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A Phase Ib Study of Alpelisib or Buparlisib Combined with Tamoxifen Plus Goserelin in Premenopausal Women with HR-Positive HER2-Negative Advanced Breast Cancer

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ABSTRACT

Purpose: This study reports the MTD, recommended phase 2 dose (RP2D), and preliminary efficacy of alpelisib or buparlisib used in combination with tamoxifen plus goserelin in premenopausal patients with hormone receptor–positive (HR^+), HER2-negative ($HER2^-$) advanced breast cancer (ABC).

Patients and Methods: This study enrolled premenopausal women with HR^+, $HER2^-$ ABC. Patients received tamoxifen (20 mg once daily) and goserelin acetate (3.6 mg every 28 days) with either alpelisib (350 mg once daily; $n = 16$) or buparlisib (100 mg once daily; $n = 13$) in 28-day cycles until MTD was observed.

Results: The criteria for MTD were not met for both alpelisib and buparlisib. The RP2D of alpelisib and buparlisib in combination with tamoxifen and goserelin were 350 mg and 100 mg, respectively. Both combinations met protocol-specified criteria for tolerability. The most common grade 3/4 treatment-emergent adverse events (TEAE) were hypokalemia (12.5%), hyperglycemia (6.3%), and rash (6.3%) for alpelisib and alanine aminotransferase increase (30.8%), aspartate aminotransferase increase (23.1%), and anxiety (15.4%) for buparlisib. TEAEs led to treatment discontinuation in 18.8% and 53.8% of alpelisib- and buparlisib-treated patients, respectively. Progression-free survival was 25.2 months in the alpelisib group and 20.6 months in the buparlisib group.

Conclusions: The RP2Ds of alpelisib and buparlisib were 350 mg and 100 mg, respectively. No unexpected safety findings were reported. Although an early-phase study, data suggest that alpelisib plus endocrine therapy may be a potentially efficacious treatment that warrants further evaluation for premenopausal patients with HR^+, $HER2^-$ ABC.

See related commentary by Clark et al., p. 371

Introduction

Breast cancer is the leading cancer diagnosed in women (24%) and is the most common cause of cancer-related deaths (15%) worldwide. The worldwide estimate in 2018 for newly diagnosed female breast cancer was 2.1 million, or 1 in 4 cases of cancer among women. Australia, New Zealand, Europe, and North America have the highest incidence rates of breast cancer (1).

In the United States, breast cancer predominantly affects women ages 60 years and above, whereas in East Asia, incidence peaks in women ages 40–75 years (2). Approximately 42% of women in the Asia-Pacific region and 47% in Southeastern Asia were younger than 50 years at the time of diagnosis, in contrast to 20% of women in Western countries (3, 4).

The most common molecular subtype of breast cancer is luminal disease, characterized as hormone receptor–positive (HR^+) and HER2-negative ($HER2^-$), occurring in approximately 70% of cases (5, 6). In East Asia, the prevalence rate of luminal disease is even higher in premenopausal patients with breast cancer than in postmenopausal patients (2). Treatment options for premenopausal patients with HR^+, $HER2^-$, advanced breast cancer (ABC; includes locally advanced and metastatic disease) remain limited, and are mostly inferred from trials that enrolled postmenopausal women (7–12). Current treatment recommendations for HR^+, $HER2^-$ ABC in premenopausal patients include ovarian ablation or suppression in combination with endocrine therapy with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (10, 13). Premenopausal/perimenopausal patients treated with ribociclib (CDK4/6 inhibitor) in combination with endocrine therapy demonstrated significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo and endocrine therapy in the phase III MONALEESA-7 trial (11, 12). The CDK4/6

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Translational Relevance

PI3K signaling is frequently upregulated in breast cancer and is linked to increased resistance to endocrine therapy. Inhibition of PI3K has been shown to prevent proliferation of long-term estrogen-deprived cell lines. Alpelisib and buparlisib are novel PI3K inhibitors that have demonstrated antitumor activity in preclinical studies. Results from phase III studies (SOLAR-1 and BELLE-2) showed that alpelisib or buparlisib in combination with fulvestrant was associated with clinically significant improvement in progression-free survival compared with placebo in postmenopausal patients with *PIK3CA* mutation. Inhibition of the PI3K pathway is a potential therapeutic target for treating premenopausal patients whose treatment options are largely extrapolated from guidelines for postmenopausal patients. Here, we report the results of B-YOND, a phase Ib and the first study of the combination of tamoxifen plus goserelin acetate with alpelisib or buparlisib in premenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer.

inhibitors palbociclib, ribociclib, and abemaciclib are approved in the United States for use in combination with aromatase inhibitors (AI) or fulvestrant for treating patients with HR^+, $HER2^-$ ABC (14–17). Among the countries included in this trial, palbociclib and ribociclib are approved in Hong Kong, Republic of Korea, Taiwan, and Thailand; abemaciclib is approved in Hong Kong, Republic of Korea, and Taiwan (18–23).

PI3K inhibitors are a promising treatment strategy for patients with ABC. In patients with HR^+, $HER2^-$ ABC, approximately 40% have disease with a mutation in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*; refs. 24–28). The *PIK3CA* gene encodes the catalytic p110α isoform, belonging to class IA PI3K (29). Mutations in *PIK3CA* increase the *in vitro* PI3K activity of the holoenzyme, which activates a signaling pathway (28, 29). Increased activity of the PI3K pathway has been linked to breast cancer tumorigenesis, drug resistance, and clinical outcome (29, 30).

Alpelisib and buparlisib are PI3K inhibitors. Alpelisib is an orally bioavailable, α-selective PI3K inhibitor that selectively inhibits p110α 50 times more potently than other isoforms (31, 32) and demonstrated improved PFS and overall response rate (ORR) in male and postmenopausal female patients with *PIK3CA*-mutated HR^+, $HER2^-$ ABC in combination with fulvestrant in the phase III SOLAR-1 trial (31). Buparlisib is a potent, oral, pan-class I PI3K inhibitor that demonstrated improved PFS in combination with fulvestrant in the BELLE-2 and BELLE-3 trials (25, 33). Pan-PI3K inhibitors are limited by their safety profile due to a wide range of off-target effects (25).

