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A Phase I Study of LSZ102, an Oral Selective Estrogen Receptor Degrader, with or without Ribociclib or Alpelisib, in Patients with Estrogen Receptor–Positive Breast Cancer

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ABSTRACT

Purpose: Data are sparse for oral selective estrogen receptor (ER) degraders (SERD) in cancer treatment. The investigational oral SERD LSZ102 was assessed in monotherapy and combination use in a phase I study.

Patients and Methods: A phase I, multicenter, open-label dose-escalation study (NCT02734615) of LSZ102 alone (arm A; $n = 77$) or with ribociclib (arm B; $n = 78$) or alpelisib (arm C; $n = 43$) in heavily pretreated adults with histologically confirmed ER-positive breast cancer and prior disease progression. Arm A received LSZ102 200–900 mg/day; arm B, LSZ102 200–600 mg/day plus ribociclib 300–600 mg/day; arm C, LSZ102 300–450 mg/day plus alpelisib 200–300 mg/day. Key outcomes were dose-limiting toxicities (DLT) in the first 28-day treatment cycle, adverse events (AE), laboratory parameters, pharmacokinetics, biopsy ER protein, and investigator-assessed clinical response (RECIST v1.1).

Results: The most common AEs were gastrointestinal. Treatment-related serious AEs occurred in 10% of participants (19/198), mostly in arm C [10/43 (23%)]. DLTs occurred in: arm A, 5% (4/77); arm B, 3% (2/78); and arm C, 19% (8/43). LSZ102 exposure was slightly greater than dose proportional. On-treatment biopsy ER reductions were observed, with a trend toward an LSZ102 dose response. Objective response rates (95% confidence interval) were: arm A, 1.3% (0.0–7.0); arm B, 16.9% (9.3–27.1); and arm C, 7.0% (1.5–19.1), and clinical benefit rates 7.8% (2.9–16.2), 35.1% (24.5–46.8), and 20.9% (10.0–36.0), respectively.

Conclusions: LSZ102 was well tolerated alone and with ribociclib and had a manageable safety profile with alpelisib. Preliminary clinical activity was observed in combination use.

Introduction

The estrogen receptor (ER) α signaling pathway plays a key role in tumor development for the majority of breast cancers (1, 2). Endocrine treatment for ER-positive breast cancer targets this pathway through several mechanisms, including estrogen depletion by aromatase inhibitors, use of selective ER modulators, and disruption of estrogen binding and ER depletion by selective ER degraders (SERD).

Both intrinsic and treatment-emergent resistance to endocrine treatment is common. Mechanisms include estrogen-independent ER activity via functional mutations in the ER-encoding gene *ESR1* (3, 4), decoupling of cell-cycle control from ER signaling via dysregulation of the cyclin D—cyclin-dependent kinase 4/6 (CDK4/6)—retinoblastoma protein pathway (5), and dysregulation of alternative proliferation pathways such as PI3K—protein kinase B (AKT)—mTOR (5).

There is an underlying rationale for combining endocrine therapy with inhibitors of these resistance pathways, supported by clinical data. Clinical trials in ER-positive breast cancer show progression-free survival (PFS) and overall survival benefits for single-agent fulvestrant, the only currently approved SERD, versus the aromatase inhibitor anastrozole (6, 7). Compared with fulvestrant alone, PFS and overall survival are longer for fulvestrant combined with the CDK4/6 inhibitors ribociclib (8) or abemaciclib (9, 10), and PFS is longer for fulvestrant combined with the PI3K inhibitors buparlisib (11, 12) or alpelisib (13) or with the mTOR inhibitor everolimus (14, 15).

Fulvestrant survival benefit is dose dependent (16, 17), but poor oral bioavailability mandates administration by monthly intramuscular injection, limiting clinical dosing to a maximum of 500 mg. Of note, data from the plasmaMATCH study, a multiple parallel-cohort trial of circulating tumor DNA (ctDNA)-directed therapy, failed to meet prespecified efficacy criteria despite extended-dose fulvestrant (500 mg every 2 weeks) in patients with *ESR1* mutations (18). Orally available

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

The utility of fulvestrant, the only approved selective estrogen receptor (ER) degrader (SERD), for treating ER-positive breast cancer, is restricted by dosing/exposure limitations imposed by intramuscular administration. Investigational oral SERDs could potentially suppress ER more effectively and achieve high systemic exposures and activity against *ESR1* mutations, resulting in greater clinical activity. However, clinical data for these oral agents remain sparse, including combination use with inhibitors of endocrine therapy resistance pathways that are effective and FDA-approved for use with fulvestrant. This first-in-human study of oral SERD LSZ102 demonstrated good tolerability over a range of doses alone or with the cyclin D–cyclin-dependent kinase 4/6 (CDK4/6) inhibitor ribociclib, and a manageable safety profile with the PI3Kα-specific inhibitor alpelisib. Preliminary clinical activity was noted in combination use, particularly with ribociclib. These initial data demonstrate the feasibility of combination treatment of ER-positive breast cancer with oral SERDs plus CDK4/6 or PI3K inhibitors.

SERDs may achieve more complete ER degradation than fulvestrant (19), potentially conferring greater clinical activity. LSZ102 is an investigational oral SERD that shows single-agent activity against *ESR1*-mutant models and synergistic activity with ribociclib and alpelisib in preclinical models of ER-positive breast cancer (19). We report data from a phase I, first-in-human trial of LSZ102, with or without ribociclib or alpelisib, in adults with ER-positive breast cancer.

Materials and Methods

Study design and participants

This was an open-label, multinational, multicenter, first-in-human, phase I/Ib, dose-escalation study (NCT02734615) of LSZ102 alone or in combination with ribociclib or alpelisib in adults with advanced or metastatic breast cancer and progression on or after endocrine therapy. The escalation study design is shown in **Fig. 1A**. The protocol and statistical analysis plan are provided in Supplementary Data S1 and S2, respectively.

Participants were initially recruited in cohorts of 3–6 to receive LSZ102 alone (arm A) starting at 200 mg once daily. Escalation in combination with ribociclib (arm B) or alpelisib (arm C) was started sequentially after a safe and tolerable single-agent dose was established. Drugs were administered on a 28-day cycle with continuous dosing for LSZ102 and alpelisib and either continuous or 3 weeks on/1 week off administration of ribociclib. LSZ102 ± ribociclib was administered fasted, fed, or without regard to food; LSZ102 with alpelisib was administered with food.

