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Oncologic Drugs Advisory Committee (ODAC) Meeting

April 30, 2026

NDA# 220359

Drug name: camizestrant

Applicant: AstraZeneca UK Limited

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug [camizestrant NDA# 220359] to this advisory committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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Glossary

Abbreviation or special term	Explanation
1L	First line
2L	Second line
ABC	Advanced breast cancer, includes locally advanced breast cancer treated without curative intent and metastatic breast cancer
ADC	Antibody-drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
AKT	Serine/threonine specific protein kinase
ASCO	American Society of Clinical Oncology
AZD9833	Camizestrant
BICR	Blinded Independent Central Review
CBR	Clinical benefit rate
CBR24	Clinical benefit rate at 24 weeks
CDK4/6(i)	Cyclin-dependent kinase 4/6 (inhibitor)
CDx	Companion diagnostics
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCO	Data cut-off
DFS	Disease-free survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EHR	Electronic Health Record
EMA	European Medicines Agency

Abbreviation or special term	Explanation
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire
ER	Estrogen receptor
ERα	Estrogen receptor-α
ESMO	European Society for Medical Oncology
ESR1	Estrogen receptor alpha gene
*ESR1*m	Estrogen receptor alpha gene mutation
ET	Endocrine therapy
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GHS	Global Health Status
HBV	Hepatitis B virus
HER2-	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-Related Quality of Life
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IF	Information fraction
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent to treat
LHRH	Luteinizing hormone releasing hormone
LVEF	Left ventricular ejection fraction
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application

Abbreviation or special term	Explanation
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective response rate
OS	Overall survival
PARP(i)	Poly (ADP-ribose) polymerase (inhibitor)
PD	Progressive disease
PDX	Patient-derived xenograft
PFS	Progression-free survival
PFS2	Time to second progression or death
PgR+	Progesterone receptor positive
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PR	Partial response
PRO	Patient-reported outcomes
PTEN	Phosphatase and tensin homolog
QoL	Quality of life
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
QTcI	Individual-specific QT correction
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SERD	Selective estrogen receptor degrader
SoC	Standard of care
TdP	Torsade de Pointes
TFST	Time to first subsequent therapy or death
TSST	Time to second subsequent therapy or death
TTD	Time to deterioration
VAF	Variant allele frequency
vs	Versus
VSAQ	Visual Symptom Assessment Questionnaire
US	United States

Abbreviation or special term	Explanation
USPI	United States Prescribing Information

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1. Introduction

1.1 Proposed Indication(s)

Camizestrant (AZD9833) is a next-generation oral selective estrogen receptor degrader (SERD) and complete estrogen receptor (ER) antagonist, indicated in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), locally advanced or metastatic breast cancer upon emergence of estrogen receptor alpha gene mutation (*ESR1*m) during first-line (1L) endocrine-based therapy.

1.2 Purpose of the Meeting

The FDA's Position:

The FDA convenes this Oncology Drugs Advisory Committee (ODAC) meeting to discuss whether a favorable benefit-risk profile has been established for camizestrant in combination with a CDK4/6 inhibitor for treatment of adult patients with HR+HER2- locally advanced or metastatic breast cancer (ABC) at detection of *ESR1*m during first-line (1L) endocrine-based therapy (ET) based on results from the SERENA-6 trial. The treatment paradigm evaluated in SERENA-6 is new, and currently, no drugs have FDA approval for switching treatment in patients based on detection of an *ESR1*m prior to radiographic progression. It is unclear whether changing treatment at this earlier timepoint, prior to radiographic progression, results in long-term benefit for patients with an incurable disease.

SERENA-6 is a randomized (1:1), double-blind, placebo-controlled, two-part clinical trial that enrolled patients with ER+HER2- ABC who had been treated with an aromatase inhibitor (AI) and CDK4/6 inhibitor for at least six months. In the first part, testing of patients for *ESR1*m in circulating tumor DNA (ctDNA) occurred every two to three months. Patients with an *ESR1*m detected and who had no evidence of disease progression were screened for the second part of the trial. In the second part, eligible patients were randomly assigned (1:1) to either switch ET to camizestrant with continued CDK4/6 inhibitor or continue AI in combination with CDK4/6 inhibitor. The primary endpoint was progression-free survival (PFS), defined as time from randomization at detection of *ESR1*m until radiographic disease progression or death. Progression-free survival 2 (PFS2) and overall survival (OS) were key secondary endpoints.

The trial met its PFS endpoint with an estimated median PFS of 16 months (95% CI: 12.7, 18.2) on the camizestrant and CDK4/6 inhibitor arm and 9.2 months (95% CI: 7.2, 9.5) on the AI and CDK4/6 inhibitor arm (HR 0.44, 95% CI: 0.31, 0.60, $p<0.00001$). Although the trial also met its PFS2 endpoint, the FDA does not consider PFS2 a suitable endpoint for regulatory decision making. Current OS data are immature. The safety profile for camizestrant was generally as expected for ET, with additional risks of cardiotoxicity and visual disturbances.

Despite SERENA-6 meeting its PFS endpoint, the FDA has uncertainties regarding interpretation of the results due to the following issues:

1. **Evidence is lacking to show that switching treatment at detection of *ESR1*m rather than at radiographic progression is beneficial to patients.** To assess this, a trial would have to evaluate whether the experimental strategy of receiving new therapy at *ESR1*m detection is advantageous compared to the standard approach of receiving the new therapy at radiographic progression. To our knowledge, no clinical trial has established that the experimental strategy is superior, and the SERENA-6 trial was not designed to show that changing therapy at *ESR1*m detection is better than changing therapy at radiographic progression. No crossover to camizestrant and CDK4/6 inhibitor was permitted at disease progression for patients on the control arm. Moreover, patients in SERENA-6 who were randomized to continue AI and CDK4/6 inhibitor were able to stay on this therapy for an estimated median of 9.2 months (95% CI: 7.2, 9.5) prior to disease progression or death. By switching therapy early, patients may not be maximizing the benefit of each line of treatment.