Alpelisib has recently been approved for use in the United States in combination with fulvestrant for the treatment of postmenopausal women and men with HR^+, $HER2^-$, *PIK3CA*-mutated advanced or metastatic breast cancer (34). Further study of buparlisib in breast cancer has been put on hold due to its less favorable safety profile. At the time this study was conducted, both alpelisib and buparlisib were in clinical development (phase III SOLAR-1 and BELLE-3 trials, respectively), and CDK4/6 inhibitors had not yet been approved. As such, standard systemic treatment at the time for ABC was largely composed of endocrine therapy, with selective estrogen receptor modulators/degraders or AIs, or chemotherapy for visceral crisis (35).

Here, we present the results of B-YOND, a phase Ib study of the combination of tamoxifen plus goserelin with alpelisib or buparlisib in premenopausal patients in Asia with HR^+, $HER2^-$ ABC. This is the first study of PI3K inhibitors in premenopausal patients with breast cancer.

Patients and Methods

Study design

We conducted a phase Ib, open-label, parallel-group, international, multicenter, dose deescalation study that enrolled premenopausal patients with HR^+, $HER2^-$ locally advanced or metastatic breast cancer at 15 centers in Hong Kong, Republic of Korea, Taiwan, and Thailand. The study protocol and amendments were approved by an independent ethics committee or institutional review board at each site prior to study initiation. The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

The study consisted of a dose deescalation period to estimate the MTD and recommended phase 2 dose (RP2D) for alpelisib and buparlisib in combination with tamoxifen (fixed dose of 20 mg orally once daily) and goserelin (fixed dose of 3.6 mg subcutaneously every 28 days), and an expansion period to evaluate treatment effects at the established RP2D. In the initial protocol, patients were randomized 1:1:1 to either alpelisib, buparlisib, or the control group (**Fig. 1**). After a protocol amendment, the control group was omitted. Patients randomized to the control group were allowed to continue treatment with tamoxifen and goserelin until disease progression, unacceptable toxicity, or patient withdrawal from treatment. Data for this group are available in the Supplementary Appendix.

Patients received tamoxifen and goserelin with either alpelisib (350 mg once daily; Group 1) or buparlisib (100 mg once daily; Group 2) on a continuous dosing schedule in 28-day cycles. Treatment continued until disease progression, unacceptable toxicity, patient withdrawal, or discontinuation for any other reason. Patients were enrolled until the MTD was observed. Six to 12 patients were to be enrolled in the alpelisib and buparlisib group during the deescalation period; 3 or 6 patients were treated at each dose level depending on the type and degree of dose-limiting toxicities (DLT) observed. The MTD was considered to have been exceeded if at least 2 patients in any cohort of up to 6 patients experienced a DLT. Once the MTD was reached in each treatment group, 12 to 18 additional patients were enrolled at those doses in each treatment group, with 12 patients receiving the highest tolerable dose.

Dose deescalation scheme

This study aimed to investigate the possibility of combining PI3K inhibitors with the standard combination of tamoxifen plus ovarian suppression. A phase Ib dose deescalation approach was used to evaluate the MTD and RP2D of daily alpelisib or buparlisib with this combination in premenopausal patients with breast cancer. The starting dose level for alpelisib and buparlisib was 350 mg once daily and 100 mg once daily, respectively. The first dose reduction level for alpelisib and buparlisib was 300 mg once daily and 80 mg once daily, whereas the second dose reduction level was 250 mg once daily and 60 mg once daily, respectively. Dose reduction was based on the worst preceding toxicity. Each patient was allowed up to two sequential dose modifications, after which either alpelisib or buparlisib was withheld. If treatment was withheld for >28 days, or if reduction below the second dose reduction level was required, treatment was permanently discontinued. If treatment was resumed at a lower dose and the same

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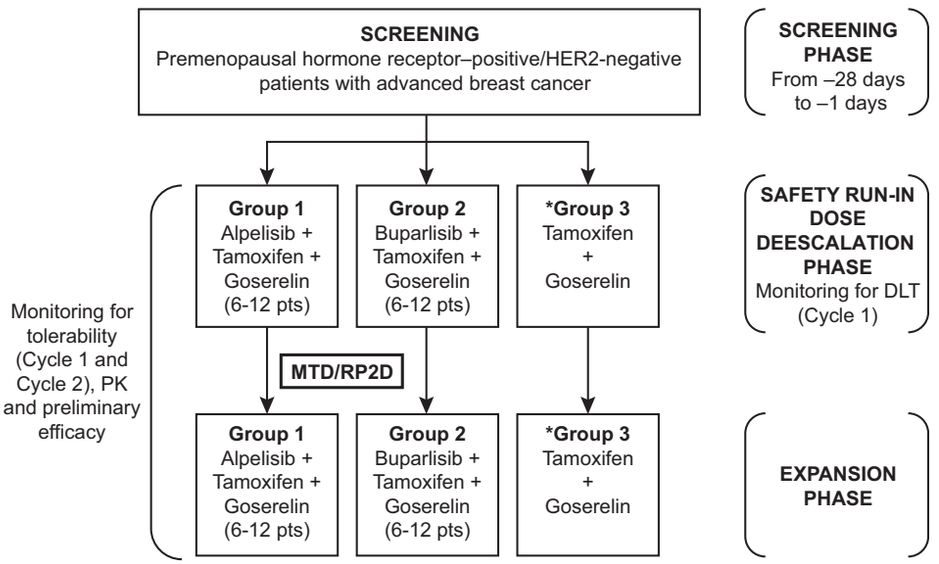

Figure 1.
Study design. *From Amendment 1: No additional patients were allocated to the control group (Group 3 in the figure) after the amendment. PK, pharmacokinetics.

toxicity (except for hyperglycemia) recurred with the same severity, treatment was to resume at a lower dose.

