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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Conflicts of interest

Dr Jhaveri reports personal fees and other financial relationships with Novartis, Genentech, Lilly, Pfizer, AstraZeneca, and ADC therapeutics; personal fees only from AbbVie, Bristol-Myers Squibb, Taiho Oncology, Jounce Therapeutics, Spectrum Pharmaceuticals, Blueprint Medicines, and Seattle Genetics; and other financial relationships only with Immunomedics, Zymeworks, Puma Biotechnology, Novita Pharmaceuticals, and Debiopharm. **Dr Curigliano** reports other financial relationships with Novartis, Roche, AstraZeneca, Lilly, Veracyte, Genomic Health, Ellipsis, and Daiichi Sankyo. **Dr Juric** reports institutional grants and personal fees from Novartis, Genentech, Eisai, and Syros; institutional grants only from Pfizer, Infinity Pharmaceuticals, Takeda, InventisBio, Arvinas, Ribon Therapeutics, and Acetylon Pharmaceuticals; and personal fees only from Relay Therapeutics, MapKure, and Vibliome Therapeutics. **Dr Yap** reports personal fees and non-financial support from Novartis, Pfizer, Lilly, AstraZeneca, Roche, and Eisai; and personal fees only from MSD and Inviata. **Dr Layman** reports other financial relationships with Novartis. **Dr Duhoux** reports other financial relationships with Novartis, Roche, Pfizer, AstraZeneca, Lilly, Amgen, Teva, Pierre Fabre, and Daiichi Sankyo. **Dr Takahashi** reports grants and personal fees from Novartis, Eisai, Daiichi Sankyo, and Taiho. **Dr Huober** reports grants and personal fees from Novartis; grants only from Hexal; personal fees only from Lilly, AbbVie, AstraZeneca, MSD, and Celgene; personal fees and other financial relationships with Pfizer and Roche; and other financial relationships only with Daiichi Sankyo. **Drs Kundamal, Sheng, Balbin, Ji, He, Crystal** and **De Vita** are current or former employees of Novartis at the time of the work described, and **Dr Crystal** is now an employee and shareholder of C4 Therapeutics. **Drs Cresta** and **Terret** have nothing to disclose.

Author Contributions

Komal Jhaveri and Giuseppe Curigliano: enrolled and managed patients on study, wrote and reviewed manuscript; **Dejan Juric, Yoon-Sim Yap, Sara Cresta, Rachel M. Layman, Francois P. Duboux, Catherine Terret, Shunji Takahashi, Jens Huober**: enrolled and managed patients on study, reviewed and approved manuscript; **Qing Sheng, Alejandro Balbin:** performed translational analysis, reviewed and approved manuscript; **Yan Ji:** performed PK analysis, reviewed and approved manuscript; **Wei He:** performed statistical analysis, reviewed and approved manuscript; **Nicole Kundamal, Adam Crystal:** Initiated the study concept and supervised the trial, analyzed clinical data, reviewed and approved manuscript; **Serena De Vita:** provided general supervision to the program, analyzed and interpreted data, wrote, reviewed and approved manuscript.

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Translational Relevance

The utility of fulvestrant, the only approved selective estrogen receptor degrader (SERD), for treating estrogen receptor (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 phosphatidylinositol 3-kinase (PI3K)α-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.

Abstract

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

Materials 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 (DLTs) in the first 28-day treatment cycle, adverse events (AEs), 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); 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% CI) were: arm A, 1.3% (0.0–7.0); arm B, 16.9% (9.3–27.1); 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 α (ER) signaling pathway plays a key role in tumor development for the majority of breast cancers(1,2). Endocrine treatment (ET) 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 (SERDs).

Both intrinsic and treatment-emergent resistance to ET 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 phosphatidylinositol 3-kinase (PI3K)—protein kinase B (AKT)—mechanistic target of rapamycin (mTOR)(5).

There is an underlying rationale for combining ET 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—vs. 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 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 ET. The escalation study design is shown in **Figure 1A**. The protocol and statistical analysis plan are provided in **Supplements 1 and 2**, respectively.