2. **The starting time for PFS, upon detection of an *ESR1*m, is new, and the clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain.** The FDA has accepted PFS as an endpoint in HR+HER2- ABC based on the premise that clinical trials are enrolling patients (and measuring PFS) at times when a new treatment is clearly needed, i.e., after diagnosis of advanced or metastatic disease (1L trials) or after a patient experiences radiographic progression on current therapy (2L and later trials). The clinical meaningfulness of a PFS improvement measured from detection of a resistance mutation to current therapy with an AI is uncertain, and the magnitude that may translate into longer-term benefit for a patient is unknown.

3. **PFS2 is inadequate to show evidence of clinical benefit.** The FDA does not typically use PFS2 for regulatory decision-making as it does not isolate the effect of the experimental drug. Additionally, PFS2 is unreliable because the timing and choice of next treatment in SERENA-6 was at investigator's discretion and influenced by factors such as regional availability and local standards, and no crossover to camizestrant and CDK4/6 inhibitor was permitted at disease progression for patients on the control arm. Along with radiographic progression based on RECIST v1.1, investigators could also consider non-RECIST radiographic progression or clinical progression as a PFS2 progression event, adding more subjectivity into this endpoint. Furthermore, in SERENA-6, PFS2 also did not address whether the experimental strategy of receiving the new treatment at detection of *ESR1*m is beneficial compared to receiving it at radiographic disease progression because the trial was not designed to do so. At PFS2, patients on the experimental arm would have received two new treatments since randomization, and patients on the control arm would have continued their previous regimen (AI and CDK4/6 inhibitor) and received one new treatment regimen. There would be an imbalance in the number of new treatment regimens patients received on the two arms without an assessment of whether changing regimens at *ESR1*m is beneficial compared to changing regimens at radiographic progression.

4. **OS is immature, underpowered, and may not reach statistical significance.** OS benefit for camizestrant in SERENA-6 could overcome the uncertainties related to whether changing therapy at *ESR1*m detection rather than at radiographic progression offers long-term benefit to patients. However, the current OS information fraction (IF) is 58%, and the final OS analysis is

not anticipated until approximately 2028. Furthermore, given that the target power for the final OS analysis is 63%, FDA is concerned that SERENA-6 may not reach statistical significance for OS.

5. **Camizestrant is associated with heart lowering and QT prolonging effects, and when combined with drugs that can prolong the QT interval (such as ribociclib) may predispose patients to cardiac arrhythmias.** One patient in the camizestrant development program who received camizestrant with ribociclib at the dosages used in SERENA-6 experienced bradycardia, QT prolongation (QT interval >500 msec) and, ultimately, Torsades de Pointes (TdP).

In summary, the FDA is uncertain that overall positive benefit-risk for camizestrant has been demonstrated based on results of the SERENA-6 trial. Whether changing treatment at *ESR1*m detection prior to radiographic progression provides long-term benefit to patients is unknown, the clinical meaningfulness of the PFS result is uncertain, and OS data are immature and may not reach statistical significance.

We ask the committee to discuss the uncertainties regarding interpretation of the SERENA-6 results and vote on the following question:

Based on the results of SERENA-6, is the benefit-risk assessment favorable for camizestrant in combination with a CDK4/6 inhibitor in patients with HR+HER2- advanced breast cancer upon detection of an *ESR1* mutation while receiving a CDK4/6 inhibitor plus aromatase inhibitor?

Notes:

The new drug application (NDA) for camizestrant was submitted by AstraZeneca who will be referred to as "the Applicant" throughout this briefing document.

The FDA refers to camizestrant as an oral estrogen receptor antagonist rather than a selective estrogen receptor degrader. "Estrogen receptor antagonist" is the established pharmacologic class (EPC) for drugs like camizestrant.

1.3 Regulatory History

The Applicant's Position:

Scientific advice received from the FDA for camizestrant in relation to SERENA-6 study before and since the primary completion of the study is summarized below:

- Type C Pre-Phase III SERENA-6 trial meeting minutes (reference number: 4741322; 08 February 2021):
  FDA generally agreed with the overall proposals on population, study design, endpoints, statistical considerations and patient identification plan.

- Type C NDA format and content Written Response Only (reference number: 5473700; 04 November 2024):
  FDA generally agreed with the proposed content and format of the NDA for SERENA-6.

- Type B Pre-NDA meeting minutes (reference number: 5565413; 11 April 2025):
  FDA agreed that SERENA-6 efficacy and safety data support filing of an NDA submission, indicating that the precise indication would be a review issue. Additionally, FDA agreed with AstraZeneca's proposal for provision of updated safety and efficacy data during the NDA review.

Fast Track designation (reference number: 4990319; 26 May 2022) was granted for the investigation of camizestrant in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (palbociclib or abemaciclib) for the treatment of HR-positive, HER2-negative metastatic breast cancer (mBC) patients with detectable levels of *ESR1*m who are currently being treated with 1L therapy with an aromatase inhibitor (anastrozole or letrozole), and a CDK4/6 inhibitor (palbociclib or abemaciclib) therapy and have not had clinical or radiological disease progression (please note that the Fast Track designation was granted before data from the combination of camizestrant and ribociclib were available).

Following the positive results of the interim analysis of SERENA-6, Breakthrough Therapy designation (reference number: 5597179; 23 May 2025) was granted for the indication of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer upon emergence of *ESR1* mutation during 1L endocrine-based therapy.

The FDA's Position:

The FDA provides the following additional information and clarifications regarding key interactions with the Applicant during the design and conduct of the SERENA-6 trial.

- **Type C Pre-Phase 3 meeting** (February 3, 2021): The FDA provided preliminary comments to the Applicant that they should justify conducting *ESR1*m surveillance and switching therapy in patients who had not experienced disease progression. At a minimum, the FDA required that patients be consented that they could be forgoing a therapy from which they are benefiting by switching treatment prior to radiographic progression.

- **Type C Content and Format Meeting** (November 4, 2024): The FDA cautioned in a written response that PFS2 would not be acceptable as a regulatory endpoint for efficacy in this trial design.

- **Type B: Pre-NDA Meeting** (April 4, 2025): The FDA communicated that the NDA for camizestrant may be submitted. However, whether the results supported approval would be determined during the review. The FDA also requested that the Applicant provide a summary of the second-line therapies patients received by treatment arm in the NDA submission.