If the patient developed grade 2 hyperglycemia [fasting plasma glucose (FPG) of >160–250 mg/dL (>8.9–13.9 mmol/L)] that did not resolve within 21 days after institution of appropriate antihyperglycemic treatment, alpelisib dose was reduced by 1 dose level. The alpelisib dose was interrupted if the patient developed grade 3 hyperglycemia [FPG >250–500 mg/dL (>13.9–27.8 mmol/L)] and was resumed at 1 dose level lower if FPG resolved to ≤ grade 1 within 3 to 5 days. Confirmed grade 4 hyperglycemia [FPG >500 mg/dL (>27.8 mmol/L)] warranted permanent discontinuation of alpelisib.

For buparlisib, the dose was interrupted if the patient developed grade 2 hyperglycemia with signs or symptoms (e.g., mental status changes, excessive thirst, polyuria). If the patient was asymptomatic, the dose was maintained and monitored for 14 days. If hyperglycemia did not resolve to ≤ grade 1 after appropriate antihyperglycemic therapy, the buparlisib dose was reduced. The buparlisib dose was omitted if the patient developed grade 3 hyperglycemia and was resumed at 1 dose level lower if FPG resolved to ≤ grade 1 within 7 days. If FPG remained > grade 1 for >7 days, buparlisib was discontinued. Buparlisib was discontinued if grade 4 hyperglycemia was confirmed.

Patients

Key inclusion criteria

Premenopausal women ≥18 years of age with histologically or cytologically confirmed, inoperable locally advanced or metastatic breast cancer were eligible for enrollment. Premenopausal status was defined as a patient who either had her last menstrual period within the previous 12 months, had received tamoxifen within the past 3 months, or had chemotherapy-induced amenorrhea. For patients who received tamoxifen or had chemotherapy-induced amenorrhea, plasma estradiol needed to be ≥10 pg/mL and follicle-stimulating hormone ≤40 IU/L or within premenopausal range according to local laboratory guidelines. Patients must have had laboratory-confirmed HR^+ and $HER2^-$ status and measurable or nonmeasurable (lytic or mixed bone lesions) disease per RECIST v1.1. Patients with previous history of endocrine therapy in the metastatic setting were allowed if the treatment lasted <3 weeks or the patient had ≤1 injection of a luteinizing hormone-releasing hormone (LHRH) agonist, and if they discontinued therapy for a reason other than suspected or confirmed disease progression. Patients with prior adjuvant endocrine therapy were eligible. Patients who received ≤1 prior chemotherapy line for metastatic breast cancer were eligible. All patients provided written informed consent at screening.

Key exclusion criteria

Patients were excluded if they received prior endocrine therapy for metastatic disease or treatment with >1 chemotherapy line for metastatic disease, or had received a prior PI3K, AKT, or mammalian target of rapamycin (mTOR) inhibitor. Patients with grade ≥3 anxiety per Common Terminology Criteria for Adverse Events v4.03 or who had a history of or active major depression, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, suicidal attempt or ideation, homicidal ideation, or active severe personality disorder (according to *Diagnostic and Statistical Manual of Mental Disorders-IV*) were also excluded.

Endpoints

The primary endpoint was the MTD of the combination treatment, which was based on the incidence of DLTs in Cycle 1 for patients in the dose-determining analysis set (DDS). Key secondary endpoints were PFS, ORR, and clinical benefit rate (CBR), all assessed according to RECIST v1.1, safety, and patient-reported outcomes. Treatment-emergent adverse events (TEAE) were included in the safety analysis and were defined as events that started or worsened after the first administration of the study treatment until the last dose of study treatment plus 28 days. Laboratory assessments were performed and methodologic details are available in the Supplementary Appendix.

The EuroQol-5D (EQ-5D-5L) and Work Productivity and Activity Impairment Questionnaire—General Health (WPAI-GH) were used to evaluate patient health status and impact on work, whereas the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 Scale (GAD-7) were used to monitor indications of new anxiety or depression.

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Statistical analysis

For dose finding, analysis was performed on the DDS, which consisted of all patients from the safety analysis set (SAF) who received ≥75% of planned daily doses of alpelisib or buparlisib (≥21 of the planned 28 daily doses) and ≥75% of planned daily doses of tamoxifen (≥21 of the planned 28 daily doses) in the first cycle, or who discontinued earlier due to a DLT. Safety analyses were conducted in the SAF, which consisted of all patients who received at least 1 dose of study medication and who had at least 1 postbaseline safety assessment. Analyses of efficacy and baseline characteristics were to be determined on the full analysis set (FAS), which was defined as all patients who received at least 1 dose of study treatment.

Results

Patient characteristics and disposition

Between May 6, 2014 and May 15, 2015, 52 patients were screened and 40 patients were identified as eligible for enrollment. Overall, 39 patients received treatment: 16 patients in the alpelisib group, 13 patients in the buparlisib group, and 10 patients in the control group. All patients were Asian, of whom 48.7% were Chinese and 51.3% were of other ethnicity, with a mean age of 45.3 years and mean body mass index of 22.92 kg/m^2. All but one patient in the alpelisib group (43.8% de novo, 50% recurrent), and all patients in the buparlisib group (46.2% de novo, 53.8% recurrent) had metastatic disease. Approximately 30% of patients received tamoxifen in the adjuvant setting in the alpelisib ($n = 5$) and buparlisib groups ($n = 3$). Additional demographic and patient disease characteristics for the control group and overall population are detailed in **Table 1** and Supplementary Table S1.

A total of 23 patients (59%) remained on treatment until disease progression or death: 10 patients (62.5%) in the alpelisib group, 4 patients (30.8%) in the buparlisib group, and 9 patients (90%) in the control group ($n = 10$). In the alpelisib group, 3 (18.8%) patients discontinued because of an AE and 1 (6.3%) patient each due to administrative reasons, withdrawal of consent by the patient, and investigator's decision. In the buparlisib group, 6 (46.2%) patients discontinued because of an AE and 1 (7.7%) patient each due to

Table 1. Patient demographics and baseline characteristics and disease characteristics.