Arm A tested LSZ102 200–900 mg once daily or 200–300 mg twice daily. Arm B tested LSZ102 200–600 mg once daily with ribociclib 300–600 mg once daily (3 weeks on/1 week off), LSZ102 450 or 600 mg once daily with ribociclib 300 or 400 mg once daily (continuous), or LSZ102 200 or 300 mg twice daily with ribociclib 200 mg twice daily (continuous). Arm C tested LSZ102 300 or 450 mg once daily with alpelisib 200–300 mg once daily.

In all arms, decisions to escalate and proceed to the next dose level were established by agreement between the sponsor and investigators after a review of all available safety, pharmacokinetics, and pharmacodynamics data. A planned dose-expansion phase was closed for reasons unrelated to drug safety after the first 2 expansion participants initiated LSZ102 450 mg once daily plus ribociclib 400 mg once daily (3 weeks on/1 week off). These 2 participants are combined with the arm B escalation group in these analyses. Data are drawn from first participant first visit on June 14, 2016, to data cutoff on January 15, 2020.

Eligible participants were adults (≥18 years old) with locally diagnosed, histologically and/or cytologically confirmed inoperable, locally advanced, or metastatic ER-positive breast cancer and an Eastern Cooperative Oncology Group performance status of 0 or 1. For escalation, objective evidence was required of either progression after endocrine therapy for metastatic/locally advanced disease not amenable to curative therapy or recurrence on or within 12 months of adjuvant treatment including an aromatase inhibitor. Pre- and perimenopausal participants required concurrent ovarian suppression. In dose escalation, there was no limit to the number of prior treatment lines, and prior use of CDK4/6 or mTOR inhibitors was allowed. In arm C, prior PI3K or AKT inhibitor use was not permitted, and PI3K mutations were not required.

Participants were excluded for symptomatic central nervous system (CNS) metastases or visceral disease or a history of inflammatory breast disease, carcinomatous meningitis, diffuse lymphangitic carcinomatosis, or significant endometrial disorders (excluding reproductive metastases). Those with type 1 or uncontrolled type 2 diabetes (fasting plasma glucose >140 mg/dL or glycated hemoglobin $A_{1c} \geq 6.5\%$), history of gestational diabetes, or steroid-induced diabetes were not eligible for arm C.

The study was undertaken in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, the ethical principles originating in the Declaration of Helsinki, and all applicable local regulations. The study protocol and informed consent forms were approved by the relevant local independent ethics committees or institutional review boards. All participants provided written informed consent.

Objectives and endpoints

The primary objectives were to characterize the safety and tolerability of LSZ102 alone or with ribociclib or alpelisib and to identify recommended expansion doses. Secondary objectives included characterizing (i) the preliminary antitumor efficacy and pharmacokinetics of LSZ102 alone or in combination, (ii) the effect of food on LSZ102 pharmacokinetics under fasted and fed dosing conditions, and (iii) pharmacodynamic markers using IHC. Note that the food-effect substudy is not described. *Post hoc* exploratory assessments evaluated the effect of treatment on ctDNA, explored the evolution and clinical effect of ctDNA mutations, and investigated multivariate predictors of disease progression on treatment.

The primary endpoint was the frequency of dose-limiting toxicities (DLT) comprising protocol-defined adverse events (AE) or laboratory abnormalities in the first treatment cycle. The probability of a DLT at different doses was estimated from observed data using a Bayesian logistic regression model (BLRM; ref. 20). Other safety endpoints included the incidence and severity of AEs and serious AEs, tolerability, laboratory parameters, vital signs, and electrocardiography. The definition and grading of AEs were per the Common Terminology Criteria for Adverse Events version 4.03.

Efficacy endpoints were per Response Evaluation Criteria in Solid Tumors version 1.1 (21) by local investigator assessment: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and non-CR/non-PD (NCRNPD) for those with non-target lesions only. Overall response rate (ORR) was defined as the

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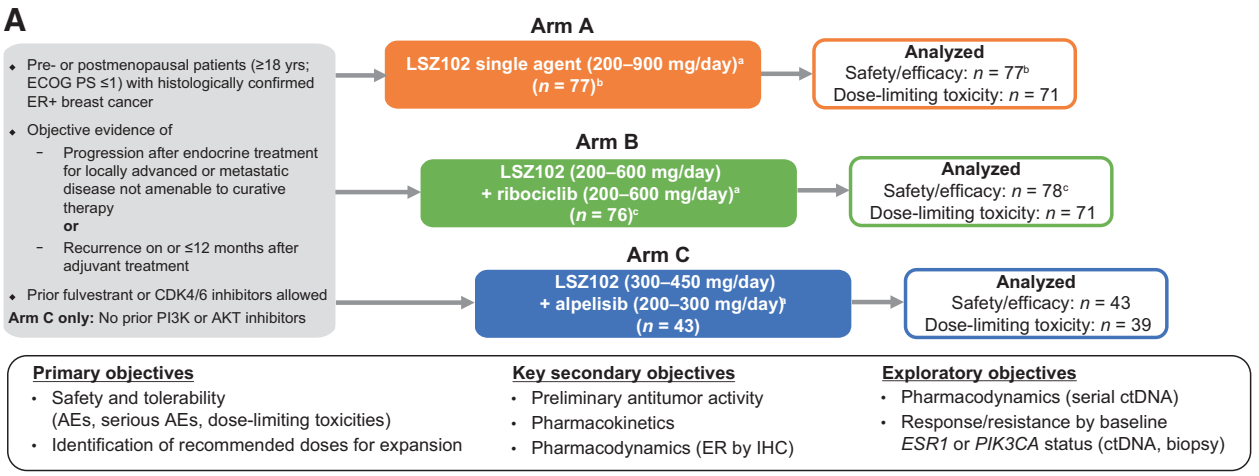

Enrollment was not randomized.

[a]LSZ102 QD was tested alone or with ribociclib QD (3 weeks on/1 week off or continuous) or alpelisib QD; LSZ102 BID alone and LSZ102 BID + ribociclib BID in continuous regimens were also explored.

[b]Total single-agent enrollment *n* = 78; 1 patient discontinued during food effect run-in period before entering cycle 1 and is not included in analyses.

[c]Arm B analyses also included 2 patients enrolled into dose expansion (total *n* = 78).