- **Fast Track Designation Request** (FTDR; May 26, 2022): Camizestrant received FTDR based on results from SERENA-1, a phase 1 dose escalation and dose expansion trial, showing that 3 out of 13 patients with measurable ER+, HER2- ABC and an *ESR1*m who received camizestrant 75 mg monotherapy experienced a partial response.
- **Breakthrough Therapy Designation Request** (BTDR; May 23, 2025): The FDA agrees that they granted a BTDR to camizestrant based on preliminary evidence of improved PFS in a unique patient population with a life-threatening disease in SERENA-6. A drug qualifies for BTD if it is intended to treat a serious or life-threatening condition and preliminary clinical evidence indicates it may demonstrate substantial improvement over available therapies. Granting a BTDR does not constitute a favorable benefit-risk assessment for camizestrant or evidence of substantial effectiveness and safety.

The dates presented by FDA represent the day that preliminary responses were provided to the Applicant and may differ from the dates that the Applicant responded to FDA's preliminary comments and withdrew the meeting requests.

2. Efficacy

2.1 Description of Clinical Setting

2.1.1 Serious Nature of *ESR1*m/HR+/HER2- ABC

The Applicant's Position:

Breast cancer represents the second most prevalent cancer globally and constitutes the most diagnosed cancer in women (Bray et al 2024). In 2022, more than 2.3 million patients were diagnosed with breast cancer worldwide (Bray et al 2024), and in the US, 324,580 new patient cases and 42,670 deaths are projected for 2026 (Siegel et al 2026). Approximately 70% of patients present with HR-positive (estrogen receptor-positive [ER+] and/or progesterone receptor-positive [PgR+]), HER2-negative (HER2 0, 1+, 2+, ISH negative) disease (American Cancer Society 2024-2025), making it the most common subtype in both females and males.

Despite advances in care, disease recurrence still commonly occurs and HR+/HER2- locally advanced (inoperable) and/or metastatic breast cancer (advanced breast cancer; ABC) remains incurable, with treatment goals being palliative, aiming to delay disease progression, reduce cancer-related symptoms, preserve quality of life (QoL), delay the initiation of chemotherapy, and prolong survival.

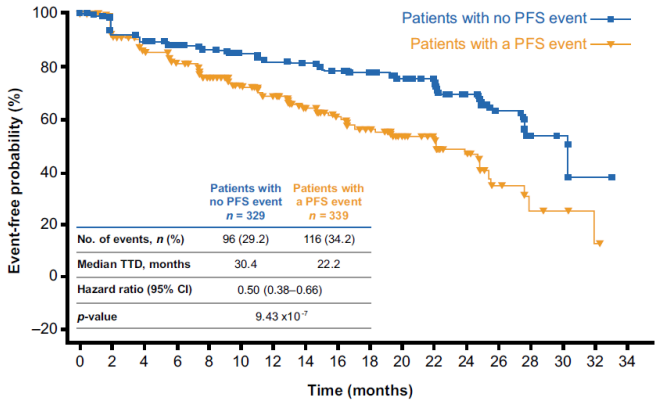
American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines have established an aromatase inhibitor (AI) in combination with CDK4/6 inhibitor as the predominant standard of care (SoC) in the 1L for HR+/HER2-negative ABC (Burstain et al 2024, NCCN 2026) for patients with endocrine-sensitive disease. This recommendation was based on data from large Phase III studies and real-world evidence demonstrating prolonged progression-free survival (PFS) and Overall Survival (OS) compared with endocrine therapy (ET) alone (Bardia et al 2020, Berton Giachetti et al 2025, Sledge et al

2017, Johnston et al 2019, Slamon et al 2018, Neven et al 2023, Hortobagyi et al 2022, Cristofanilli et al 2016, Im et al 2019, Finn et al 2016, Rugo et al 2019).

Despite the proven efficacy of 1L ET + CDK4/6 inhibitor combinations, resistance invariably develops and most patients eventually succumb to their disease. Disease progression following 1L treatment of HR+/HER2- ABC is associated with increased tumor burden, worsening symptoms, and greater tumor heterogeneity, which limits the effectiveness of subsequent therapies (Kingston et al 2021).

Several studies have shown that disease progression in patients with ABC also has a significant negative impact on Health-Related Quality of Life (HRQoL) (Fasching et al 2020, Marschner et al 2020, Müller et al 2018, Galipeau et al 2019). Patients who had not yet experienced disease progression on 1L ET plus the CDK4/6 inhibitor ribociclib in the MONALEESA-2 1L Phase III trial had better QoL than patients whose disease had progressed, which highlights the value of delaying progression and prolonging PFS in 1L to maintain QoL (Harbeck et al 2020, Verma et al 2018) (Figure 1).

Figure 1 **A Significantly Greater Delay in Time to Deterioration (TTD) (≥ 10% decrease from baseline) in EORTC QLQ-C30 global health status (GHS)/QoL was Observed in Patients Without (blue) versus With (gold) a PFS Event (Disease Progression or Death) Across Both Arms in the MONALEESA-2 Study**



Source: Figure 3c in Verma et al 2018

Activating mutations in the estrogen receptor alpha gene (*ESR1*m) emerge under selective pressure on AI treatment and represent a highly specific marker of resistance to AI. The prevalence of *ESR1*m increases substantially during a patient's treatment journey, rising from approximately 4% at initial diagnosis of HR+/HER2- ABC (Bardia et al 2020, Goetz et al 2024, Hortobagyi et al 2018) to approximately 40% in patients at the end of 1L AI + CDK4/6 inhibitor therapy, and exceeding 50% in patients treated for more than one year (Bidard et al 2022b, Bhave et al 2024, Chaudhary et al 2024).

*ESR1*m lead to constitutive (estrogen-independent) activation of estrogen receptor-α (ERα), rendering therapy with AI, which inhibit the production of estrogen, futile, while retaining variable sensitivity to ER degraders (Fribbens et al 2016, Slamon et al 2020, Tolaney et al 2019,

André et al 2023, Razavi et al 2018). Tumors with an *ESR1*m have a more aggressive biology (e.g. *ESR1*m are frequently detected in liver metastases) and poor treatment PFS and OS outcomes (Turner et al 2020, Turner et al 2023, Boscolo Bielo et al 2024).

The FDA's Position:
The FDA agrees with the Applicant's description of HR+HER2- ABC and that this is a serious and life-threatening condition.