		Alpelisib + tamoxifen + goserelin (*n* = 16)	Buparlisib + tamoxifen + goserelin (*n* = 13)
Age, years	Median (range)	45.5 (28–54)	46.0 (36–54)
Age group, *n* (%)	18–35 years	1 (6.3)	0
	36–45 years	7 (43.8)	5 (38.5)
	46–55 years	8 (50.0)	8 (61.5)
ECOG performance status, *n* (%)	0	15 (93.8)	9 (69.2)
	1	1 (6.3)	4 (30.8)
Disease status, *n* (%)	Metastatic	15 (93.8)	13 (100)
	De novo	7 (43.8)	6 (46.2)
	Recurrent	8 (50.0)	7 (53.8)
	Locally advanced	1 (6.3)	0
Liver and/or lung disease, *n* (%)	Present	9 (56.3)	7 (53.8)
	Absent	7 (43.8)	6 (46.2)
Measurable disease per RECIST version 1.1, *n* (%)	Yes	16 (100)	11 (84.6)
	No	0	2 (15.4)
Bone-only metastases, *n* (%)	Yes	5 (33.3)	1 (7.7)
	No	10 (66.7)	12 (92.3)
Previous chemotherapy, *n* (%)	Metastatic setting	1 (6.3)	0
	Adjuvant/neoadjuvant only	6 (37.5)	7 (53.8)
	None	9 (56.3)	6 (46.2)
Previous endocrine therapy in adjuvant setting, *n* (%)	Yes	5 (31.3)	3 (23.1)
	No	11 (68.8)	10 (76.9)
Previous treatment with tamoxifen in adjuvant setting, *n* (%)	Yes	5 (31.3)	3 (23.1)
	No	11 (68.8)	10 (76.9)
Tamoxifen-resistant disease, *n* (%)[a]	Yes	4 (25.0)	2 (15.4)
Underwent primary surgery for breast cancer, *n* (%)	Lumpectomy	2 (12.5)	2 (15.4)
	Mastectomy	6 (37.5)	6 (46.2)
	Axillary LN dissection	0	3 (23.1)
	None	8 (50.0)	2 (15.4)
Previous radiotherapy, *n* (%)	Adjuvant	3 (18.8)	3 (23.1)
	Metastatic	0	1 (7.7)
	No	13 (81.3)	9 (69.2)
Histology/cytology, *n* (%)	Invasive ductal carcinoma	13 (81.3)	10 (76.9)
	Invasive lobular carcinoma	3 (18.8)	2 (15.4)
	Other	0	1 (7.7)

Note: Percentages were calculated using the FAS as the denominator, except for sites of metastatic disease. Percentages of patients with a recorded site of metastatic disease were calculated using the number of patients with any metastatic disease as the denominator.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LN, lymph node; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Tamoxifen-resistant disease is defined as disease recurrence during treatment with tamoxifen in the adjuvant setting.

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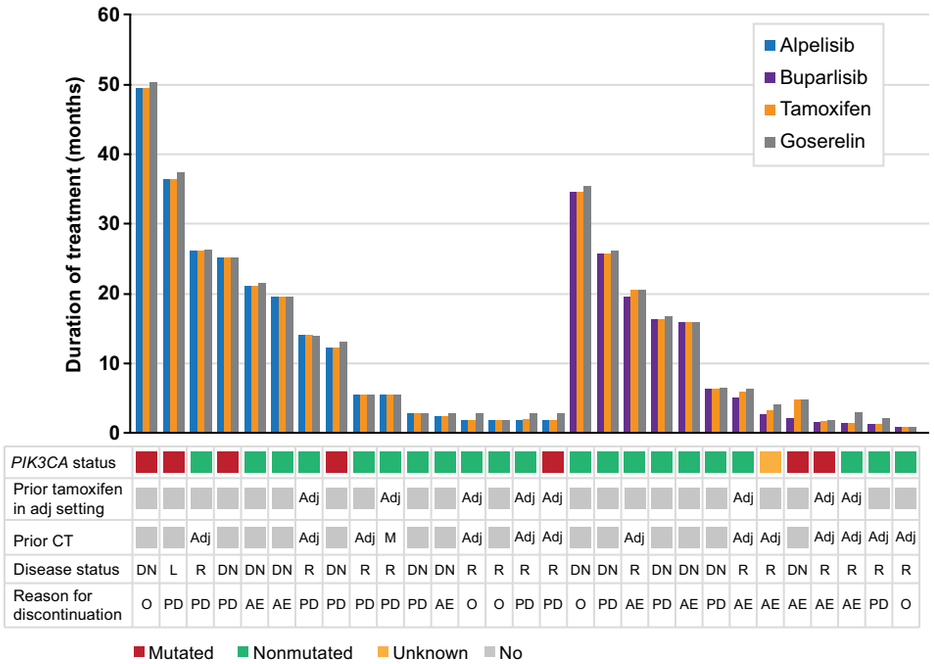

Figure 2.
Patient characteristics, duration of treatment, and reason for treatment discontinuation (SAF). Other reasons for treatment discontinuation include administrative reasons, investigator decision in the patient's best interest, and subject withdrew consent. There were no patients who had treatment discontinuation due to lost to follow-up, death, and/or protocol deviation. Adj, (neo)adjuvant; CT, chemotherapy; DN, de novo; L, locally advanced; M, metastatic; O, other; R, recurrent.

administrative reasons and withdrawal of consent by the patient; 1 (7.7%) patient in this group was lost to follow-up.

In the alpelisib group and buparlisib groups, 31.3% and 23.1% of patients received prior endocrine therapy in the adjuvant setting, all of whom received tamoxifen. A total of 43.8% and 53.8% of patients in the alpelisib and buparlisib groups received prior chemotherapy [(neo) adjuvant: 37.5% in alpelisib, 53.8% in buparlisib; metastatic: 6.3% in alpelisib, none in buparlisib]. A total of 18.8% and 30.8% of patients in the alpelisib and buparlisib groups had prior radiotherapy. Half of patients in the alpelisib group underwent primary surgery for breast cancer: 12.5% underwent lumpectomy and 37.5% underwent mastectomy. In the buparlisib group, 84.6% underwent primary surgery for breast cancer: 15.4% underwent lumpectomy, 46.2% underwent mastectomy, and 23.1% had axillary lymph node dissection.