Participants were initially recruited in cohorts of 3–6 to receive LSZ102 alone (arm A) starting at 200 mg once daily (QD). 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 (3w/1w) 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 QD or 200–300 mg twice daily (BID). Arm B tested LSZ102 200–600 mg QD with ribociclib 300–600 mg QD (3w/1w), LSZ102 450 or 600 mg QD with ribociclib 300 or 400 mg QD (continuous), or LSZ102 200 or 300 mg BID with ribociclib 200 mg BID (continuous). Arm C tested LSZ102 300 or 450 mg QD with alpelisib 200–300 mg QD.

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 (PK), 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 QD plus ribociclib 400 mg QD (3w/1w). 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 ET 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 (1) the preliminary antitumor efficacy and PK of LSZ102 alone or in combination, (2) the effect of food on LSZ102 PK under fasted and fed dosing conditions, and (3) pharmacodynamic markers using immunohistochemistry. 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 (DLTs) comprising protocol-defined adverse events (AEs) 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)(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 nontarget lesions only. Overall response rate (ORR) was defined as the percentage of confirmed CR+PR in patients with measurable disease among all patients; similarly, the 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 PK 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 3w/1w) 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 PK over the range of 200 to 900 mg QD (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 immunohistochemistry using the H-score method(23).

Statistical methods

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 QD/BID 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 modelling 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 vs. absence of *ESR1* mutations; prior exposure to fulvestrant (yes vs. no); prior exposure to CDK4/6 inhibitors (yes vs. no); presence vs. absence of visceral metastases; presence vs. 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 1**). 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 3w/1w 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 2**. 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 3w/1w ribociclib groups

DLTs were only seen at the highest tested doses of LSZ102 600 mg plus ribociclib 400 mg QD. 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.

Based on these and the PK, pharmacodynamic, and efficacy data below, recommended doses for the planned expansion phases were LSZ102 450 mg QD alone or with ribociclib 400 mg QD (3w/1w or continuous; fasted or with a snack or low-/regular-calorie meal), or LSZ102 300 mg QD plus alpelisib 250 mg QD with a regular meal. High-fat meals were not recommended because PK 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 PK data are shown in **Figure 2A** and **Supplementary Table 3**. LSZ102 was rapidly absorbed under fasted conditions, with a median time to maximum concentration (C_{max}) of 2–3 hours and showed moderate to large PK variability across the QD dosing range. In general, and considering the PK variability of LSZ1002, concomitant ribociclib or alpelisib at their recommended expansion doses did not appear to affect LSZ102 exposure substantially, and LSZ102 450 mg PK did not appear to be substantially affected by administration with or without a regular meal (**Supplementary Table 3**). Steady-state LSZ102 C_{max} was dose-proportional for 200 to 900 mg/day (β = 1.03 [90% 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 (β = 1.27 [90% confidence interval (CI), 1.02–1.52]) (**Supplementary Fig. 1**).

Immunohistochemistry 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. 2**)

Preliminary efficacy

Individual treatment durations are shown in **Figure 3**, and best overall responses are summarized in **Supplementary Table 4**. 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; 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 3w/1w 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 vs. 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] vs. 13.3% [10/75; 6.6–23.2]), but lower for those with vs. 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 non-measurable 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. 3**). 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. 4**). 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. 4**): *ESR1*

mutations were present in 38% (6/16) of those with clinical benefit on treatment vs. 52% (45/87) without; *PIK3CA* mutations in 19% (3/16) vs. 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. 5**).

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. 6**).

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 PK 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 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 vs. 3w/1w, 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. 7**), 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. 7**. 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)(26), SAR439859 (amcenestrant)(27), GDC9545 (giredestrant)(28) and RAD1901(elacestrant)(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.

