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Original Article

Everolimus-Induced Hyperglycemia and its Clinical Significance: A Retrospective Study

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ABSTRACT

Background: Hyperglycemia frequently occurs during clinical administration of Everolimus (EVL). We investigated hyperglycemia occurrence after EVL administration in 52 Japanese patients with breast cancer, the treatment course for hyperglycemia, and its effects on treating the underlying disease. **Materials and Methods:** Patient background, treatment course, and laboratory data were retrospectively reviewed using electronic medical records. EVL drug-induced hyperglycemia occurred in 28 of the 52 patients. **Results:** When comparing the hyperglycemic and non-hyperglycemic groups, BMI was identified as a contributing factor. Only one of the 28 patients who developed hyperglycemia was prescribed a hypoglycemic and recovered to baseline. The other 27 patients were not prescribed hypoglycemic medications and completed EVL treatment without worsening hyperglycemia. The time to treatment failure was 231.0 and 168.0 days in the hyperglycemic and non-hyperglycemic groups, respectively, with no significant difference (p=0.601) No patient discontinued treatment owing to hyperglycemia. **Conclusion:** Patients with high BMI at the start of EVL treatment require close monitoring for hyperglycemia. EVL-induced hyperglycemia occurs frequently; however, the drug generally allows for treatment completion with appropriate follow-up. Careful management and countermeasures are important when administering this drug, considering that it may cause severe hyperglycemia in rare cases.

Keywords: BMI, Breast cancer, Everolimus, Hyperglycemia, mTOR.

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INTRODUCTION

Everolimus (EVL), the first oral mammalian Target of Rapamycin (mTOR) inhibitor introduced in Japan, is thought to inhibit tumor cell growth by blocking cell growth signals through the mTOR pathway (André *et al.*, 2014). It was launched in Japan in April 2010 for the treatment of "renal cell carcinoma that cannot be curatively resected or is metastatic. In addition to estrogen signaling, the Phosphoinositide 3-Kinase (PI3K)/ Protein Kinase B (Akt)/mTOR pathway plays a pivotal role in Estrogen Receptor (ER)-positive breast cancer. This pathway is more activated in Luminal B breast cancer than in Luminal A breast cancer and is also involved in endocrine therapy resistance (Baselga *et al.*, 2012). When the PI3K/Akt/mTOR signaling pathway is activated in patients with breast cancer, its inhibition by EVL is thought to be highly effective (Bouchi *et al.*, 2023). An international phase III clinical trial (BOLERO-2) was conducted to compare EVL with placebo in patients with locally advanced or metastatic, postmenopausal, ER-positive, and human epidermal growth factor receptor 2 (HER2)-negative breast cancer that was refractory to letrozole or anastrozole (Franz *et al.*, 2013). The primary endpoint, median Progression-Free Survival (PFS), was significantly longer in the EVL group (6.93 months) than in the placebo group (2.83 months), demonstrating a significant benefit with EVL. As a result, in March 2014, an additional indication for "inoperable or recurrent breast cancer" was approved for EVL in Japan.

Conversely, in the BOLERO-2 study, hyperglycemia (including diabetes) was reported in 12.4% of patients, which is not a rare adverse event. Among the 724 patients enrolled in the study, 106 were Japanese. Notably, there were no previous reports on EVL-induced hyperglycemia in Japanese patients with breast cancer.

Investigating the occurrence and management of hyperglycemia in clinical practice will provide useful information for understanding EVL drug characteristics and ensuring long-term therapy continuation. In this study, we investigated the occurrence of hyperglycemia after EVL administration in Japanese patients

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with breast cancer, the course of hyperglycemia treatment, and its effect on the treatment of the underlying disease.

MATERIALS AND METHODS

Subjects

Eighty-two patients with ER-and/or Progesterone Receptor (PR)-positive recurrent/stage IV breast cancer who were initiated on EVL plus an endocrine therapy agent combination therapy between January 1, 2019, and December 31, 2023, at the Osaka International Cancer Center were included. The observation period extended through March 31, 2024.