Dose finding: MTD and RP2D

No patient in the alpelisib group experienced a DLT during Cycle 1 of the study; hence, the MTD was not exceeded. The RP2D of alpelisib in combination with tamoxifen and goserelin was determined to be 350 mg once daily. Two patients (15.4%) in the buparlisib group experienced DLTs of hyperglycemia and rash that were suspected by the investigator to be related to buparlisib treatment; however, these 2 patients were enrolled at different time points and in separate dose cohorts. The criteria for MTD were not met, and the estimated RP2D of buparlisib in combination with tamoxifen and goserelin was 100 mg once daily.

Safety outcomes

Median durations of treatment for the combination therapies were 9.4, 6.4, and 5.3 months in the alpelisib, buparlisib, and control groups, respectively. The median durations of treatment for alpelisib and buparlisib alone were 9 and 5.1 months, respectively. Median durations of treatment for tamoxifen were 9, 6, and 4.9 months for the alpelisib, buparlisib, and control groups, respectively, whereas the median durations of treatment for goserelin were 9.3, 6.4, and 5.3 months for the alpelisib, buparlisib, and control groups, respectively. **Figure 2** summarizes the treatment durations and reasons for discontinuation for both treatment groups.

The most common reason for dose change/interruption in both groups was AE, recorded in 10 patients each in the alpelisib group (62.5%) and buparlisib group (76.9%). Nine months after the first dose, the proportions of patients alive and without disease progression were 50% (8/16) in the alpelisib group, 38.5% (5/13) in the buparlisib group, and 30% (3/10) in the control group. Two patients died during the study: 1 patient in the buparlisib group died 27 days after study treatment discontinuation due to hepatic failure, and 1 patient in the control group died from complications of oral candidiasis while receiving treatment. Neither of the deaths was suspected to be related to study treatment or disease under investigation.

Alpelisib and buparlisib met the protocol-specified criteria for tolerability (defined as the ability to continue treatment for ≥2 consecutive cycles without development of DLTs) and reported safety findings were consistent with their known safety profiles. The most common TEAEs by preferred term in the SAF (alpelisib $n = 16$, buparlisib $n = 13$) are listed in **Table 2**. Most TEAEs (>75%) were grades 2–4 in both groups. Grade 3–4 TEAEs were reported in 8 patients (50%) treated with alpelisib and 10 patients (76.9%) treated with buparlisib. The most commonly reported (≥5% in the overall population) ≥ grade 3 TEAEs were increased alanine aminotransferase [ALT; 4 patients (30.8%) in the buparlisib group], increased aspartate aminotransferase [AST; 3 patients (23.1%) in the buparlisib group], hypokalemia [2 patients (12.5%) in the alpelisib group and 1 patient (7.7%) in the buparlisib group], hyperglycemia [1 patient (6.3%) in the alpelisib group and 1 patient (7.7%) in the buparlisib group], anxiety [2 patients (15.4%) in the buparlisib group], and rash [1 patient (6.3%) in the alpelisib group and 1 patient (7.7%) in the buparlisib group]. Nine patients (31%) experienced treatment-emergent serious AEs: 4 patients (25.0%) in the alpelisib group and 5 patients (38.5%) in the buparlisib group. Two of the patients in the buparlisib group had

Table 2. Treatment-emergent adverse events by preferred term (safety analysis set).

Treatment-emergent adverse events (≥20% in any group) by preferred term		
Preferred term, *n* (%)	**Alpelisib (*n* = 16)**	**Buparlisib (*n* = 13)**
Patients with at least 1 TEAE	16 (100)	13 (100)
Rash	7 (43.8)	8 (61.5)
Decreased appetite	9 (56.3)	4 (30.8)
Stomatitis	6 (37.5)	6 (46.2)
Nausea	6 (37.5)	3 (23.1)
Hyperglycemia	5 (31.3)	6 (46.2)
Alopecia	7 (43.8)	2 (15.4)
Hot flush	7 (43.8)	1 (7.7)
Diarrhea	6 (37.5)	2 (15.4)
Fatigue	5 (31.3)	3 (23.1)
ALT increased	2 (12.5)	6 (46.2)
Pruritus	3 (18.8)	5 (38.5)
AST increased	1 (6.3)	6 (46.2)
Weight decreased	8 (50.0)	0
Dizziness	3 (18.8)	3 (23.1)
Edema peripheral	2 (12.5)	2 (15.4)
Insomnia	0	4 (30.8)
Arthralgia	1 (6.3)	2 (15.4)
Abdominal pain upper	1 (6.3)	3 (23.1)
Face edema	4 (25.0)	0
Noncardiac chest pain	1 (6.3)	1 (7.7)
Pain in extremity	2 (12.5)	0
Hypertension	1 (6.3)	3 (23.1)
Anemia	1 (6.3)	0
Neutrophil count decreased	0	1 (7.7)
Treatment-emergent adverse events of grade 3 or grade 4 (≥5% in any group) by preferred term		
Patients with at least 1 ≥ grade 3 TEAE	8 (50)	10 (76.9)
ALT increased	0	4 (30.8)
AST increased	0	3 (23.1)
Hypokalemia	2 (12.5)	1 (7.7)
Hyperglycemia	1 (6.3)	1 (7.7)
Anxiety	0	2 (15.4)
Rash	1 (6.3)	1 (7.7)

Note: TEAEs were defined as events that started or worsened after the first administration of the study treatment until the date of last dose of study treatment + 28 days. Patients with multiple occurrences of TEAE under a treatment were counted only once in the TEAE category for that treatment. Patients with multiple TEAEs within a PT were counted only once for that PT; PTs are presented in descending order of frequency overall among TEAEs of at least grade 1. Percentages were calculated using the SAF as the denominator.
Abbreviations: PT, preferred term; SAF, safety analysis set.

5 treatment-emergent serious AEs that were suspected by the investigator to be related to buparlisib treatment. Three patients (18.8%) in the alpelisib group and 7 patients (53.8%) in the buparlisib group experienced at least 1 TEAE that led to discontinuation of study drug. In the alpelisib group, these were, by preferred term, rash, colitis, and prolonged QT interval on ECG, whereas in the buparlisib group, these were rash, gingival pain, increased ALT, hyperglycemia, hypokalemia, drug intoxication/toxicity to various agents/injury, poisoning and procedural complications, and anxiety. All TEAEs in the buparlisib group and 93.8% of TEAEs in the alpelisib group were suspected to be related to buparlisib and alpelisib, respectively.