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Data sharing

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 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 co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

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508

509 **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 (3679)
≥ 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			

Endocrine therapy	4.0 (0–10) 2.0 (0–7)	4.0 (0–10) 2.0 (0–5)	3.0 (0–15) 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: CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; estrogen receptor 1; *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 (ET) outcome before study treatment: "sensitive" indicated ≥ 24 months of adjuvant ET or demonstrated clinical benefit with ET for metastatic or locally advanced disease (complete or partial response or stable disease ≥ 24 weeks); "resistant" indicated <24 months adjuvant ET or no clinical benefit with metastatic/locally advanced ET; and "unknown" indicated no valid tumor assessment from last ET.

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	300+250		300+300		450+200				

	(*n*=11)	(*n*=5)	(*n*=11)	(*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.

Figure Legends

Figure 1. (**A**) CLSZ102X2101 (NCT02734615) dose escalation study design; and (**B**) common treatment-related adverse events occurring in ≥ 10% of participants.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ESR1, estrogen receptor 1; ER+, estrogen receptor-positive; IHC, immunohistochemistry; PI3K, phosphatidylinositol 3-kinase; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit α gene; QD, once daily; WBC, white blood cells.

Figure 2. PK and pharmacodynamics of LSZ102 as a single agent.

(**A**) Steady-state concentration-time profiles and PK 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, non–complete response/non–progressive disease; PD, progressive disease; PK, pharmacokinetics; RIB, ribociclib; SD, stable disease.

[a] Recommended dose levels for combination expansion, all drugs once-daily, continuous cycle.

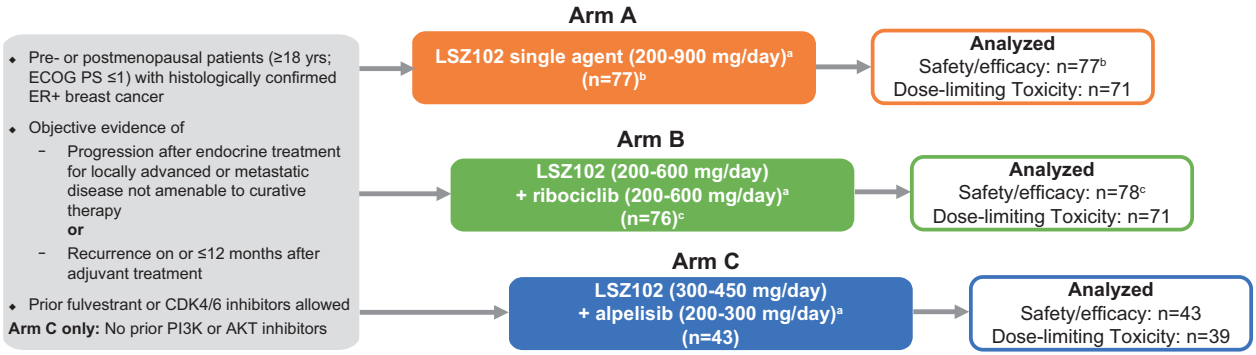
Figure 3. Individual treatment durations, prior treatment experience, baseline *ESR1* and *PIK3CA* mutational status (ctDNA), and periodic disease evaluations.

(**A**) LSZ102 as a single agent; (**B**) LSZ102 plus ribociclib; (**C**) LSZ102 plus alpelisib. Red boxes show recommended doses for the planned dose-expansion phase.

Abbreviations: ALP, alpelisib; BYL, alpelisib; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1 gene; 'No ctDNA', no detectable ctDNA identified in baseline sample; LEE, ribociclib; LSZ, LSZ102; MUT, mutant; NCRNPD, non–complete response/non–progressive disease; PD, progressive disease; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit α gene; PR, partial response; RIB, ribociclib; SD, stable disease; UNK, unknown; WT, wild type.

Figure 1

(A)



Primary objectives
- Safety and tolerability (AEs, serious AEs, dose-limiting toxicities)
- Identification of recommended doses for expansion

Key secondary objectives
- Preliminary antitumor activity
- Pharmacokinetics
- Pharmacodynamics (ER by IHC)

Exploratory objectives
- Pharmacodynamics (serial ctDNA)
- Response/resistance by baseline *ESR1* or *PIK3CA* status (ctDNA, biopsy)

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).