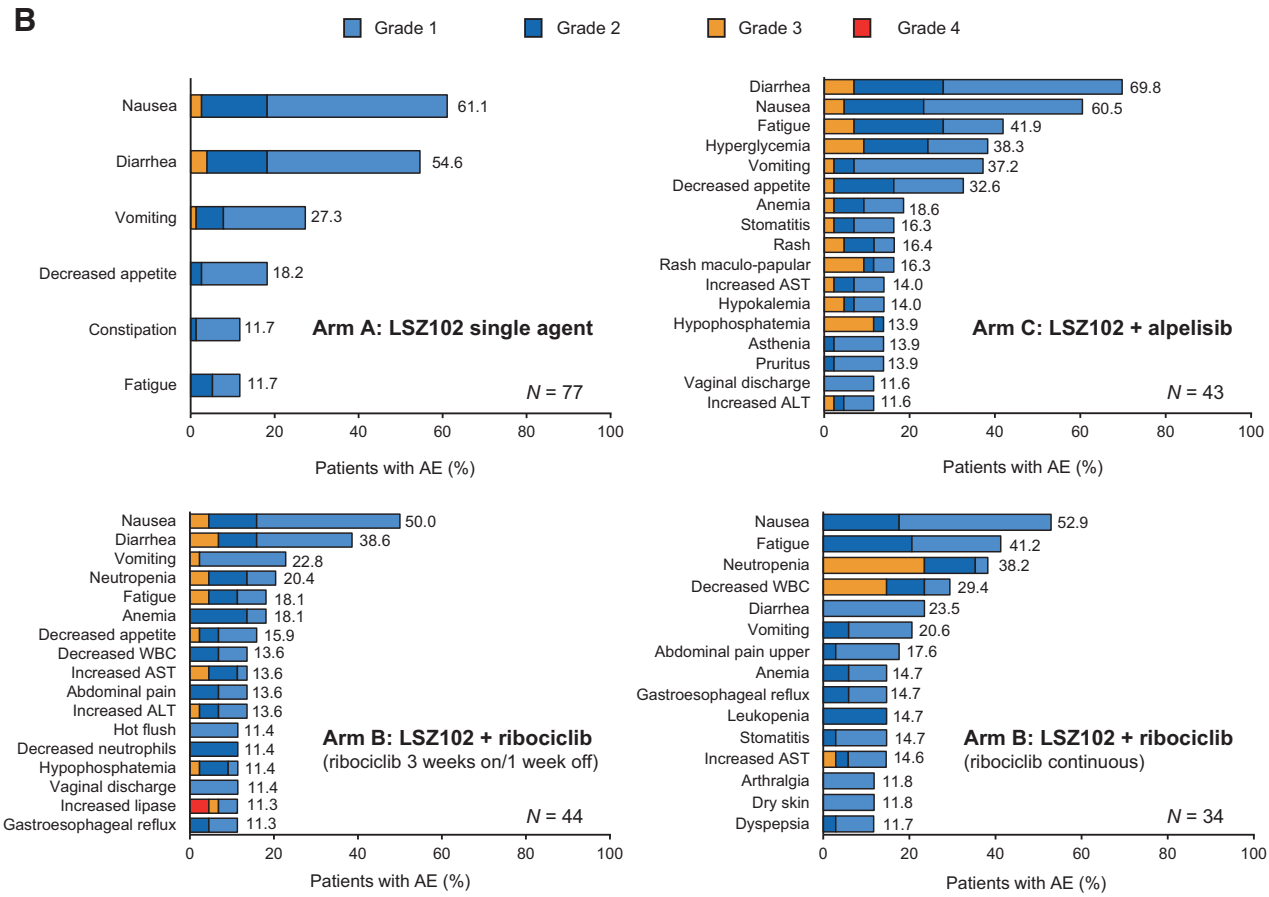

Figure 1.

CLSZ102×2101 (NCT02734615) dose-escalation study design (**A**) and common treatment-related adverse events (**B**) occurring in ≥10% of participants. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ER+, estrogen receptor positive; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit α gene; QD, once daily; WBC, white blood cells.

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percentage of confirmed CR+PR in patients with measurable disease among all patients; similarly, the clinical benefit response (CBR) was defined as the percentage of CR+PR+(SD and NCRNPD maintained for at least 24 weeks) among all patients. PFS was assessed by Kaplan–Meier analysis.

Blood samples for pharmacokinetic analyses were drawn in cycle 1 predose and at 0.5, 1, 2, 4, 6, 8, and 24 hours after the morning dose on day 1 and either day 21 (for arm B, ribociclib 3 weeks on/1 week off) or day 28, and predose only on days 8 and 15. Predose samples were also collected on day 1 of cycles 2 to 6. Drugs and metabolites were measured in serum using a validated liquid chromatography–tandem mass spectrometry assay. The dose proportionality of LSZ102 pharmacokinetics over the range of 200 to 900 mg once daily (fasted) was assessed using the power model (22).

Blood samples for ctDNA assessment were drawn before the dose on the first day of cycles 1, 3, and 5, at every other radiographic assessment after cycle 6, and at disease progression. Error-corrected deep sequencing was performed in cell-free DNA at screening, on treatment, and at disease progression using the Novartis NGS cell-free DNA 2.0 PanCancer gene panel (see Supplementary Information).

Paired tissue biopsies were taken at screening and on day 15 of cycle 1. ER protein levels were measured semiquantitatively by IHC using the H-score method (23).

Statistical analysis

DLT rates in the treated population were estimated using a hierarchical BLRM for LSZ102 as a single agent and nonhierarchical BLRM for combination therapy. All models used estimation with overdose control (24) criteria to ensure that the estimated risk of excessive toxicity at the next planned dose was <25%. Target toxicity rates were considered from 16% to <33%. The maximum tolerated dose was defined as the highest tested dose with an estimated DLT risk of <33%.

The full analysis set (FAS) included all participants who received ≥ 1 dose of study drug. The safety set comprised members of the FAS with ≥ 1 valid postbaseline safety assessment. The dose-determining set for evaluating DLT frequency comprised all participants in the escalation safety set with a DLT in cycle 1 or who had received ≥ 75% of their planned cycle 1 doses and were followed for ≥ 28 days after the first dose.

Data are presented by total daily dose of study agent(s) and/or once daily/twice daily administration as appropriate. Data for fed, fasted, or without regard to food administration were pooled.

A *post hoc*, multivariable exploratory analysis of predictors of disease progression in each treatment arm was undertaken by Cox proportional hazard modeling of progression as an event. Categorical covariates for the model were: biopsy ER H-score change from baseline to cycle 1 day 15 (≤median of arm vs. >median of arm), presence versus absence of *ESR1* mutations; prior exposure to fulvestrant (yes vs. no), prior exposure to CDK4/6 inhibitors (yes vs. no), presence versus absence of visceral metastases, presence versus absence of endocrine resistance (defined as receipt of <24 months adjuvant endocrine therapy or absence of clinical benefit from the last endocrine therapy regimen in the metastatic or locally advanced setting), and number of prior lines of therapy in the metastatic or locally advanced setting (2, 3, 4, and ≥5 lines, vs. 1).