Fifteen patients (93.8%) in the alpelisib group and 13 patients (100.0%) in the buparlisib group experienced at least 1 TEAE of special interest of any grade during the study. In the alpelisib group, the most commonly reported (>3 patients) TEAEs of special interest were rash (43.8%), stomatitis (37.5%), fatigue (31.3%), and hyperglycemia (31.3%). All incidences of fatigue were reported as grade ≤2. Grade ≥3 rash, stomatitis, and hyperglycemia were each reported in only 1 patient (6.3%) in the alpelisib group. In the buparlisib group, the most commonly reported (>3 patients) TEAEs of special interest were rash (61.5%), stomatitis (46.2%), and hyperglycemia (46.2%). Of the patients who reported a TEAE of special interest in the buparlisib group, 4 patients (30.8%) reported a grade 3 TEAE (asthenia, hyperglycemia, rash, and hypertension) and 1 patient (7.7%) had grade 4 hepatotoxicity. Hyperglycemia was reported in the first two treatment cycles in 4 patients (25.0%) in the alpelisib group and 6 patients (46.2%) in the buparlisib group. In the control group, 2 patients (20%) developed rash and 1 patient (10%) experienced fatigue. There were no reported TEAEs of hyperglycemia or stomatitis in the control group. TEAEs in the control group are available in the Supplementary Appendix (Supplementary Table S2).

Efficacy

PFS

All patients (alpelisib $n = 16$, buparlisib $n = 13$) who received at least one dose of study treatment were included in the FAS. At the time of data cutoff (October 17, 2018), 9 patients (56.3%) in the alpelisib group and 5 patients (38.5%) in the buparlisib group had disease progression according to RECIST v1.1 or died (**Fig. 3**). Median PFS was 25.2 months [95% confidence interval (CI), 2.7–36.3] in the alpelisib group and 20.6 months (95% CI, 2.9 to not reached) in the buparlisib group. In the alpelisib group, the longest confirmed PFS was 47.6 months. This was reported in a 43-year-old patient with *PIK3CA*-positive metastatic (bone) invasive lobular carcinoma. In the buparlisib group, the longest confirmed PFS was 33.5 months for a 36-year-old patient with metastatic (bone) *PIK3CA* nonmutant invasive carcinoma of no special histologic category. Because of the low number of patients ($n = 10$) in the control group, PFS was not reported in this group.

Best overall response, ORR, and CBR

In the alpelisib group, 8 patients (ORR 50.0%; 95% CI, 25–75) had a best overall response (BOR) of partial response (PR), including the patient with the longest PFS; 4 patients (25.0%) had stable disease (SD); 3 patients (18.8%) had progressive disease (PD); and 1 patient (6.3%) was not evaluable. In the buparlisib group, 3 patients (ORR 23.1%; 95% CI, 5–54) had a BOR of PR, 9 patients (69.2%) had SD (including the patient with the longest PFS and the 2 patients with nonmeasurable disease), and 1 patient (7.7%) had a BOR of noncomplete response (CR)/non-PD. In the control group, 5 patients (50.0%) had a BOR of SD and 5 patients (50.0%) had PD. No patient in any group achieved a BOR of CR.

The CBR, defined as the proportion of patients with a BOR of CR or PR, or SD lasting >24 weeks, was 56% (95% CI, 30–80) in the alpelisib group, 46% (95% CI, 19–75) in the buparlisib group, and 50% (95% CI, 19–81) in the control group.

BOR and CBR results for the control group are available in the Supplementary Appendix (Supplementary Tables S3 and S4).

Analyses by *PIK3CA* mutation status

The *PIK3CA* mutation status was determined in 28 of 29 patients in the alpelisib and buparlisib groups (16 in the alpelisib group, 12 in the buparlisib group). Plasma samples were analyzed for 8 somatic mutations (E542K, E545K, E545G, Q546K, M1043I, H1047Y,

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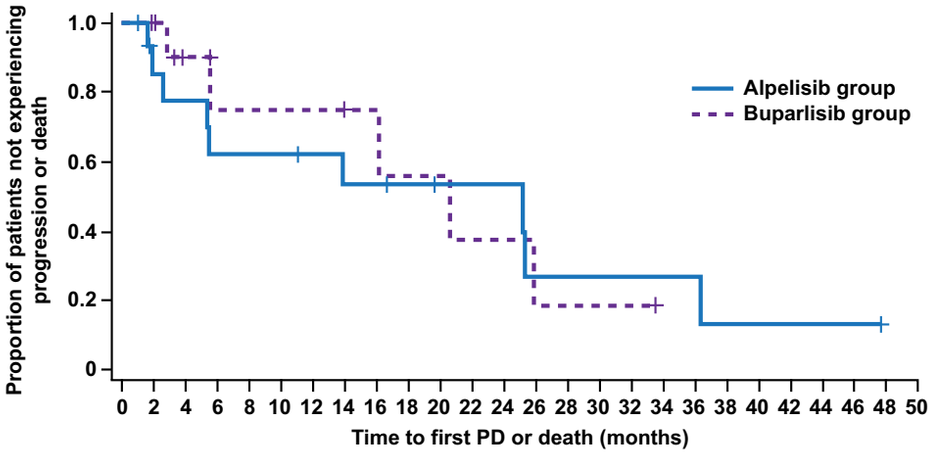

Figure 3.
Kaplan–Meier (KM) plot of progression of disease or death (FAS). In accordance with the SAP, a KM curve for PFS was not calculated for the control group due to the low number of patients. SAP, statistical analysis plan.