(B)

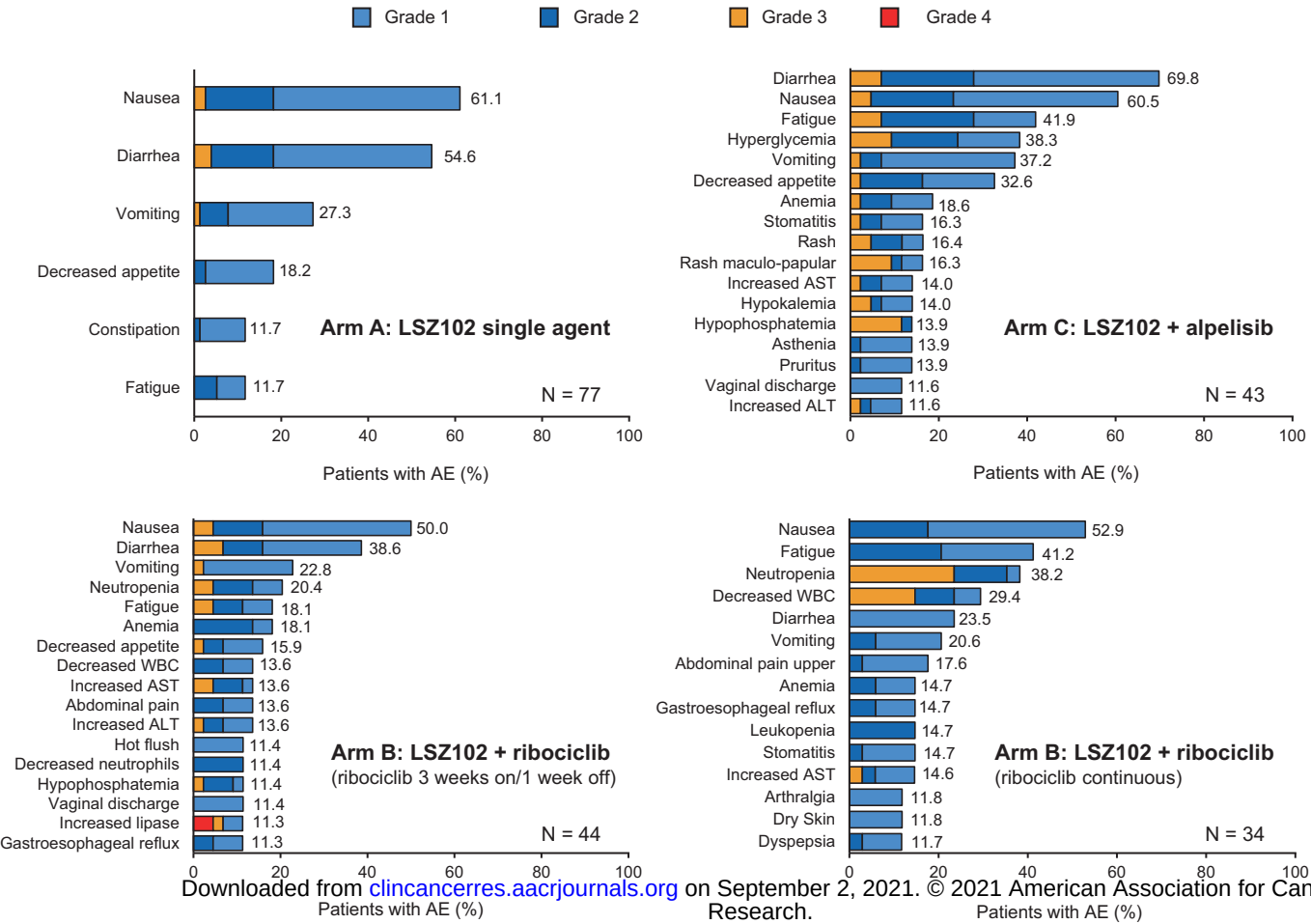
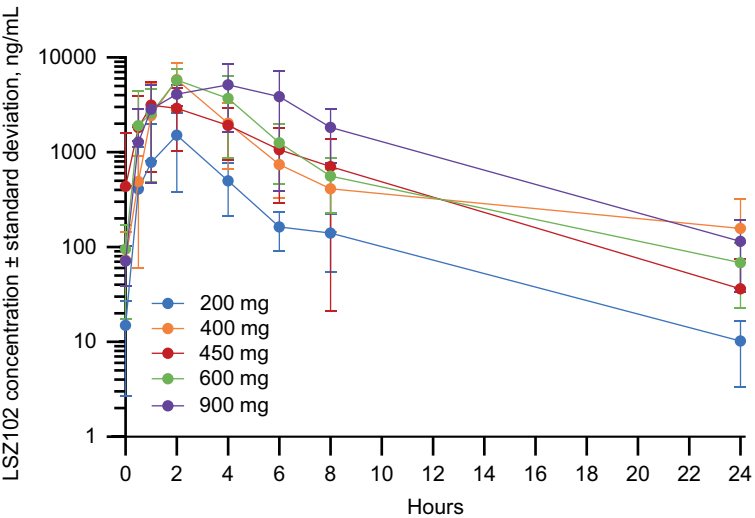