Data Collection and Evaluation

Patient background information, including sex, age, height and weight (used to calculate Body Mass Index (BMI)), prior treatment regimen, concomitant hormonal medications, steroid use within the past year, daily EVL dose, reasons for EVL dose reduction, increase, or withdrawal, total duration of EVL treatment, reasons for EVL discontinuation, hemoglobin A1c (*HbA1C*) levels prior to EVL initiation, blood glucose and *HbA1C* levels during EVL treatment, and baseline laboratory values (Total Bilirubin (T-Bil), Alkaline Phosphatase (ALP), aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Serum Albumin (ALB), Serum Creatinine (SCr), estimated Creatinine Clearance (CG-CCr) calculated using the Cockcroft-Gault formula), were investigated. The total treatment duration was defined as the number of days from EVL initiation until treatment cessation study discontinuation or patient death. The number of pretreatment regimens included both those in preoperative and postoperative adjuvant chemotherapy.

Chemotherapeutic drug-induced adverse events were classified using the Common Terminology Criteria for Adverse Events (CTCAE). The latest version, CTCAE v5.0, lacks clear numerical thresholds for hyperglycemia. Per the CTCAE, hyperglycemia is categorized as follows: Grade 1: above baseline/no medical therapy required; Grade 2: requires routine changes for diabetes management/ oral hypoglycemic agents; Grade 3: insulin therapy/ hospitalization required. Therefore, in this study, a fasting blood glucose level of ≥ 110 mg/dL was defined as the onset of hyperglycemia in accordance with the Japanese diagnostic criteria for metabolic syndrome. Exclusion criteria included absence of blood glucose measurement, fasting blood glucose ≥ 110 mg/dL at baseline, pre-existing diabetes, previously undergone clinical trials, and EVL treatment duration < 4 weeks.

During the occurrence of EVL-related adverse events, EVL dose reductions or treatment withdrawals were implemented in accordance with the EVL package insert and appropriate clinical guidelines.

Time to Treatment Failure (TTF) was defined as the number of days from the date of EVL therapy initiation to treatment discontinuation, regardless of the cause, such as exacerbations and adverse events.

Ethical Considerations

The study was conducted in compliance with the "Declaration of Helsinki" and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and was approved by the Ethical Review Board of our institution (approval number: 23208). Due consideration was given to personal data protection, and the data were handled following anonymization. Information regarding this study is available on our institute's website, and we adopted an opt-out system that can respond to requests for withdrawal from the research whenever necessary.

Statistical Analysis

The Mann-Whitney U test was used for comparisons between the two groups, assuming a non-normal distribution for continuous variables. For nominal variables, Fisher's exact test was used to test the 2×2 contingency table, and the chi-square test was used to test the other contingency tables. The Mann-Whitney U, chi-square, and Fisher's exact tests were used for intergroup comparisons, as appropriate. Kaplan-Meier curves were generated to compare TTFs based on hyperglycemia status. The time from the date of the first EVL administration to treatment discontinuation was considered the survival duration, and the Cox proportional hazard model and log-rank test were used to test cumulative incidence for significant differences. Kaplan-Meier curves, Cox proportional hazards model, and log-rank test were performed to compare TTF in patients with and without hyperglycemia. All statistical analyses were performed using Excel statistics (BellCurve for Excel, Social Information Service Co., Ltd., Tokyo), with a two-tailed significance level set at $p<0.05$.

RESULTS

Patient Background and Treatment Course of Cases with Hyperglycemia

Patient background characteristics are shown in Table 1. Based on the inclusion and exclusion criteria, 52 patients were selected. All patients were female and received concomitant hormonal therapy with exemestane. The median age and BMI were 59 years (range: 34-86 years) and 21.2 kg/m^2 (14.5-28.8 kg/m^2), respectively. Initial EVL doses were 10 mg, 7.5 mg, and 5 mg for 46, two, and four patients, respectively. The median blood sampling data at the first EVL dose were all within the normal range. EVL-related drug-induced hyperglycemia occurred in 28 out of 52 patients (53.8%). BMI was identified as a contributing factor in the comparison between the hyperglycemic and non-hyperglycemic groups.

Table 2 summarizes the treatment course of the 28 patients who developed hyperglycemia. The time to first hyperglycemia onset was 28.5 days (range: 7-770 days), with a mean blood glucose

level of 119.5 mg/dL (range: 110-180 mg/dL). The median time to peak hyperglycemia was 57.5 days (range: 14-770 days), with the mean blood glucose levels at 127.5 mg/dL (range: 110-234 mg/dL). Only one of the 28 patients (3.6%) was prescribed a hypoglycemic drug and recovered to baseline (Figure 1). The other 27 patients (96.4%) were not prescribed hypoglycemic medications or insulin therapy and completed the EVL treatment with no exacerbation of hyperglycemia. Ten out of the 28 patients (35.7%) experienced weight loss during EVL treatment. Interstitial pneumonia, stomatitis, and thrombocytopenia were the primary causes of drug dose reduction; however, hyperglycemia was not the cause of drug dose reduction in any case. None of the patients discontinued EVL treatment because of hyperglycemia (data not shown).