H1047R, H1047L) in *PIK3CA* using beads, emulsions, amplification, and magnetics (BEAMing) technology. In the alpelisib group, 5 patients were found to have *PIK3CA*-mutated tumors: 3 in H1047R and 1 each in E545K and M1043I. In the buparlisib group, 2 patients had tumors with E542K and H1047R mutations. Duration of treatment and reason for treatment discontinuation by mutation status are presented in **Fig. 2**. In the alpelisib group, 4 of 5 patients (80%) with *PIK3CA* mutation surpassed 10 months of treatment compared with 4 of 11 patients (36.4%) in the non-*PIK3CA* mutation group. Among those with *PIK3CA* mutation for both groups, 4 patients (57.1%) discontinued because of disease progression versus 10 patients (42.9%) in the *PIK3CA* nonmutant population. Best percentage change from baseline according to *PIK3CA* mutation status and treatment group is shown in **Fig. 4**. In terms of tumor size reduction, 4 of 5 patients in the alpelisib group with *PIK3CA* mutation showed decrease in tumor size after treatment, with 60% surpassing the PR threshold, compared with 50% in the *PIK3CA* nonmutant group. In patients with *PIK3CA*-mutated disease, 4/5 (80%) and 1/2 (50%) in the alpelisib and buparlisib groups achieved PR, respectively.

Patient-reported outcomes

No notable pattern was observed over time for changes in the EQ-5D-5L total health index scores, WPAI-GH scores, and GAD-7 scores in any treatment group. Shifts from a PHQ-9 score of "none" or "mild" at baseline to a score of "moderate" or "severe" were recorded during the scheduled visits in the treatment or follow-up periods for the buparlisib group only; this was not observed in the alpelisib or control groups. One patient (7.7%) in the buparlisib group reported a worst postbaseline score of "severe" during the study ("none" at baseline). An additional 4 patients (30.8%) in the buparlisib group reported a worst postbaseline score of "moderate" ("none" or "mild" at baseline). Detailed results are reported in Supplementary Tables S5 and S6.

Discussion

The aim of this phase Ib, open-label, parallel-group, multicenter, dose deescalation study was to evaluate the MTD and RP2D, safety, and preliminary efficacy of alpelisib and buparlisib in combination with tamoxifen plus goserelin in premenopausal Asian women with HR^+, $HER2^-$ ABC. In the last two decades, one of the most important findings for the treatment of advanced premenopausal patients with HR^+ breast cancer was the superiority of the combination of tamoxifen plus LHRH agonists compared with tamoxifen or LHRH monotherapies (36). Despite advances in the treatment of postmenopausal HR^+ breast cancer over the last decade, improvement in the treatment

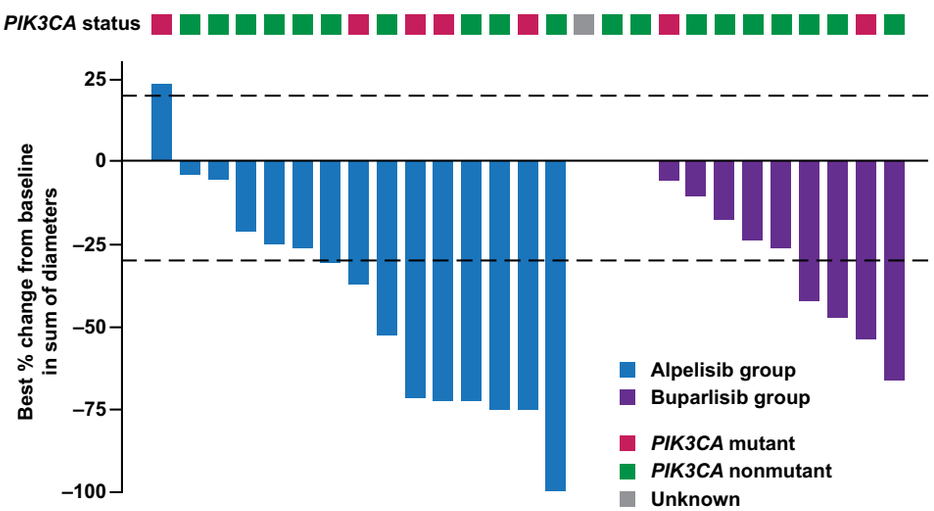

Figure 4.
Best percentage change from baseline in sum of longest diameters. The horizontal dashed lines represent thresholds for PR (−30% change from baseline in sum of diameters) and PD (+20% change from baseline in sum of diameters), per RECIST 1.1. No tumor measurements are available for 2 patients. They have both *PIK3CA* status nonmutant.

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options for premenopausal patients remains limited (34). A recently concluded phase III study (MONALEESA-7) in premenopausal/perimenopausal women with HR^+, $HER2^-$ ABC showed significantly longer OS and PFS in patients treated with ribociclib and endocrine therapy compared with placebo and endocrine therapy (11, 12). The results of our study represent the first investigation of alpelisib in premenopausal women. At the time the study was conducted, CDK4/6 inhibitors had not been approved; thus, no patient had received prior CDK4/6 inhibitor therapy.

No patient in the alpelisib group experienced DLTs; hence, MTD was not reached. The RP2D for alpelisib was estimated to be 350 mg once daily. In the buparlisib group, 2 patients experienced DLTs of hyperglycemia and rash that were determined to be related to buparlisib. However, the criteria for MTD were not met as both patients belonged to different phase cohorts (deescalation and expansion phases). Hence, the RP2D for buparlisib was determined to be 100 mg once daily. These doses are consistent with results of previous dose-finding studies on alpelisib and buparlisib monotherapy in Asian patients with advanced solid tumors (37, 38). The RP2D of alpelisib 350 mg from this study is higher than the dose used in SOLAR-1 (300 mg; refs. 31, 39); this study was conducted prior to SOLAR-1 and while BELLE-2 was ongoing. Criteria for DLTs in this study were generally similar to phase I trials for alpelisib and buparlisib (Supplementary Table S7), except mood alteration was included as a DLT in the phase I buparlisib study.

Treatment discontinuation due to an AE in the buparlisib group was 53.8% and 18.8% in the alpelisib group. For these two treatment groups, a total of 14 patients (73.7%) completed treatment up to disease progression or death: 81.2% in the alpelisib group and 53.8% in the buparlisib group. The results observed here for the α-selective PI3K inhibitor alpelisib demonstrate a manageable safety profile, which is consistent with the safety profile in the phase III SOLAR-1 study (31). For the pan-PI3K inhibitor buparlisib, the profile observed here supports a narrow therapeutic index, as has been shown in other studies of pan-PI3K inhibitors (33). While neither alpelisib nor buparlisib groups reached MTD, high rates of dose modification/interruption and discontinuation due to AEs were observed in both groups. Lower dose of alpelisib or buparlisib might mitigate this without compromising efficacy. This is supported by SOLAR-1, which utilized 300-mg alpelisib and reported permanent discontinuation due to AEs occurring in 25% of patients (31).