FDA disagrees with the Applicant's use of Global Health Status as a measure of worsening HRQoL in the setting of disease progression. Generally, FDA examines more proximal measures of symptoms and functioning that are directly related to the disease and treatment being studied in a trial using prospectively defined endpoints and prespecified analyses. Furthermore, use of time to deterioration PRO-based endpoints are fraught with interpretability issues, which FDA outlines in Section 4 of this document, as they pertain to the SERENA-6 PRO results.

The FDA agrees with the Applicant that *ESR1*m develops after exposure to AI therapy and results in both ligand dependent and independent activation of the estrogen receptor, negating some of the effects of AI treatment. However, the timing of when patients with an *ESR1*m stop benefiting from treatment with an AI and CDK4/6 inhibitor is not completely understood. Patients may continue to derive benefit from AI and CDK4/6 inhibitor for a period of time after detection of an *ESR1*m.

2.1.2 Unmet Medical Need in *ESR1*m/HR+/HER2- ABC

The Applicant's Position:

For patients with *ESR1*m/HR+/HER2- ABC who progress on 1L AI plus CDK4/6 inhibitor therapy, the optimal next treatment is unclear and there is no established SoC. In the absence of visceral crisis (in which cytotoxic treatments are recommended), current treatment guidelines endorse endocrine-based sequencing regimens, with the choice between several options determined by patient-specific clinical factors (co-morbidities, performance status, symptom burden, patient preference), molecular context (additional actionable genomic alterations, such as alterations of the phosphatidylinositol-4,5-bisphosphate 3-kinase [PI3K]/serine/threonine specific protein kinase [AKT] pathway, breast cancer gene [BRCA] mutations, etc.), and local access/practice patterns.

In the second-line setting and beyond (≥2L), currently approved treatment options for patients with *ESR1*m/HR+/HER2- ABC include:

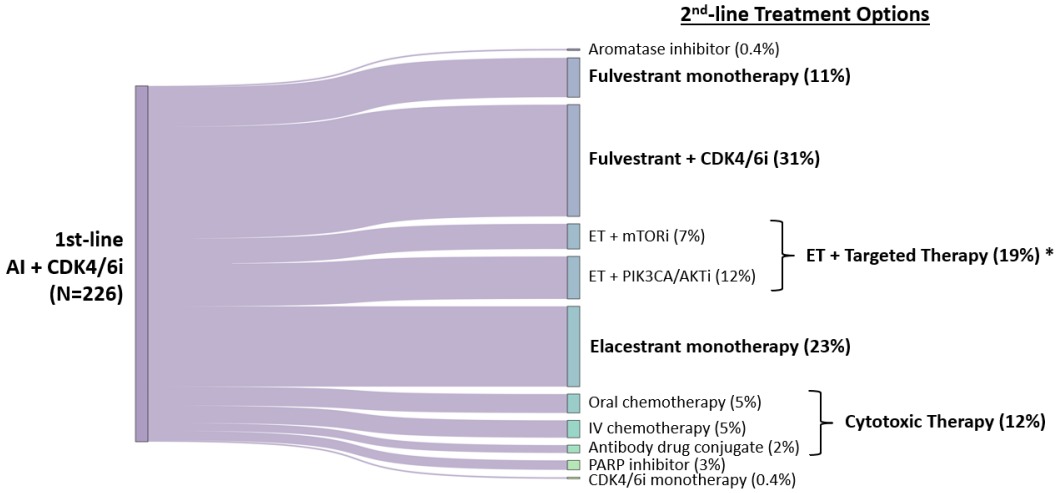
- ET-based options:
    - The only approved therapies specifically targeting *ESR1*m in ≥2L are elacestrant and imlunestrant, which are both approved in the US as monotherapies.
    - If tumors have concurrent PI3K/AKT pathway alterations, PI3K/AKT pathway inhibitors + fulvestrant are indicated.
    - Other 2L therapies used for (but not targeted to) patients with *ESR1*m include ET

(exemestane or fulvestrant) + everolimus (mTOR inhibitor), fulvestrant + a different CDK4/6 inhibitor from that used in 1L, or fulvestrant monotherapy.

- For patients with concurrent BRCA mutations: poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) therapy.
- Cytotoxic therapies (oral or IV chemotherapy, or antibody-drug conjugates [ADCs]).

AstraZeneca performed an analysis of real-world data from patients with confirmed *ESR1*m whose tumors progressed during 1L AI + CDK4/6 inhibitor (US Electronic Health Record [EHR] from Flatiron Health database) (James et al 2026). The analysis of this US-based data set, which described the patterns of 2L treatments in patients with *ESR1*m, showed treatment patterns are aligned with guidelines, with ET being the most prevalent treatment, used in more than 80% (n = 192) of patients. Elacestrant monotherapy was used in 22.6% (n = 51) of patients (Figure 2).

Figure 2 **Diverse Treatment Patterns in HR+/HER2- mBC Patients with *ESR1* Mutation Detected During 1L Therapy (US EHR Flatiron Health Database)**



* combinations with CDK4/6 inhibitor are provided separately

This real-world analysis included adult patients with a confirmed diagnosis of *ESR1*m/HR+/HER2- mBC from January 2015 to June 2025 with positive *ESR1*m test at initiation of second-line therapy.