Results

Participant characteristics and disposition

Overall, 199 participants received LSZ102 alone ($n = 78$) or with ribociclib ($n = 78$) or alpelisib ($n = 43$). One participant (single agent) from the food-effect substudy discontinued in the run-in period due to an increased lipase level prior to starting day 1 of cycle 1 and was excluded from efficacy, safety, and biomarker analyses, resulting in 77 participants assessed in arm A. An additional 17 participants were excluded from the dose-determining set: both patients from the closed LSZ102 plus ribociclib expansion cohort otherwise analyzed as part of arm B, plus 15 who did not receive the prespecified amount of treatment during cycle 1 (Supplementary Table S1). Baseline characteristics and disposition are summarized in **Table 1**. Participants were heavily pretreated for metastatic or locally advanced disease, with a median of 3 to 4 prior treatment lines across treatment arms. Across all arms, approximately half had received prior fulvestrant and/or CDK4/6 inhibitors.

Safety

Common treatment-related AEs were mostly mild or moderate (**Fig. 1B**), and gastrointestinal events (nausea, diarrhea, vomiting) were the most frequent. Other common AEs of combination treatment, including those with a higher proportion of grade 3 severity, were consistent with the safety profiles of ribociclib (leukopenia, neutropenia, aspartate aminotransferase increase) or alpelisib (skin rash, hyperglycemia, decreased appetite). Common treatment-related AEs in arm B were broadly similar between continuous and 3 weeks on/1 week off ribociclib, although continuous ribociclib showed a higher overall incidence of neutropenia [38.2% (13/34) vs. 20.5% (9/44)] and white blood cell decreases [29.4% (10/34) vs. 13.6% (6/44)], together with a higher incidence of grade 3 severity for both conditions [neutropenia 23.5% (8/34) vs. 4.5% (2/44); white blood cell decrease 14.7% (5/34) vs. 0%].

Nineteen participants (10%) experienced treatment-related serious AEs: 1 in arm A, 8 in arm B, and 10 in arm C. Details are given in Supplementary Table S2. There were 11 deaths on treatment or within 30 days from the last dose: 5 in arm A, 3 in arm B, and 3 in arm C. All but 1 was due to disease progression. One participant (arm C) died from infectious pneumonia in the context of immunosuppression, suspected to be treatment-related in a clinical picture of disease progression.

DLTs are summarized in **Table 2**. Dose-limiting diarrhea occurred in one third of those receiving LSZ102 900 mg/day in arm A, but DLTs were uncommon or absent at lower doses. In arm B, no DLTs occurred in the continuous ribociclib dosing groups, and in the 3 weeks on/1 week off ribociclib groups DLTs were only seen at the highest tested doses of LSZ102 600 mg plus ribociclib 400 mg once daily. In arm C, DLTs occurred in all groups, and most events (stomatitis, hyperglycemia, rash) were consistent with the safety profile of alpelisib. All DLTs had resolved or were resolving at last follow-up.

On the basis of these and the pharmacokinetic, pharmacodynamic, and efficacy data below, recommended doses for the planned expansion phases were LSZ102 450 mg once daily alone or with ribociclib 400 mg once daily (3 weeks on/1 week off or continuous; fasted or with a snack or low-/regular-calorie meal), or LSZ102 300 mg once daily plus alpelisib 250 mg once daily with a regular meal. High-fat meals were not recommended because pharmacokinetic data had previously shown an approximate 2-fold increase in LSZ102 exposure when administered with a high-fat high-calorie meal (25).

Pharmacokinetics and pharmacodynamics

Steady-state (cycle 1, day 28) LSZ102 plasma pharmacokinetic data are shown in **Fig. 2A** and Supplementary Table S3. LSZ102 was rapidly absorbed under fasted conditions, with a median time to maximum

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Table 1. Baseline characteristics and disposition.

	Arm A ($n = 78$)	Arm B[a] ($n = 78$)	Arm C ($n = 43$)
Age, median (range) years	59.0 (30–77)	59.5 (33–79)	55.0 (36–79)
≥65 years, *n* (%)	21 (26.9)	26 (33.3)	6 (14.0)
Race, *n* (%)			
Caucasian	58 (74.4)	61 (78.2)	35 (81.4)
Black	0	5 (6.4)	2 (4.7)
Asian	14 (17.9)	6 (7.7)	4 (9.3)
Other/unknown	6 (7.7)	6 (7.7)	2 (4.7)
ECOG performance status, *n* (%)			
0	53 (67.9)	59 (75.6)	31 (72.1)
1	25 (32.1)	19 (24.4)	12 (27.9)
Visceral metastases, *n* (%)[b]	59 (76.6)	60 (76.9)	33 (76.7)
Tumor mutational status (ctDNA), *n/N* (%)[c]			
ESR1 mutated	30/72 (41.7)	30/78 (38.5)	10/40 (25.0)
PIK3CA mutated	21/72 (29.2)	30/78 (38.5)	18/40 (45.0)
Endocrine sensitivity status, *n* (%)[d]			
Sensitive	24 (30.8)	27 (34.6)	13 (30.2)
Resistant	15 (19.2)	15 (19.2)	10 (23.3)
Unknown/missing	39 (50.0)	36 (46.2)	20 (46.5)
Prior antineoplastic therapy (metastatic/locally advanced), *n* (%)[b]	74 (96.1)	75 (96.2)	42 (97.7)
Previous endocrine therapy	72 (93.5)	73 (93.6)	42 (97.7)
Previous CDK4/6 inhibitor	43 (55.8)	27 (34.6)	28 (65.1)
Previous fulvestrant	46 (59.7)	47 (60.3)	20 (46.5)
Previous chemotherapy	53 (68.8)	52 (66.7)	27 (62.8)
No. of previous lines of antineoplastic therapy (metastatic/locally advanced), median (range)			
Any treatment	4.0 (0–10)	4.0 (0–10)	3.0 (0–15)
Endocrine therapy	2.0 (0–7)	2.0 (0–5)	2.0 (0–6)
Treatment ongoing at data cutoff, *n* (%)	0	8 (10.3)	5 (11.6)
Discontinuations from study treatment, *n* (%)	78 (100)	70 (89.7)	38 (88.4)
Progressive disease	71 (91.0)	64 (82.1)	29 (67.4)
Adverse event	2 (2.6)	2 (2.6)	2 (4.7)
Physician decision	1 (1.3)	1 (1.3)	1 (2.3)
Participant decision	4 (5.1)	3 (3.8)	2 (4.7)
Death	0	0	4 (9.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *ESRN1*, estrogen receptor 1 gene; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit α gene.
[a]Includes 2 participants recruited to LSZ102 + ribociclib dose expansion.
[b]Denominators for percentages are the full analysis set for each treatment arm: single agent, $n = 77$ (see text); LSZ102 + ribociclib, $n = 78$; and LSZ102 + alpelisib, $n = 43$.
[c]Denominators shown are the number of participants in each treatment arm with valid baseline ctDNA data.
[d]Endocrine sensitivity status determined by last endocrine therapy outcome before study treatment: "sensitive" indicated ≥ 24 months of adjuvant endocrine therapy or demonstrated clinical benefit with endocrine therapy for metastatic or locally advanced disease (complete or partial response or stable disease ≥ 24 weeks); "resistant" indicated <24 months adjuvant endocrine therapy or no clinical benefit with metastatic/locally advanced endocrine therapy; and "unknown" indicated no valid tumor assessment from last endocrine therapy.