The majority of patients in the alpelisib group (93.8%) and all patients in the buparlisib group reported an AE of special interest. The most common TEAEs of special interest were rash, stomatitis, fatigue, and hyperglycemia. These AEs in alpelisib-treated patients were consistent with SOLAR-1, wherein rash, hyperglycemia, stomatitis, nausea, decreased appetite, fatigue, and weight loss were most commonly reported (>20% of patients; ref. 31). Hyperglycemia was the most frequent AE in both the SOLAR-1 and BELLE-3 trials (25, 31), and is an expected effect of PI3K inhibition (31, 32, 40) due to loss of insulin signaling in pancreatic β-cells and peripheral tissues (31, 32, 40). The development of rash is also commonly observed with PI3K inhibitors (41). PI3K inhibitor–associated dermatitis is characterized by dermal hypersensitivity reaction or perivascular lymphocytic inflammation (42).

This study had a longer duration of exposure to the study drug compared with other studies of alpelisib and buparlisib. Median duration of treatment in the alpelisib group was approximately 9 months and approximately 6 months in the buparlisib group. In the SOLAR-1 trial, the median duration of exposure to alpelisib was 5.5 months in the *PIK3CA* mutant cohort and 5.6 months in the *PIK3CA* nonmutant cohort (31). The longer duration of treatment observed here, particularly for the combination of alpelisib and tamoxifen plus goserelin, could be due to better tolerability or a more endocrine-sensitive population compared with SOLAR-1. Furthermore, the data presented here suggest that premenopausal women may tolerate the FDA-approved dose (300 mg) of alpelisib better than the population in SOLAR-1, which was primarily postmenopausal women (31, 39).

In the alpelisib group, duration of treatment tended to be longer for patients with *PIK3CA*-mutated tumors (**Fig. 2**) and *PIK3CA*-mutated tumors demonstrated a greater decrease in size from baseline compared with *PIK3CA* nonmutated tumors (**Fig. 4**). This is consistent with alpelisib's known selectivity in targeting the PI3Kα expressed by the *PIK3CA* gene (43). In the SOLAR-1 trial, the alpelisib plus fulvestrant combination demonstrated a 35% risk reduction in PFS compared with placebo plus fulvestrant for patients in the *PIK3CA*-mutant cohort (31). In this study, PFS was reported to be 25.2 months for alpelisib (longest confirmed PFS: 47.6 months) and 20.6 months for buparlisib (longest confirmed PFS: 33.5 months). This study demonstrates improved responses and a tolerable safety profile for longer durations of exposure in premenopausal patients with HR^+, $HER2^-$ ABC treated with alpelisib or buparlisib in combination with tamoxifen and goserelin.

This study is limited by its small sample size; hence, the results of this study should be interpreted with caution. Further development of buparlisib has been discontinued for breast cancer due to its less favorable safety profile (25, 33). This study demonstrated favorable results for alpelisib and supports the need for further studies in premenopausal patients with HR^+, HER^- ABC. Another limitation of this study is the lack of pharmacokinetic and pharmacodynamic assessments. Further study is appropriate to elucidate any drug–drug interaction between alpelisib and tamoxifen and confirm pharmacodynamic suppression of the PI3K pathway.

In conclusion, the MTD was not exceeded for either alpelisib or buparlisib, and the RP2D was determined to be 350 mg once daily for alpelisib and 100 mg once daily for buparlisib. The safety profiles for both treatment groups were consistent with previously reported studies, with no unexpected safety findings. Both alpelisib and buparlisib demonstrated clinical activity, with longer PFS and higher response rates observed in the alpelisib group. Although this is an early-phase study in a small group of patients, these data suggest that alpelisib in combination with endocrine therapy may potentially be a tolerable and efficacious treatment for premenopausal women with HR^+, $HER2^-$ ABC; further research is warranted exploring this possibility.

Authors' Disclosures

Y.-S. Lu reports grants and personal fees from Novartis (clinical trial and speaker fee) and Merck (clinical trial and speaker fee); personal fees from Pfizer (speaker fee) and Eli Lilly (speaker fee); and personal fees and other from Roche (speaker fee, clinical trial support) during the conduct of the study. K.S. Lee reports personal fees from Roche (consulting), Lilly (consulting), and Novartis (consulting) and nonfinancial support from Dong-A ST (supplied drug) outside the submitted work. J.H. Kim reports grants from Ono Pharma Korea Co., Ltd. outside the submitted work. K. Shotelersuk reports grants from Novartis Pharmaceuticals during the conduct of the study. K.H. Jung reports personal fees from AstraZeneca, Roche, Celgene, Novartis, and Takeda Pharmaceuticals. R. Valenti reports other from Novartis Pharma AG (employee) outside the submitted work. C. Slader reports other from Novartis Pharma AG (employee, stock owner) during the conduct of the study. M. Gao reports other from Novartis (employee) during the conduct of the study and other from Novartis (employee) outside the submitted work. Y.H. Park reports grants and nonfinancial support from Pfizer, AstraZeneca, Novartis, Merck, Eisai, and Roche; grants from Hanmi; and personal fees and

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Authors' Contributions

Y.-S. Lu: Conception and design; development of methodology; acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript; study supervision. **K.S. Lee:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **T.-Y. Chao:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **L.-M. Tseng:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **I. Chitapanarux:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **S.-C. Chen:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **C.-T. Liu:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **J. Sohn:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **J.H. Kim:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **Y.-C. Chang:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **Y. Yang:** Acquisition of data (acquired and managed patients, provided facilities, etc); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **K. Shotelersuk:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **K.H. Jung:** Acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript. **R. Valenti:** Conception and design; development of methodology; analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript; study supervision. **C. Slader:** Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript; study supervision. **M. Gao:** Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript; study supervision. **Y.H. Park:** Conception and design; development of methodology; acquisition of data (acquired and managed patients, provided facilities, etc.); analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis); writing, review, and/or revision of the manuscript; study supervision.

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