Source: James et al 2026

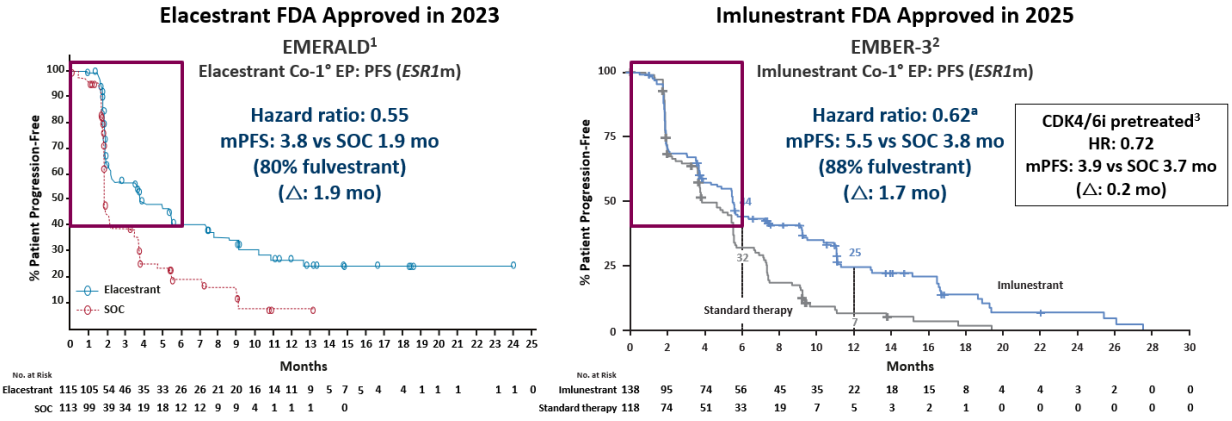
As the disease progresses on 1L AI + CDK4/6 inhibitor therapy, tumor genomic complexity increases, and multifactorial resistance mechanisms to ER targeting and CDK4/6 inhibition accumulate. Approved novel endocrine monotherapy regimens targeting patients with *ESR1*m/HR+/HER2- ABC after disease progression show limited efficacy in registrational trials (elacestrant median PFS ~ 3.8 months, imlunestrant median PFS ~ 3.9 months; Table 1). Additionally, a substantial proportion of these patients with *ESR1*m/HR+/HER2- ABC treated with endocrine monotherapy in 2L, experience early and rapid disease progression (about 60% of patients have disease progression in the first 6 months from start of treatment, with a majority of those experiencing no disease control and progression at the first scan) (Bidard et al 2022b, Jhaveri et al 2025) (Figure 3).

Table 1 **Efficacy Summary of Approved Monotherapy Regimens in Patients Previously Treated with ET + CDK4/6 inhibitor in ABC Setting**

Registrational Trial	EMERALD [1]	EMBER-3 [2]	EMBER-3 (subgroup analysis) [3]
Comparison	Elacestrant vs Fulvestrant or an AI	Imlunestrant vs Fulvestrant or Exemestane	Imlunestrant vs Fulvestrant or Exemestane
N	115/113	138/118	93/85
Population	Post progression on ET + CDK4/6i 2L, 3L	Post progression on AI ± CDK4/6i 2L	Post progression on ET + CDK4/6i 2L
Prior ET + CDK4/6i in ABC setting	100%	67% vs 72%	100%
Number of PFS events, n (%)	62 (54) vs 78 (69)	109 (79) vs 102 (86)	80 (86) vs 71 (84)
mPFS in months	3.8 vs 1.9	5.5 vs 3.8	3.9 vs 3.7
PFS HR (95% CI); p-value	0.55 (0.39, 0.77); 0.0005	0.62 (0.46, 0.82); 0.0008	0.72 (0.52, 1.01); 0.246

Source: 1. Elacestrant USPI, Shah et al 2024; 2. Imlunestrant USPI, Figure 21 in Imlunestrant EMA Assessment Report; 3. Imlunestrant EMA SmPC, Figure 21 in Imlunestrant EMA Assessment Report

Figure 3 **Consistent Poor Outcomes in Patients with *ESR1*m After Progression on ET + CDK4/6 Inhibitor in Recent Phase III Studies vs SoC**



[a] 33% of patients in this cohort were CDK4/6 inhibitor naive.

For the left-hand panel, elacestrant is depicted in blue and the SOC is depicted in red. For the right-hand panel, imlunestrant is depicted in blue and the standard therapy is depicted in gray.

Source: 1. Bidard et al 2022b; 2. Jhaveri et al 2025; 3. Imlunestrant EMA SmPC

Everolimus (mTOR inhibitor) in combination with ET is an alternative 2L therapeutic strategy which does not target specific genetic alterations and is used in patients with *ESR1*m/HR+/HER2- ABC but with limited effect (Baselga et al 2012). In addition, multiple studies have evaluated the continuation of CDK4/6 inhibition (either the same or a different agent) in combination with fulvestrant in unselected patients after progression on AI + CDK4/6 inhibitor therapy (Mayer et al 2024, Kalinsky et al 2023, Kalinsky et al 2025), yielding mixed results and limited PFS benefit. Together, these observations support the hypothesis that the greater genomic diversity of tumors in the 2L setting reduces ER-signaling dependency and responsiveness to current endocrine-based therapies, and furthermore that earlier intervention targeting patients with *ESR1*m/HR+/HER2- before disease progression, to switch from AI to a therapy with activity against *ESR1*m, may be advantageous.

In summary, delaying progression on 1L ET + CDK4/6 inhibitor represents a significant unmet clinical need which could be met by offering patients with HR+/HER2- ABC with emergent *ESR1*m longer duration of benefit in 1L while maintaining QoL with a very well-tolerated regimen, potentially preventing the development of more complex resistance mechanisms. Currently, there are no therapies specifically approved for the 1L treatment of patients with *ESR1*m/HR+/HER2- ABC prior to radiographic or clinical progression.

The FDA's Position:

The FDA disagrees with the Applicant's characterization that there are no established standard of care (SOC) treatments in 2L or later (2L+) for patients with HR+HER2- ABC. The options outlined by the Applicant largely represent SOC. Some of these therapies are for biomarker-defined populations, including two drugs which are approved for treatment of patients with tumor *ESR1*m (elacestrant and imlunestrant). The FDA agrees with the Applicant that global treatment patterns vary due to differences in guidelines, practice patterns, patient factors, and access, leading to variation in the 2L therapies patients receive.

The FDA disagrees with the Applicant's representation of U.S. practice patterns from real-world data, as this study (James et al 2026) spans a period from 2015 to 2025, during which several new drugs were approved for patients with HR+HER2- ABC. If anything, the data represent an early adoption period, which may underestimate the use of recently approved oral estrogen receptor antagonists.

The FDA also disagrees with the characterization of this real-world patient population presented in Figure 2 as having *ESR1*m detected "during first line therapy." Serial testing for *ESR1*m is not performed outside of clinical trials. In clinical practice, testing occurs when a patient is no longer receiving benefit from their first line therapy, as evidenced by clinical or radiographic progression.

The FDA acknowledges the information on elacestrant and imlunestrant shared by the Applicant, with the caveat that the post-CDK4/6 inhibitor subgroup analysis for imlunestrant from EMBER-3 is exploratory and must be interpreted with caution. The FDA notes that cross-trial comparisons of time-to-event endpoints, such as PFS, between SERENA-6 and the monotherapy trials for elacestrant and imlunestrant as 2L+ treatment would not be

interpretable, since variability in baseline demographics and disease characteristics could lead to differences in the treatment effect observed across trials. Any comparison to SERENA-6 is further complicated by the new starting point for PFS at *ESR1*m detection rather than at radiographic progression. Finally, in SERENA-6, patients continued CDK4/6 inhibitor therapy after randomization; camizestrant was not administered as monotherapy.