concentration (C_{max}) of 2–3 hours and showed moderate to large pharmacokinetic variability across the once-daily dosing range. In general, and considering the pharmacokinetic variability of LSZ1002, concomitant ribociclib or alpelisib at their recommended expansion doses did not appear to affect LSZ102 exposure substantially, and LSZ102 450 mg pharmacokinetics did not appear to be substantially affected by administration with or without a regular meal (Supplementary Table S3). Steady-state LSZ102 C_{max} was dose proportional for 200 to 900 mg/day [$\beta = 1.03$; 90% confidence interval (CI), 0.77–1.30]; the area under the LSZ102 concentration–time curve from time 0 to the last measurement was slightly more than dose proportional [$\beta = 1.27$ (90% CI, 1.02–1.52); Supplementary Fig. S1].

IHC analysis of paired biopsies at screening and cycle 1 day 15 showed a trend toward dose-dependent ER degradation for single-agent LSZ102 (**Fig. 2B**), which did not appear to be affected by ribociclib or alpelisib (Supplementary Fig. S2).

Preliminary efficacy

Individual treatment durations are shown in **Fig. 3**, and best overall responses are summarized in Supplementary Table S4. Median (range) duration of study follow-up in weeks were 15.6 (3.9–134.2) in arm A, 32.8 (3.3–127.1) in arm B, and 17.1 (4.1–107.7) in arm C.

ORR and CBR were: arm A, 1.3% (1/77 evaluable participants; 95% CI, 0.0–7.0) and 7.8% (6/77; 2.9–16.2), respectively; arm B, 16.9% (13/77; 9.3–27.1) and 35.1% (27/77; 24.5–46.8), respectively; and arm C, 7.0% (3/43; 1.5–19.1) and 20.9% (9/43; 10.0–36.0), respectively. In arm B, ORR and CBR were numerically higher for continuous ribociclib [26.5% (9/34 evaluable; 95% CI, 12.9–44.4) and 41.2% (14/34; 24.6–59.3), respectively] than 3 weeks on/1 week off ribociclib [9.3% (4/43; 2.6–22.1) and 30.2% (13/43; 17.2–46.1), respectively]. ORR and CBR in arm B were also numerically higher in those with versus without prior fulvestrant use [ORR 12.0% (9/75 evaluable; 95% CI, 5.6–21.6) vs. 5.3% (4/75; 1.5–13.1); CBR 21.3% (16/75; 12.7–32.3)

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Table 2. Dose-limiting toxicities of LSZ102 alone and in combination with ribociclib and alpelisib.

Arm A: LSZ102 single agent (*n* = 71)									
Total daily dose, mg	200 (*n* = 4)	400 (*n* = 9)		450 (*n* = 24)		600 (*n* = 28)		900 (*n* = 6)	
Dosing frequency[a]	QD	QD (*n* = 6)	BID (*n* = 3)	QD (*n* = 19)	BID (*n* = 5)	QD (*n* = 23)	BID (*n* = 5)	QD	
Participants with ≥ 1 DLT, *n* (%)	0	0	0	1 (4.2)	0	1 (3.6)	0	2 (33.3)	
ALT increased				1[b]					
AST increased				1[b]					
Vomiting						1			
Diarrhea								2	
Arm B: LSZ102 + ribociclib (ribociclib 3w/1w dosing; *n* = 38)									
Total daily dose, mg	200 + 300 (*n* = 5)	400 + 300 (*n* = 4)		400 + 400 (*n* = 3)		450 + 300 (*n* = 6)	450 + 400 (*n* = 9)	450 + 600 (*n* = 4)	600 + 300 (*n* = 4)	600 + 400 (*n* = 3)
Dosing frequency	QD	QD		QD		QD	QD	QD	QD	QD
Participants with ≥ 1 DLT, *n* (%)	0	0		0		0	0	0	0	2 (66.7)
Decreased appetite										1
Sepsis										1[b]
Febrile neutropenia										1[b]
Arm B: LSZ102 + ribociclib (continuous ribociclib dosing; *n* = 33)									
Total daily dose, mg	400 + 400 (*n* = 5)	450 + 300 (*n* = 6)		450 + 400 (*n* = 14)		600 + 300 (*n* = 4)	600 + 400 (*n* = 4)			
Dosing frequency[a]	BID	QD		QD		QD	BID			
Participants with ≥ 1 DLT, *n* (%)	0	0		0		0	0			
Arm C: LSZ102 + alpelisib (*n* = 39)									
Total daily dose, mg	300 + 200 (*n* = 11)	300 + 250 (*n* = 5)		300 + 300 (*n* = 11)		450 + 200 (*n* = 12)			
Dosing frequency	QD	QD		QD		QD			
Participants with ≥ 1 DLT, *n* (%)	1 (9.1)	1 (20.0)		5 (45.5)		1 (8.3)			
Diarrhea				1					
Rash maculo-papular	1			1		1			
Hypersensitivity		1							
Stomatitis				1					
Hyperglycemia				2					

Note: Overall ns refer to the dose-determining set, which excluded 17 participants from the full analysis set (6 in arm A, 7 in arm B, and 4 in arm C). See text for details.
Abbreviations: 3w/1w, 3 weeks on/1 week off; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DLT, dose-limiting toxicity; QD, once daily.
[a]Each BID dose was half the indicated total daily dose. In arm B, BID indicates LSZ102 BID + ribociclib BID.
[b]Events occurring in the same participant.