Comparison of TTF between Patients Who Developed and Did Not Develop Hyperglycemia

A comparison of the TTF between the 28 patients who developed hyperglycemia and the 24 who did not is shown in Figure 2. The median TTF for the hyperglycemia group was 231.0 days (95% CI: 91.1-370.9 days), compared with 168.0 days (95% CI: 128.5-207.5 days) in the non-hyperglycemic group, although the difference was not statistically significant (HR: 0.86; 95% CI: 0.49-1.51; log-rank test: p=0.601).

Case Presentation

Patient profile: sex: female; age: 53 years old; height: 162.0 cm; weight: 65.5 kg; BMI: 25.0 kg/m^2; medical history: no history of diabetes; family history: father had impaired glucose tolerance (Figure 1).

History of present illness

Eight years ago, the patient developed breast cancer (T2N1M0 stage IIB, Luminal B) and underwent a partial mastectomy with sentinel lymph node biopsy. Histopathology revealed invasive ductal carcinoma, negative margins, and World Health Organization (WHO) classification grade: 2; ER score: 3; PR score: 3; HER2: 0. The postoperative adjuvant therapy consisted of docetaxel plus cyclophosphamide, followed by tamoxifen monotherapy. Four years ago, the patient was switched to letrozole due to tamoxifen-related liver dysfunction. Subsequently, due to repeated progressive disease, the patient was switched to palbociclib + fulvestrant combination therapy, eribulin monotherapy, and capecitabine monotherapy. At the time of the current analysis (month X), the patient was switched to EVL (10 mg/day) + exemestane (25 mg/day) combination therapy because of continued lymph node metastases.

Hyperglycemia treatment progress

The blood glucose level at the start of EVL + exemestane treatment (Day 0) was 101 mg/dL. No other medications were administered concurrently. On Day 14, the blood glucose level rose to 180 mg/dL. By Day 112, it had increased to 215 mg/dL, and EVL-induced hyperglycemia was suspected; therefore, the patient was referred to the Department of Endocrinology and Metabolism. The patient also complained of poor wound healing and weight loss. On Day 129, EVL-induced diabetes was diagnosed, and metformin hydrochloride tablets (500 mg/day) were initiated on Day 147 (blood glucose: 230 mg/dL; *HbA1C*: 10.3%). The dose of metformin hydrochloride tablets was increased to 1000 mg/day on Day 203. By Day 287, blood glucose levels showed slight improvement (blood glucose: 161 mg/dL; *HbA1C*: 8.3%), but Low-Density Lipoprotein (LDL)-cholesterol level was elevated at 174 mg/dL. Sitagliptin phosphate hydrate (50 mg/day) was added to improve both LDL-cholesterol and diabetes; however, by Day 315, no improvement was observed (blood glucose: 172 mg/dL; *HbA1C*: 8.4%; LDL-cholesterol: 190 mg/dL), prompting the addition of glimepiride (2 mg/day). After achieving rapid glycemic control, glimepiride was discontinued on Day 388 (blood glucose: 92 mg/dL; *HbA1C*: 6.3%; LDL-cholesterol: 120 mg/dL). The current treatment was changed to tegafur/gimeracil/oteracil (S-1) monotherapy on Day 367, followed by weekly paclitaxel + bevacizumab on Day 409. The best supportive care policy was initiated on Day 464.

DISCUSSION

ER-positive breast cancer is commonly treated with hormone therapy; however, resistance remains a significant clinical challenge. In patients with ER-positive, HER2-negative metastatic breast cancer with prior aromatase inhibitor therapy, the mTOR inhibitor EVL and the steroidal aromatase inhibitor exemestane are used to target the PI3K/AKT/mTOR signaling pathway. This pathway is an intracellular signaling pathway that is important for cell cycle regulation and is frequently abnormal in cancer cells, with important effects on metabolism, proliferation, and motility. In breast cancer, this pathway is activated in approximately 70% of patients (Higuchi and Miyoshi, 2015).