The data on the benefit patients may experience from new combinations of endocrine therapies and CDK4/6 inhibitors after progression on prior endocrine therapy and CDK4/6 inhibitor therapy are complex and evolving. We do not agree with the Applicant that current data support the idea that endocrine therapy and CDK4/6 inhibitor started after radiographic progression on 1L therapy is ineffective.

The FDA also disagrees with the premise that SERENA-6 evaluated a strategy to extend 1L treatment, which consists of an AI and CDK4/6 inhibitor. Patients enrolled to the experimental arm in SERENA-6 started a new treatment, camizestrant, and only continued the CDK4/6 inhibitor portion of the 1L regimen. Furthermore, while the FDA believes that there is unmet medical need to improve long-term outcomes in patients with HR+HER2- ABC, it is unclear that changing treatment at detection of *ESR1*m, prior to radiographic progression, would fulfill this unmet medical need.

2.1.3 Scientific Rationale for SERENA-6 Study Design

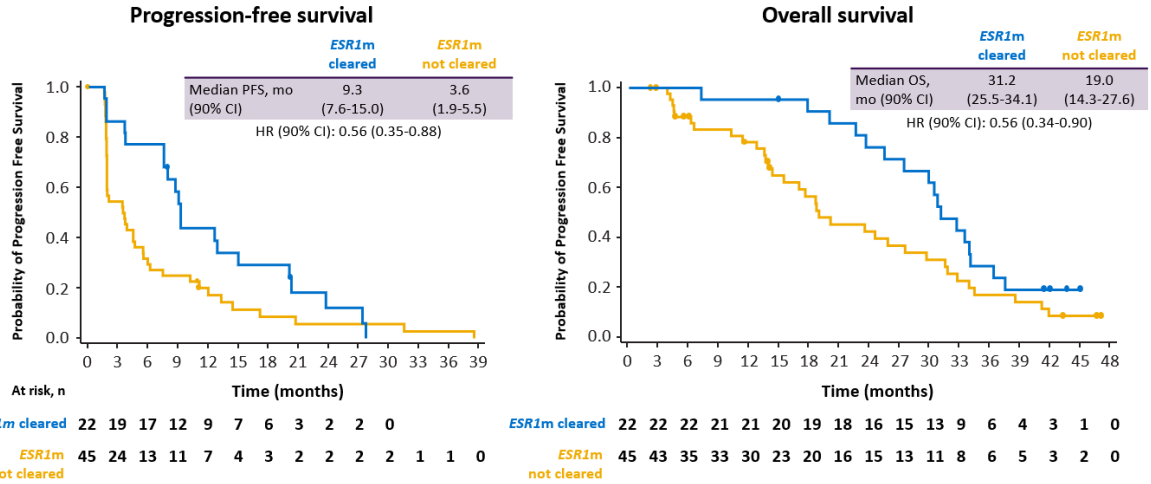
The Applicant's Position:

It is hypothesized that patients with a more genetically diverse tumor burden are more likely to be resistant to intervention with a novel agent with activity against *ESR1*m (such as a SERD), and that an early intervention, before too much genetic drift has occurred, may be advantageous. Furthermore, to fully leverage the doubling of median PFS duration observed when CDK4/6 inhibitors are added to ET in 1L, it may be advantageous to switch the AI to a SERD before disease progression.

To examine the concept of intercepting treatment resistance early by tracking the emergence of a targetable genetic alteration using circulating tumor DNA (ctDNA), the PADA-1 academic study, a randomized open-label Phase III trial, provided proof of concept for early intervention in patients on 1L treatment with AI + CDK4/6 inhibitor palbociclib. At the time of *ESR1*m detection, patients were switched from AI to fulvestrant, a SERD with some activity against *ESR1*m. This trial demonstrated an improvement in PFS (11.9 months in the fulvestrant + palbociclib group vs 5.7 months in the AI + palbociclib group) that was maintained for subsequent treatment (Bhave et al 2024, Bidard et al 2022c). In patients on the AI + palbociclib arm, a total of 68.1% (47/69) crossed over to the option of treatment with 2L fulvestrant + palbociclib after disease progression. However, this 2L treatment effect was very modest with an observed median PFS of 3.5 months (Bidard et al 2022a, Cabel et al 2025). These data demonstrate that switching from AI to fulvestrant, as soon as *ESR1*m is detected, is associated with improved disease control.

Camizestrant is a next-generation SERD and complete ER antagonist that potently inhibits and degrades both mutant (*ESR1*m) and wild-type ER and, therefore, has the potential to address resistance to AI + CDK4/6 inhibitor via the emergence of activating mutations in *ESR1.* Camizestrant has shown broad *in vivo* monotherapy activity in a range of HR+ breast cancer PDX models that express either wild-type or mutant *ESR1*, superiority to fulvestrant, and activity in combination with all currently approved CDK4/6 inhibitors (Lawson et al 2023). In the SERENA-2 Phase II clinical study, camizestrant has shown superiority over fulvestrant in a head-to-head randomized comparison, in patients with both wild-type and *ESR1*m (Oliveira et al 2024). Exploratory analysis from the SERENA-2 trial demonstrated that clearance of *ESR1*m in ctDNA by Cycle 2 Day 1 was associated with prolonged PFS and OS (Figure 4), highlighting that successfully targeting *ESR1*m is associated with improved clinical outcomes.

Figure 4 PFS and OS According to *ESR1*m ctDNA Clearance in SERENA-2



Patients on camizestrant 75 mg and 150 mg arms and fulvestrant arm combined.
*ESR1*m clearance is depicted as cleared (blue) or not cleared (gold).
Source: SERENA-6 FDA IR8 IEMT 000150 Figure 10 and Figure 12

The SERENA-6 Phase III double-blind clinical trial approach involves replacement of a failing ET backbone (AI) with a therapy with direct and potent efficacy on *ESR1*m (camizestrant) at the emergence of an *ESR1*m detected by ctDNA during 1L, prior to clinical or radiographic progression. This personalized medicine approach is driven by a specific and targetable molecular alteration (*ESR1*m), and changes only the ET to camizestrant, to restore efficacy to *ESR1*m, with no change of the CDK4/6 inhibitor partner. This approach maximizes the duration of benefit of this critical 1L ET + CDK4/6 inhibitor therapy, prior to progression to a disease that is often independent of ER-signaling, exhibits increased tumor heterogeneity, and is characterized by poorer QoL and clinical outcomes for patients.