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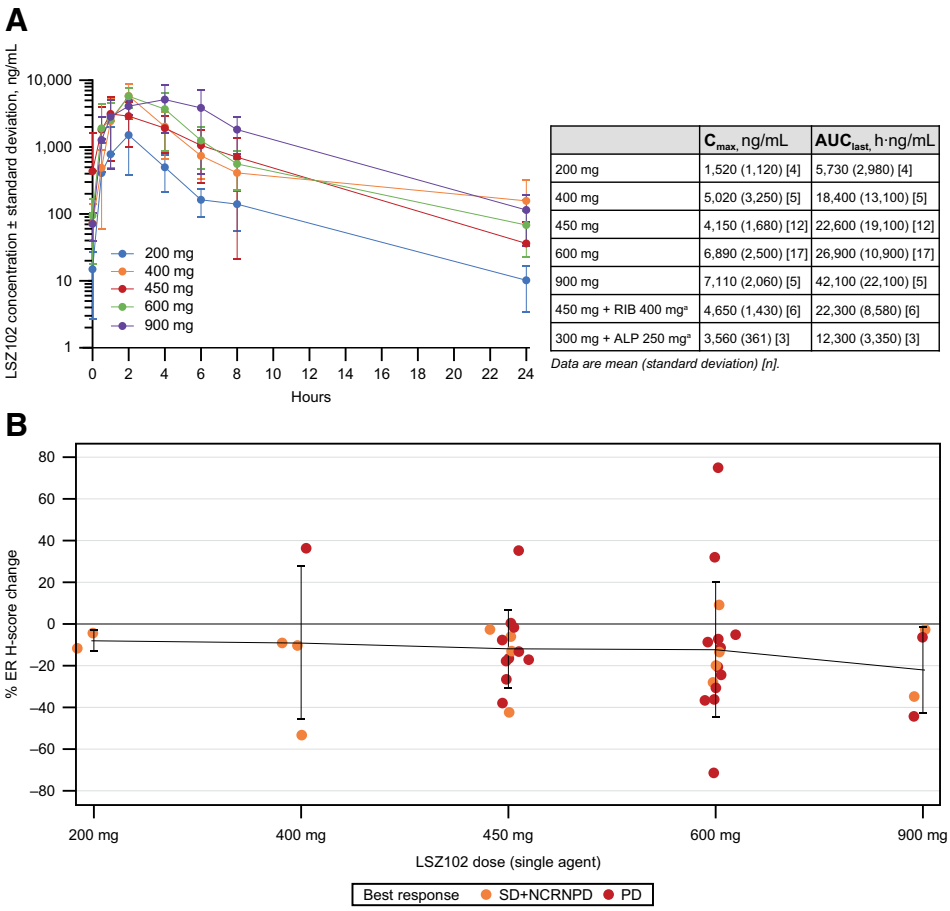

	C_{max}, ng/mL	AUC_{last}, h·ng/mL
200 mg	1,520 (1,120) [4]	5,730 (2,980) [4]
400 mg	5,020 (3,250) [5]	18,400 (13,100) [5]
450 mg	4,150 (1,680) [12]	22,600 (19,100) [12]
600 mg	6,890 (2,500) [17]	26,900 (10,900) [17]
900 mg	7,110 (2,060) [5]	42,100 (22,100) [5]
450 mg + RIB 400 mg[a]	4,650 (1,430) [6]	22,300 (8,580) [6]
300 mg + ALP 250 mg[a]	3,560 (361) [3]	12,300 (3,350) [3]

Data are mean (standard deviation) [n].

Figure 2.

Pharmacokinetics and pharmacodynamics of LSZ102 as a single agent. **A,** Steady-state concentration–time profiles and pharmacokinetic exposure parameters (cycle 1 day 28) for once-daily fasted administration. **B,** Individual percentage changes from baseline in biopsy estrogen receptor H-score (cycle 1 day 15). Abbreviations: ALP, alpelisib; AUC_{last}, area under the LSZ102 concentration–time curve to last measurement; C_{max}, maximum LSZ102 concentration; ER, estrogen receptor; NCRNPD, noncomplete response/nonprogressive disease; PD, progressive disease; PK, pharmacokinetics; RIB, ribociclib; SD, stable disease. [a]Recommended dose levels for combination expansion, all drugs once-daily, continuous cycle.

vs. 13.3% (10/75; 6.6–23.2)], but lower for those with versus without prior use of CDK4/6 inhibitors [ORR 2.7% (2/75; 0.3–9.3) vs. 14.7% (11/75; 7.6–24.7); CBR 9.3% (7/75; 3.8–18.3) vs. 25.3% (19/75; 16.0–36.7)].

There were too few responders in arms A and C to assess response by prior drug use. No participant had a CR. Confirmed PR was observed in 17/197 evaluable participants overall (9%), mostly (13 PRs) in arm B; SD and NCRNPD were observed overall in 65/173 (38%) and 26/34 (76%) evaluable participants with measurable and nonmeasurable disease, respectively.

Median PFS in months was 1.8 (95% CI, 1.7–2.5; 65/77 events) in arm A, 6.2 (5.6–6.4; 58/78) in arm B, and 3.5 (3.2–5.5; 31/43) in arm C (Supplementary Fig. S3). Median PFS in each arm was similar with or without prior use of fulvestrant or CDK4/6 inhibitors (data not shown).

Mutation/response assessment (*post hoc* exploratory)

Of 190 participants with valid baseline ctDNA data, 103 (54%) also had end-of-treatment data (Supplementary Fig. S4). The most common baseline ctDNA mutations in these 103 were in *ESR1* [50% (51/103)], *PIK3CA* [37% (38/103)], and *TP53* [35% (36/103)]. There was no clear association between baseline mutations and subsequent response (Supplementary Fig. S4): *ESR1* mutations were present in 38% (6/16) of those with clinical benefit on treatment versus 52% (45/87) without; *PIK3CA* mutations in 19% (3/16) versus 40% (35/87), respectively; and *TP53* mutations in 19% (3/16) vs. 38% (33/87), respectively. However, the caveat of small responder numbers applies, particularly in arms A ($n = 2$) and C ($n = 1$). There was no indication that ctDNA mutation frequency at end of treatment had increased overall or for particular mutations among those who experienced clinical benefit (Supplementary Fig. S5).

Predictors of disease progression (*post hoc* exploratory)

Multivariable Cox proportional hazard modeling suggested an elevated risk of disease progression in arm A for visceral metastases, in Arm B for receipt of more than one prior line of treatment, and in Arm C for prior use of CDK4/6 inhibitors. There was no apparent association between the risk of disease progression in any treatment arm and prior fulvestrant use, presence of *ESR1* mutations, endocrine resistance, or the extent of on-treatment loss of ER protein in biopsies in this dataset (Supplementary Fig. S6).

Discussion

This phase I/Ib study of LSZ102 represents the first clinical report of an oral SERD in combination with CDK4/6 and PI3Kα inhibitors. LSZ102 was generally well tolerated both alone and in combination. Gastrointestinal toxicities were the most common AEs, and most other AEs in the combination arms were consistent with the safety profile of the combination agent.

