)	7.3 (5.8-NA)

CBR: Clinical benefit rate; DoR: Duration of response; ORR: Objective response rate; PFS: Progression-free survival.

CONCLUSIONS

- METALLICA phase 2 study, met its primary endpoint and showed that MET prevents and/or reduces the incidence and severity of all-grade ALP induced hyperglycemia.
- Safety profile and efficacy of ALP in combination with MET is comparable to those reported in the SOLAR-1 and BYLieve trials.

REFERENCES

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