EVL-induced hyperglycemia is a major side effect that has been reported in 13-50% of cases during clinical use in various cancer types (Hurvitz *et al.*, 2015; Khan *et al.*, 2016; Masuda, 2015; Motzer *et al.*, 2008; Ohyama *et al.*, 2021; Pavel *et al.*, 2011). Hyperglycemia often presents with few symptoms, making early detection difficult. Additionally, the use of antidiabetic medications to treat hyperglycemia introduces an additional risk of hypoglycemia, compounding the complexity of cancer treatment. Therefore, elucidating the circumstances under which EVL-induced hyperglycemia develops is necessary for effective prevention and treatment.

Insulin-like Growth Factor-1 (IGF-1), a hormone structurally similar to insulin, functions as a tumor growth factor. EVL exerts its antitumor effects by inhibiting mTOR, a key component of IGF-1 receptor-mediated signaling. IGF-1 and insulin share many receptors and intracellular transmitters; therefore, inhibiting

IGF-1 signaling can cause hyperglycemia. EVL is thought to induce hyperglycemia by inhibiting insulin receptor signaling through mTOR inhibition, resulting in decreased insulin secretion and insulin resistance (Tanimura *et al.*, 2019; Vergès and Cariou, 2015; Vergès, 2018; Vernieri *et al.*, 2020). However, it has been reported that with temporary use, glucose intolerance is reversible, and permanent discontinuation is not necessary (Tanimura *et al.*, 2019; Vernieri *et al.*, 2021). Additionally, Ohyama *et al.* found no significant difference in the time profile of diabetes onset following EVL treatment across various cancer types (Yamamoto and Hirano, 2015).

In this current study, we report the clinical course of 28 patients with EVL-induced hyperglycemia and discuss strategies to achieve adequate glycemic control. Most patients were able to continue EVL treatment under close follow-up, which was consistent with findings from previous reports. The median time to the first hyperglycemia onset was 28.5 days, which aligns with previous reports, including the BOLERO-2 study (Franz *et al.*, 2013; Yamamoto and Hirano, 2015). However, given the possibility of rare but severe hyperglycemia, regular blood glucose monitoring before and during EVL administration is essential, as outlined in the Afinitor® Guide for Proper Use. Particular attention should be paid to hyperglycemia development during the initial treatment phase.

Vernieri *et al.* reported that patients who were normoglycemic at baseline and developed diabetes during EVL treatment had significantly lower PFS than those who were already hyperglycemic at baseline and developed diabetes during EVL treatment (Yao *et al.*, 2011). In contrast, our findings showed no significant difference in median TTF between the hyperglycemic group (231.0 days) and the non-hyperglycemic group (168.0 days). Furthermore, no discontinuations were attributed to hyperglycemia onset, suggesting that the presence or absence of hyperglycemia may not affect EVL treatment.

In this study, BMI was extracted as a contributing factor influencing hyperglycemia in the 28 patients who developed it and 24 who did not. The median BMI of the patients who developed hyperglycemia was 22.1 kg/m^2, which was within the standard BMI range. Nevertheless, careful monitoring is warranted for patients with high BMI at the start of EVL treatment.

The second edition of the "Type 2 Diabetes Treatment Algorithm" has been published, taking into consideration the evidence and the actual prescribing situation in Japan, and it emphasizes

Table 1: Background of the 52 patients with breast cancer treated with everolimus.