LSZ102 showed dose-proportional pharmacokinetics at doses of <900 mg/day, with a time to C_{max} of approximately 2 hours. LSZ102 systemic exposure did not appear to be substantially affected by ribociclib or alpelisib. Degradation of ER was observed in all treatment arms, with an apparent trend suggesting an LSZ102 dose response. It is

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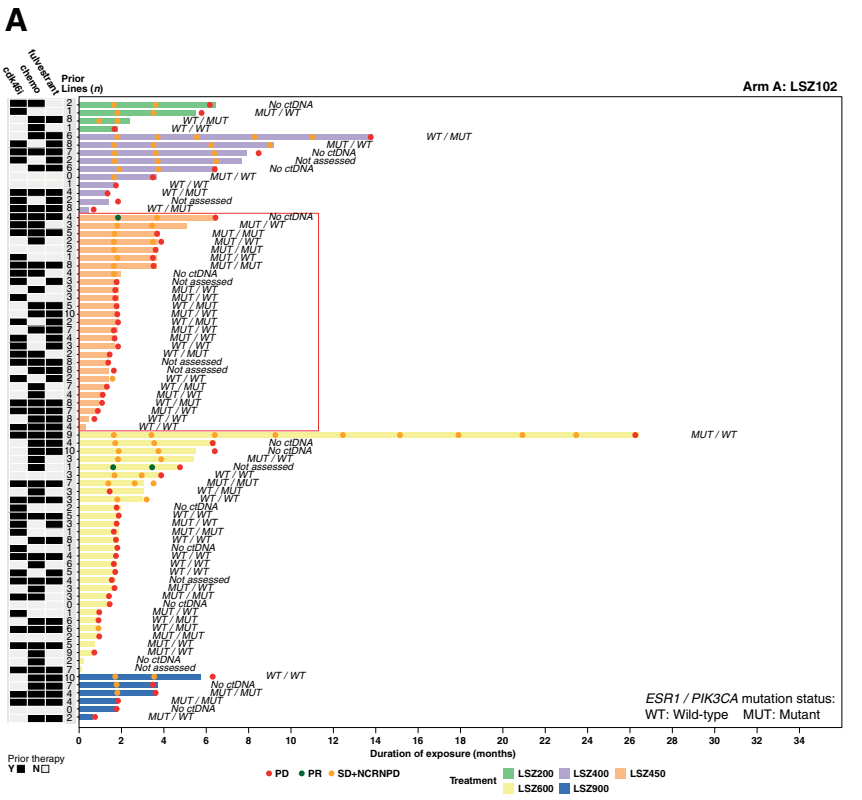

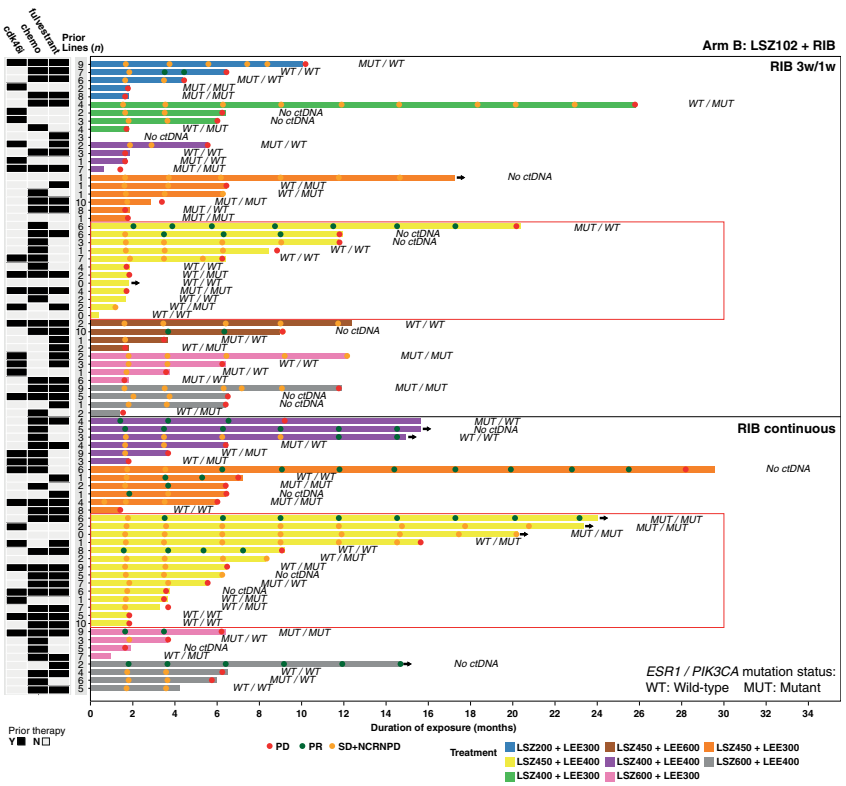

Figure 3.

Individual treatment durations, prior treatment experience, baseline *ESR1* and *PIK3CA* mutational status (ctDNA), and periodic disease evaluations. LSZ102 as a single agent (**A**), LSZ102 plus ribociclib (**B**), (*Continued on the following page.*)

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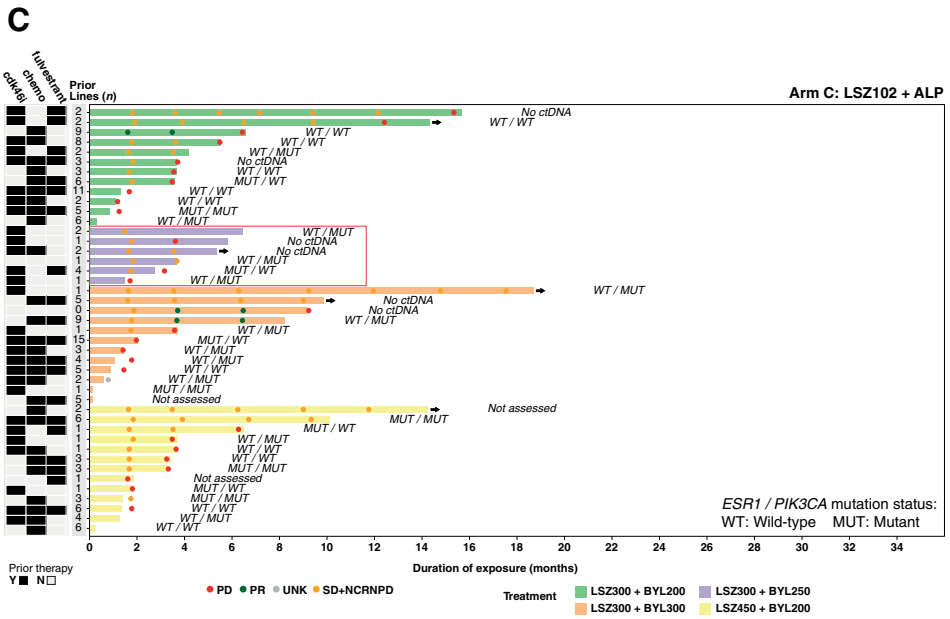

Figure 3.