The FDA's Position:

While FDA acknowledges the Applicant's rationale for designing SERENA-6, we disagree with some of the Applicant's comments regarding the PADA-1, SERENA-2, and SERENA-6 trials.

The exploratory analysis of PFS in PADA-1 in the subset of patients on the control arm who crossed over to receive fulvestrant and CDK4/6i after disease progression is insufficient to

characterize a 2L treatment effect and cannot be used to establish that switching treatment at *ESR1*m detection improves disease control. This subgroup represents only 54% of patients (47/87) enrolled on the control arm and likely constitutes a biased sample. For example, patients who crossed over may have systematic differences in baseline disease characteristics from those of patients who were randomized to and received fulvestrant and CDK4/6 inhibitor at baseline. The systematic differences render the patients noncomparable and undermine the validity of any conclusions about the randomized population. Crossover decisions also generally depend on the investigator and patient preference, which may introduce additional bias.

The FDA notes that PADA-1 included a secondary endpoint of time to strategy failure (TSF), defined as time from randomization to discontinuation of palbociclib and endocrine therapy or death (whichever occurred first). This may provide some data for exploring the effect of switching therapy earlier compared to switching at disease progression. Unlike the exploratory subgroup analysis of PFS in patients who crossed over to fulvestrant and CDK4/6i after disease progression, the analysis of TSF was conducted in all randomized patients, including those who did not cross over. The TSF HR was 1.02 (95% CI: 0.71, 1.45) with an estimated median of 11.9 months in the fulvestrant plus palbociclib group and 10.6 months in the aromatase inhibitor plus palbociclib group. However, FDA emphasizes that TSF is considered an exploratory endpoint. As acknowledged in Bidard et al 2022c, interpretability of TSF is limited for many reasons, including patient selection bias in the optional crossover cohort, uncontrolled time from tumor progression to subsequent treatment start, subsequent evaluation-time bias, and non-prespecified therapies in patients who did not cross over and in the post-trial setting.

Overall, FDA disagrees that the PADA-1 results demonstrate an association between switching treatment at *ESR1*m and improved disease control. PADA-1 was not designed to demonstrate that switching treatment at detection of *ESR1*m is beneficial compared to switching at radiographic progression. To evaluate the benefit of early treatment-switching (e.g., at detection of *ESR1*m), a trial design that randomizes patients to a prespecified treatment sequence (including both 1L and 2L therapy after radiographic progression) may produce more interpretable results than those from PADA-1.

SERENA-2 is an exploratory trial because false positive findings (i.e., Type I error) were not controlled at the regulatory standard of a two-sided alpha of 0.05. FDA considers any results hypothesis-generating only and not sufficient to establish the superiority of camizestrant. The Applicant also asserts that clearance of ctDNA was associated with improved PFS and OS, supporting clinical benefit. While this finding is intriguing, it is based on a small number of patients in an exploratory trial. The relevance of the Cycle 2 Day 1 timepoint, the validity of the ctDNA assessment methods, and the association of ctDNA clearance with long-term outcomes like PFS and OS would need to be replicated in more patients across more studies.

Finally, the FDA does not agree with the Applicant's position that SERENA-6 represents continued first-line ET and CDK4/6 inhibitor for the investigational arm since at progression this arm has received two ET of different classes, rather than one ET on the control arm after detection of an *ESR1*m. The FDA also disagrees with the Applicant's characterization that switching treatment at *ESR1*m restores efficacy to ET as patients may still derive benefit from AI

and CDK4/6 inhibitor after *ESR1*m detection. By switching treatment, patients may be forgoing some time on an effective therapy to start a new therapy which otherwise could have been available at radiographic progression.

2.2 Summary of Clinical Trials Supporting Efficacy

2.2.1 SERENA-6 Study Design

The Applicant's Position:

SERENA-6 is a Phase III, parallel, randomized, double-blind, 2-arm, matched placebo, multicenter, international study assessing the efficacy and safety of switching to camizestrant + CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) compared with continuing AI (anastrozole or letrozole) + CDK4/6 inhibitor in patients with HR+/HER2- ABC that have *ESR1* mutations detected in ctDNA using the FDA-approved Guardant360® CDx assay without disease progression during standard 1L treatment with AI + CDK4/6 inhibitor.

The SERENA-6 study had a 2-step design. In STEP 1 (*ESR1*m detection phase), patients with HR+/HER2- ABC on 1L treatment with AI + CDK4/6 inhibitor for at least 6 months without disease progression were eligible for screening for detection of *ESR1*m in ctDNA. During STEP 1, blood samples for ctDNA were collected every 2 to 3 months as part of routine clinical visits.

A patient with detectable *ESR1*m disease was defined based on a centrally tested plasma sample, that returned a mutation in the *ESR1* gene with at least one of the following amino acid changes: E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S or D538G. These mutations represent the most prevalent *ESR1*m detected in metastatic HR-positive breast cancer (Rinaldi et al 2020), causing constitutive activation of ERα in preclinical studies (Toy et al 2013).

If *ESR1*m was detected without evidence of clinical or radiographic disease progression, and all other eligibility criteria were met, patients entered the randomized treatment phase of the study (STEP 2, randomized treatment phase).

Within 28 days before randomization, patients underwent radiological tumor assessments to establish a new baseline prior to study treatment initiation, which is consistent with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) standard practice.