	Overall (*n*=52)	Hyperglycemia expressing (*n*=28)	Hyperglycemia non-expressing (*n*=24)	*p* value
Sex (female/male)	52/0	28/0	24/0	1.000
Age (years)	59 (34-86)	56 (34-86)	61(53-83)	0.175
Body mass index (kg/m^2)	21.2 (14.5-28.8)	22.1 (14.5-28.8)	20.3 (15.6-26.5)	0.038
Metastatic or recurrent breast cancer (yes/no)	52/0	28/0	24/0	1.000
Pretreatment line (counts)	5 (1-10)	4 (1-10)	5 (1-9)	0.853
Combination hormone therapy (exemestane/ other)	52/0	28/0	24/0	1.000
Initial dose of everolimus (mg/body; 10/7.5/5)	46/2/4	26/2/0	20/0/4	0.206
Existing diabetes (yes/no)	0/52	0/28	0/24	1.000
Steroid administration in the past year (yes/no)	8/44	3/25	5/19	0.447
At baseline				
Blood glucose level (mg/dL)	96 (75-108)	98.5 (75-108)	90 (75-104)	0.051
Total bilirubin (mg/dL)	0.5 (0.2-1.4)	0.5 (0.2-1.2)	0.5 (0.3-1.4)	0.642
Alkaline phosphatase (IU/L)	70 (27-293)	68.5 (27-293)	73.5 (33-162)	0.600
Aspartate transaminase (IU/L)	24.5 (13-111)	24.5 (13-111)	24 (16-64)	0.906
Alanine aminotransferase (IU/L)	16 (6-106)	16 (6-106)	15.5 (8-101)	0.830
Serum albumin (g/dL)	4.2 (3.2-4.8)	4.1 (3.3-4.7)	4.25 (3.2-4.8)	0.319
Serum creatinine (mg/dL)	0.66 (0.38-1.13)	0.63 (0.38-1.13)	0.655 (0.44-1.11)	0.716
Cockcroft-Gault creatinine clearance (mL/min)	79 (38-172)	88 (40-172)	78 (38-106)	0.068

*Data are expressed as median (range).

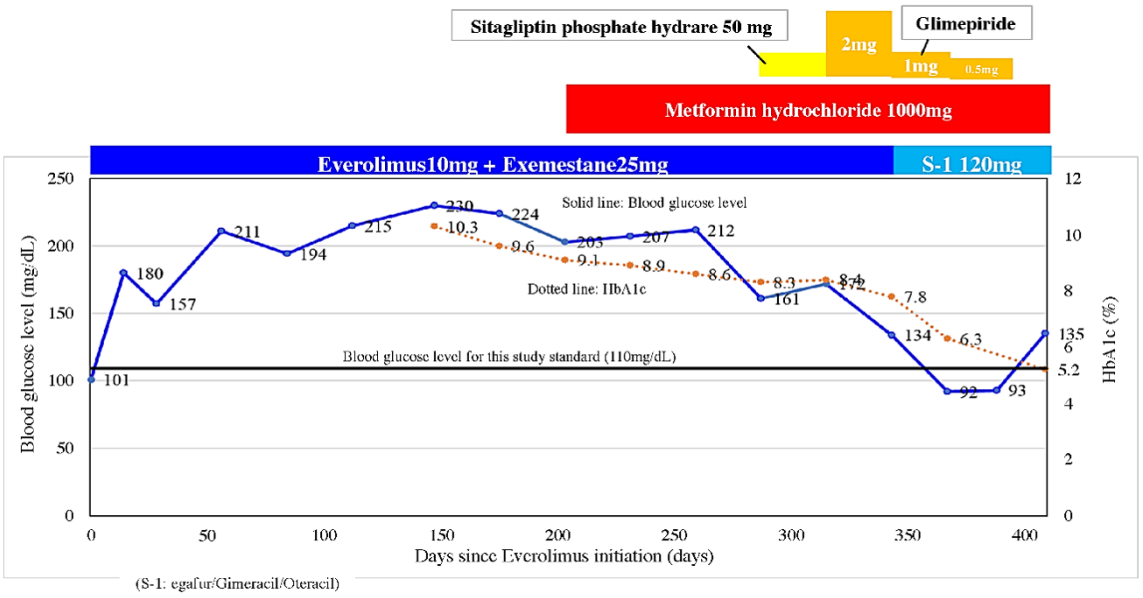

Figure 1: Clinical course of case 1.

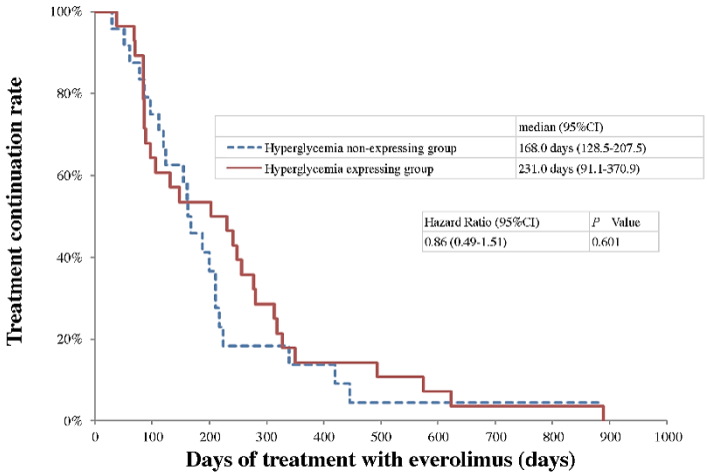

Figure 2: Comparison of TTF between patients who developed and did not develop hyperglycemia.