(*Continued.*) and LSZ102 plus alpelisib (**C**). Red boxes show recommended doses for the planned dose-expansion phase. Abbreviations: ALP, alpelisib; BYL, alpelisib; *ESR1*, estrogen receptor 1 gene; "No ctDNA", no detectable ctDNA identified in baseline sample; LEE, ribociclib; LSZ, LSZ102; MUT, mutant; NCRNPD, noncomplete response/nonprogressive disease; PD, progressive disease; PR, partial response; RIB, ribociclib; SD, stable disease; UNK, unknown; WT, wild-type.

unknown whether maximum degradation was achieved at the time of analysis (cycle 1 day 15).

Preliminary LSZ102 clinical activity was modest as a single agent. Higher responses were observed in combination treatment with ribociclib (17% ORR; 35% CBR) and alpelisib (7% ORR; 21% CBR). Response rates were numerically higher for continuous ribociclib versus 3 weeks on/1 week off, but the small number of samples limits any conclusions. Combination arm PFS was numerically similar with and without baseline *ESR1* or *PIK3CA* mutations (Supplementary Fig. S7), although these data also require cautious interpretation given the small sample sizes.

Exploratory Cox proportional hazard modeling also identified no apparent association between baseline *ESR1* mutation status and the risk of disease progression, consistent with the Kaplan–Meier PFS analysis in Supplementary Fig. S7. Although the hazard model also requires cautious interpretation due to the small sample size and the broad confidence intervals, the results were largely consistent with visceral metastases and extent of previous metastatic treatment being associated with an increased risk of progression on LSZ102-based treatment, but did not show an apparent association between progression in this study and the reduction of ER protein.

The ctDNA mutational landscape was dominated by *ESR1*, *PIK3CA*, and *TP53* variants. Exploratory analyses showed clinical activity in all arms without clear associations with baseline mutations or evidence of mutational enrichment. However, these data are limited, and larger trials are needed to power any evaluation of LSZ102 activity—alone or in combination—on specific mutations in a less heavily pretreated cohort.

The modest clinical activity of LSZ102 as a single agent and the existence of several other oral SERDs advancing in clinical development, such as AZD9833 (camizestrant; ref. 26), SAR439859 (amcenestrant; ref. 27), GDC9545 (giredestrant; ref. 28), and RAD1901 (elacestrant; ref. 29) resulted in the decision to discontinue further development of LSZ102. Nevertheless, the initial data presented here demonstrate for the first time the feasibility of combination treatment of ER-positive breast cancer with oral SERDs and CDK4/6 or PI3K inhibitors. These data provide the first comprehensive characterization of an oral SERD in combination with either partner and support the rationale for oral SERDs as an alternative ER-targeting modality for both wild-type and mutant ESR1.

Data sharing

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be reidentified. Phase I studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase I studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where codevelopment agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

Authors' Disclosures

K. Jhaveri reports personal fees from Novartis, Genentech, Lilly Pharmaceuticals, Taiho Oncology, Pfizer, Jounce Therapeutics, AstraZeneca, Spectrum Pharmaceuticals, Blueprint Medicines, Seattle Genetics, ADC Therapeutics, AbbVie, and BMS, as well as other support from Novartis, Pfizer, AstraZeneca, Genentech, Lilly Pharmaceuticals, Immunomedics, Zymeworks, Puma Biotechnology, Novita Pharmaceuticals, ADC Therapeutics, and Debio Pharmaceuticals outside the submitted work. D. Juric reports grants from Novartis during the conduct of the study. D. Juric also reports grants and personal fees from Novartis, Genentech, Eisai, and Syros; personal fees from Ipsen, EMD Serono, Relay Therapeutics, MapKure, Vibliome, and PIC Therapeutics; and grants from Takeda, Pfizer, Amgen, InventisBio, Infinity Pharmaceuticals, Arvinas, and Ribon Therapeutics outside the submitted work. Y.-S. Yap reports personal fees and non-financial support from Novartis, Pfizer, Lilly, AstraZeneca, and Eisai; non-financial support from Roche; and personal fees from MSD, and Inivata outside the submitted work. R.M. Layman reports grants, personal fees, and non-financial support from Novartis during the conduct of the study. R.M. Layman also reports grants, personal fees, and non-financial support from Pfizer; grants and personal fees from Eli Lilly; and grants from GlaxoSmithKline, Puma, Genentech/Roche, and Zentalis outside the submitted work. F.P. Duhoux reports other support from Novartis during the conduct of the study, as well as other support from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Amgen, and Teva outside the submitted work. C. Terret reports other support from Novartis during the conduct of the study, as well as other support from GSK and non-financial support from Mundi Pharma outside the submitted work. S. Takahashi reports grants and personal fees from Novartis during the conduct of the study, as well as grants and personal fees from MSD, Eisai, Taiho, AstraZeneca, Chugai, Bayer, and Daiichi Sankyo outside the submitted work. J. Huober reports

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Authors' Contributions

K. Jhaveri: Resources, writing–original draft, writing–review and editing, enrolled and managed patients on study. **D. Juric:** Resources, writing–review and editing, enrolled and managed patients on study. **Y.-S. Yap:** Resources, writing–review and editing, enrolled and managed patients on study. **S. Cresta:** Resources, writing–review and editing, enrolled and managed patients on study. **R.M. Layman:** Resources, writing–review and editing, enrolled and managed patients on study. **F.P. Duhoux:** Resources, writing–review and editing, enrolled and managed patients on study. **C. Terret:** Resources, writing–review and editing, enrolled and managed patients on study. **S. Takahashi:** Resources, writing–review and editing, enrolled and managed patients on study. **J. Huober:** Resources, writing–review and editing, enrolled and managed patients on study. **N. Kundamal:** Conceptualization, formal analysis, supervision, writing–original draft, writing–review and editing. **Q. Sheng:** Formal analysis, writing–review and editing. **A. Balbin:** Formal analysis (translational), writing–review and editing. **Y. Ji:** Formal analysis (PK), writing–review and editing. **W. He:** Formal analysis (statistical), writing–review and editing. **A. Crystal:** Conceptualization, supervision, writing–review and editing, formal analysis. **S. De Vita:** Formal analysis, supervision, writing–original draft, project administration, writing–review and editing. **G. Curigliano:** Resources, writing–original draft, writing–review and editing, enrolled and managed patients on study.

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Clinical Cancer Research

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