Figure 2

(A)



	$C_{max,}$ ng/mL	$AUC_{last,}$ h·ng/mL
200 mg	1520 (1120) [4]	5730 (2980) [4]
400 mg	5020 (3250) [5]	18400 (13100) [5]
450 mg	4150 (1680) [12]	22600 (19100) [12]
600 mg	6890 (2500) [17]	26900 (10900) [17]
900 mg	7110 (2060) [5]	42100 (22100) [5]
450 mg + RIB 400 mg[a]	4650 (1430) [6]	22300 (8580) [6]
300 mg + ALP 250 mg[a]	3560 (361) [3]	12300 (3350) [3]

Data are mean (standard deviation) [n].

(B)

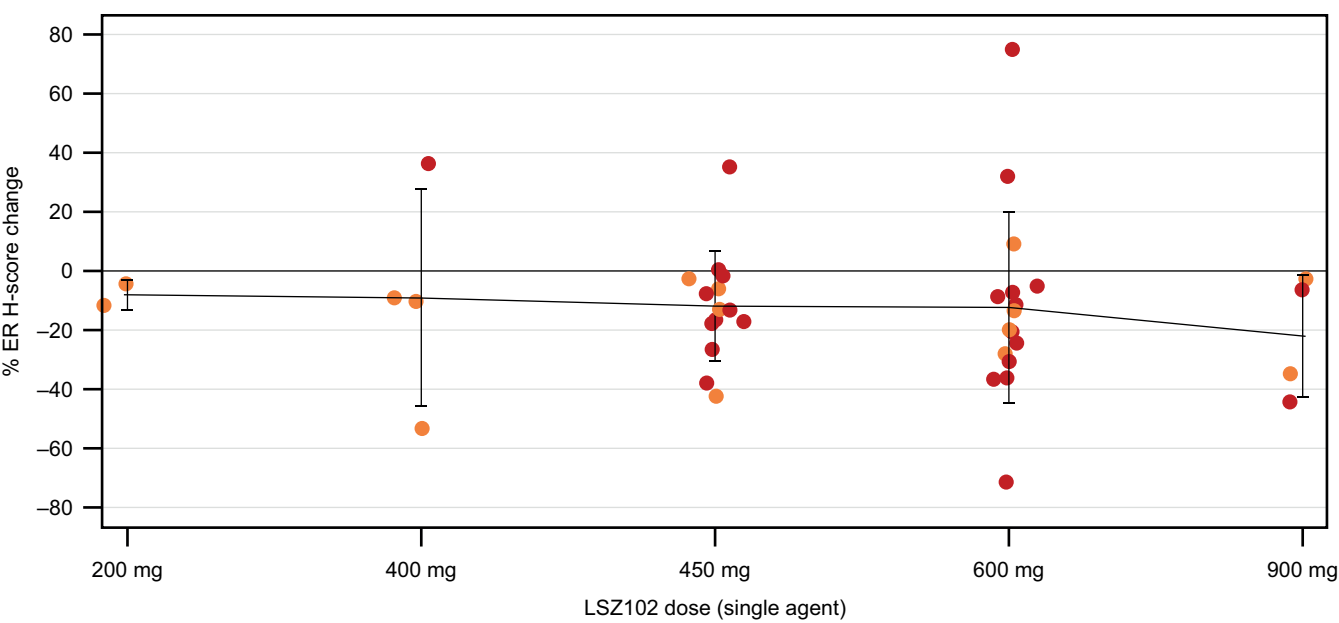


Figure 3A

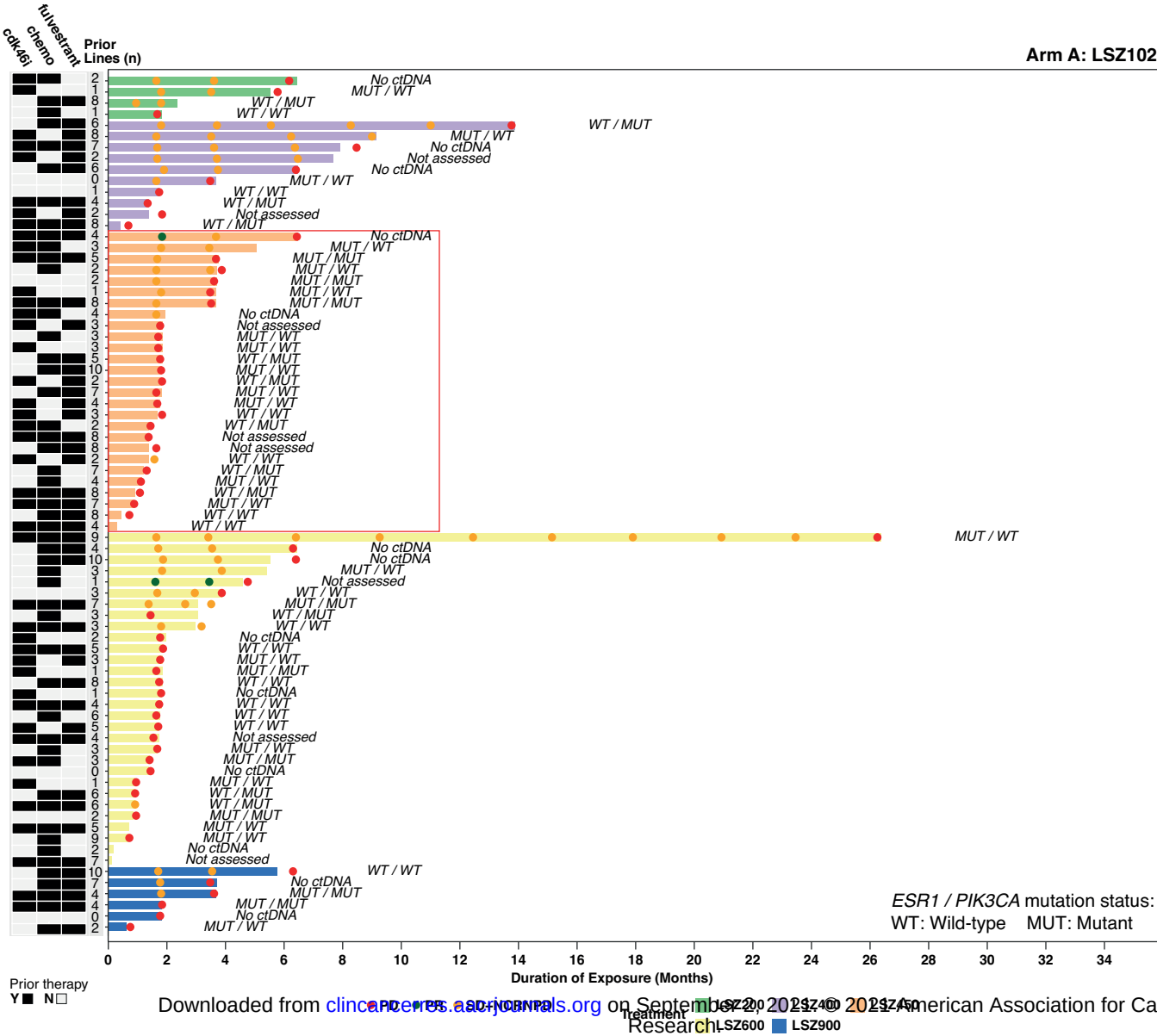


Figure 3B

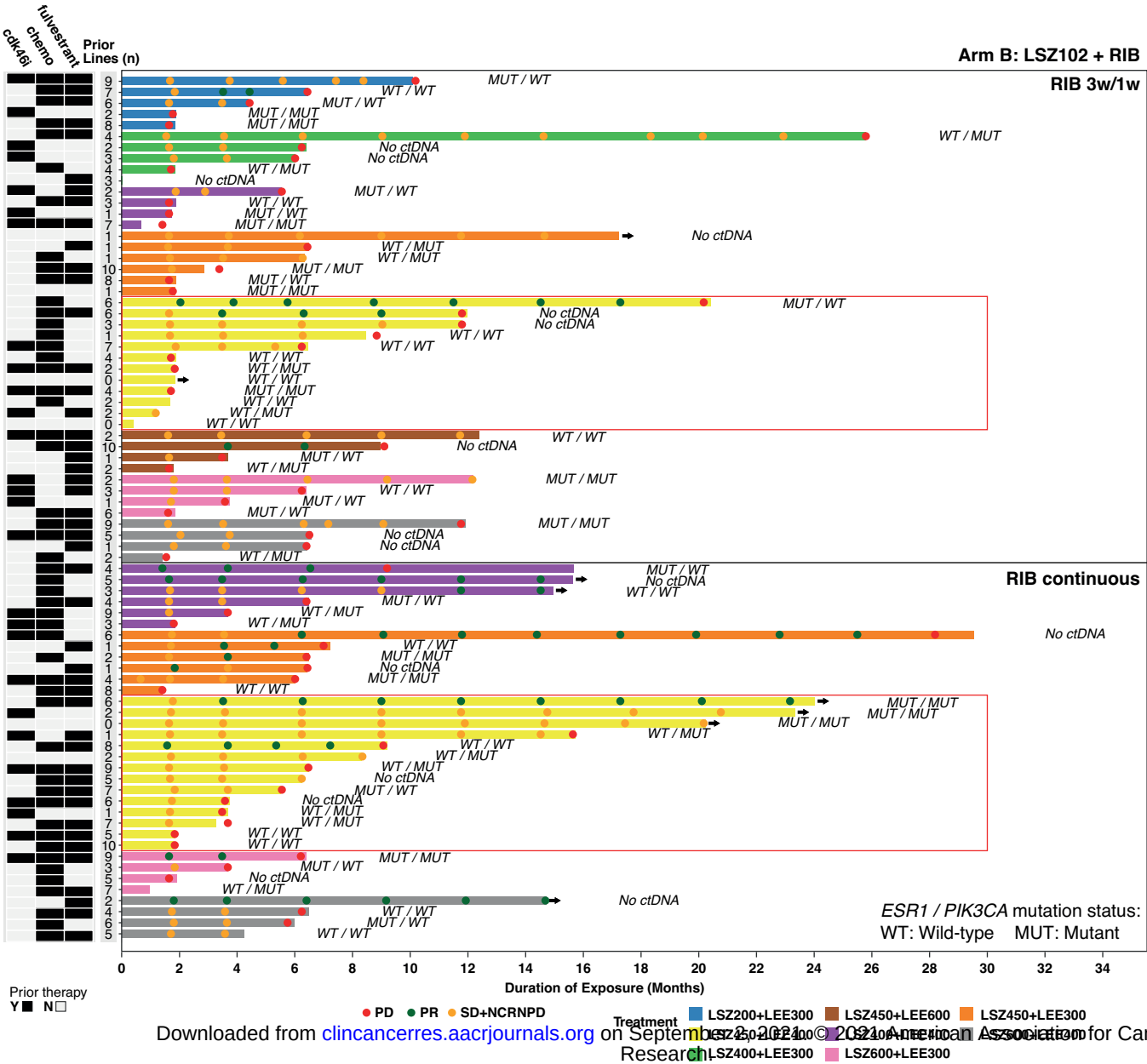
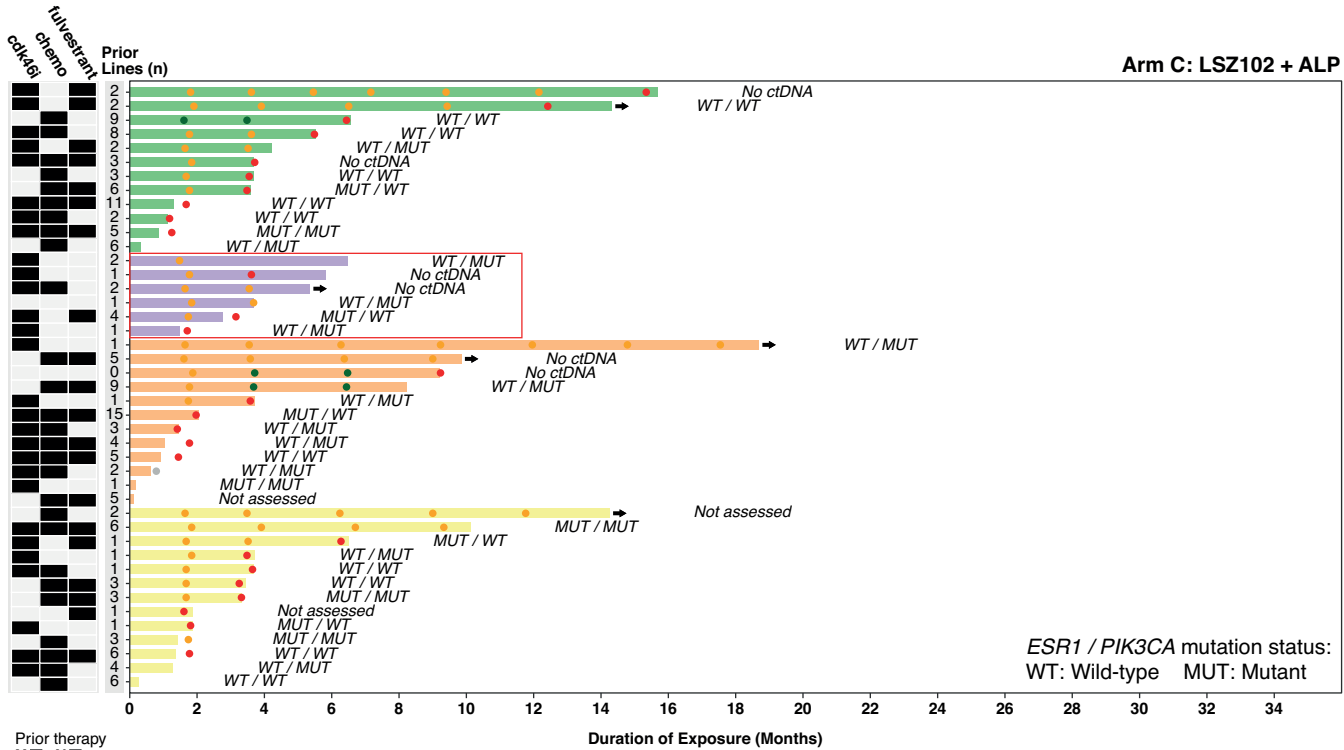


Figure 3C



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Clinical Cancer Research

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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