the importance of tailoring the selection of therapeutic agents according to the pathological condition of diabetes (Yamamoto and Hirano, 2015; Zoncu *et al.*, 2011). According to this algorithm, the presence or absence of obesity can be used as a clinical indicator to discriminate the pathogenesis of type 2 diabetes. Obesity, defined in Japan as a BMI ≥ 25 kg/m^2, is a key factor in selecting drugs for type 2 diabetes treatment. Since BMI positively correlates with insulin resistance, higher BMI may contribute to the pathogenesis of insulin-resistant type 2 diabetes; therefore, drug selection should be considered. Moreover, it is important to note that Asians, including Japanese, have more visceral fat accumulation than Westerners, even at low BMI. This predisposes them to insulin resistance due to visceral fat accumulation in some cases, even in individuals classified as non-obese according to the BMI scale. Metformin has the same *HbA1C*-lowering effect in non-obese Japanese patients as in patients with obesity, suggesting that it may be a candidate drug for patients without obesity. The hypoglycemic effect of metformin is dose-dependent, with higher doses having a potent hypoglycemic effect. In the case presented in this study, the patient's BMI was 25.0 kg/m^2, which is on the borderline between obese and non-obese. Treatment with metformin (1000 mg/day) showed mild improvement in hyperglycemia and *HbA1C* levels. Subsequent addition of glimepiride, a sulfonylurea drug, resulted in rapid glycemic improvement. These findings suggest that the practical application of the Type 2 Diabetes Treatment Algorithm 2nd Edition response was also successful in this case.

Nonetheless, the study had some limitations, such as its small number of cases at a single institution and the electronic medical record-based retrospective study design, which may introduce various biases owing to the lack of power. Additionally, the total

Table 2: Treatment course of 28 cases of hyperglycemia.

	Hyperglycemia expressing (*n*=28)
Baseline blood glucose level (mg/dL)	98.5 (75-108)
Blood glucose level at first onset and date of onset (mg/dL • days)	119.5 (110-180) • 28.5 (7-770)
Maximum blood glucose level and date of onset (mg/dL • days)	127.5 (110-234) • 57.5 (14-770)
Newly prescribed hypoglycemic drug after onset of hyperglycemia (yes/no)	1/27
Whether everolimus dose was reduced (yes/no)	10/18
Reasons for 10 cases of everolimus dose reduction (interstitial pneumonia/stomatitis/ thrombocytopenia)	4/5/1
Everolimus treatment duration (days)	217 (38-889)

*Data are expressed as median (range).

corticosteroid dose administered to each patient was unknown, representing a potential source of bias. Furthermore, this study was limited to the Japanese population, thereby limiting the generalizability of the findings to other races. Therefore, we believe that a more accurate evaluation based on the accumulation of cases in multicenter studies is needed.

CONCLUSION

In conclusion, the management of breast cancer is very important, particularly because long-term survival is achievable with effective drug control. While EVL-induced hyperglycemia occurs early and frequently, treatment with the drug is often successfully completed with appropriate follow-up. Nevertheless, it is important to keep in mind that EVL can cause serious hyperglycemia in rare cases, and careful management and countermeasures are important when administering this drug.

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ABBREVIATIONS

EVL: Everolimus; **mTOR:** Mammalian target of rapamycin; **PI3K:** Phosphoinositide 3-kinase; **Akt:** Protein kinase B; **ER:** Estrogen receptor; **HR:** Hazard ratio; **CI:** Confidence interval; **HER2:** Human epidermal growth factor receptor 2; **PFS:** Progression-free survival; **PR:** Progesterone receptor; **BMI:** Body mass index; **HbA1C:** Hemoglobin A1c; **AST:** Aspartate aminotransferase; **ALP:** Alkaline phosphatase; **T-Bil:** Total bilirubin; **ALT:** Alanine aminotransferase; **ALB:** Serum albumin; **SCr:** Serum creatinine; **CTCAE:** Common Terminology Criteria for Adverse Events; **TTF:** Time to treatment failure; **LDL:** Low-density lipoprotein; **S-1:** Tegafur/gimeracil/oteracil; **IGF-1:** Insulin-like growth factor-1.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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