In STEP 2, patients were randomized in a 1:1 ratio to one of the following treatments:

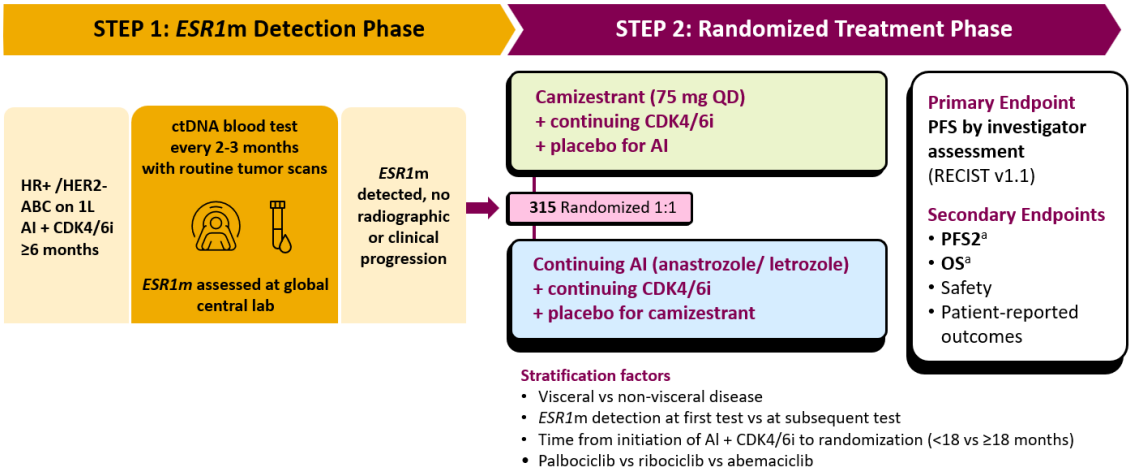
- Camizestrant arm: camizestrant (75 mg oral, once daily) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when *ESR1*m was detected) + placebo for AI.
- Control arm: AI (continuing anastrozole 1 mg oral, once daily or letrozole 2.5 mg oral, once daily) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when *ESR1*m was detected) + placebo for camizestrant.

Consistent with other trials in HR+/HER2− ABC, particularly those in the 1L setting, SERENA-6 used PFS as its primary endpoint, as this is an endpoint acceptable to regulators for HR+/HER2− registrational trials.

As *ESR1m* may be acquired at varying times during 1L AI + CDK4/6i therapy, or not at all, randomization in SERENA-6 was anchored to the time of *ESR1*m detection rather than 1L therapy initiation, enabling RECIST-based assessment of treatment effect and reducing imbalance via stratification factors. Randomization was stratified by 4 factors: disease site (visceral disease versus non-visceral disease), *ESR1*m detectable at first versus subsequent ctDNA tests, time from initiation of AI + CDK4/6 inhibitor to randomization (< 18 months versus ≥ 18 months), and CDK4/6 inhibitor (palbociclib versus abemaciclib versus ribociclib).

The study schema presented in Figure 5 shows the study design and key eligibility criteria.

Figure 5 Schematic of Study Design



[a] Key secondary endpoints
Step 1 is depicted in yellow; step 2 is depicted in purple.
ABC, locally advanced or metastatic breast cancer; AI, aromatase inhibitor
Source: SERENA-6 Clin Overview Fig 3

Major protocol amendments are summarized in Appendix 1.

2.2.2 Patient Selection

The Applicant's Position:

The study enrolled adult (at least 18 years of age) female (pre/peri-menopausal or postmenopausal) and male patients with a diagnosis of locoregionally recurrent or metastatic ER+, HER2- breast cancer and who were receiving treatment with an AI + CDK4/6 inhibitor in the 1L setting without evidence of disease progression.

For STEP 1 - *ESR1*m Detection Phase, patients who were on AI + CDK4/6 inhibitor treatment for ≥ 6 months without disease progression were eligible for screening. This screening strategy was built on PADA-1 insights that the prevalence of *ESR1*m is low at initial ABC diagnosis and increases after 6 months of 1L AI + CDK4/6 inhibitor treatment. Targeting patients who have

been treated with AI + CDK4/6 inhibitor for ≥ 6 months enriches the screening population with patients with acquired resistance disease and excludes patients with primary AI + CDK4/6 inhibitor resistance. For ctDNA testing, there was no upper limit on the length of prior 1L AI + CDK4/6 inhibitor treatment. This refined approach allowed a large pool of patients to be screened rapidly to identify patients with detectable *ESR1*m. Additionally, this approach reflects the clinical setting where oncologists see patients who have already been on AI + CDK4/6i for varying amounts of time.

For STEP 2 - Randomization Phase: Patients were eligible to participate in the randomized treatment phase of the study if they had an *ESR1* mutation detected by a central test and no evidence of clinical or radiological disease progression per investigator assessment. The patients must have had an ECOG status of 0 or 1 and at least one evaluable lesion.

2.2.3 Efficacy Endpoints

The Applicant's Position:

The primary objective of SERENA-6 was to demonstrate superiority of camizestrant plus continued CDK4/6 inhibitor compared with AI plus continued CDK4/6 inhibitor by investigator assessment of PFS in the Full Analysis Set (FAS), defined as all patients randomized in the study.

The primary efficacy endpoint assessed in the study using investigator-assessed PFS per RECIST 1.1 was agreed with the FDA.

Primary and secondary efficacy endpoints are defined below.

Primary Efficacy Endpoint:

- Progression-free survival (PFS) by investigator assessment: Time from the date of randomization until the date of objective disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy or clinically progressed prior to RECIST 1.1 progression. PFS is determined by investigator assessment.

Secondary Efficacy Endpoints:

- Time to second progression or death (PFS2) (*Key Secondary Endpoint*): Time from randomization to the earliest of second disease progression (after the first objective disease progression and after starting the next therapy) or death.

  The date of second progression, as assessed by the investigator using local clinical practice (clinical progression or radiological progression per RECIST 1.1 or per local standards), is the primary measure of PFS2.

  In a supplementary analysis, PFS2 is assessed using RECIST 1.1-defined progression as assessed by the investigator at the local site.

- Overall survival (OS) (*Key Secondary Endpoint*): Time from the date of randomization until death due to any cause regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy.

- Chemotherapy-free survival: Time from randomization until the earlier of the start date of chemotherapy (including ADC) or death due to any cause.

- Objective response rate (ORR): Proportion of patients who have a complete response (CR) or partial response (PR), as determined by the investigator at local site per RECIST 1.1.

- Clinical benefit rate (CBR) at 24 weeks: Percentage of patients who have a CR or PR or who have stable disease (SD) per RECIST 1.1 as assessed by the investigator at local site or at least 23 weeks after randomization.

- Time to first subsequent therapy or death (TFST): Time from randomization until the earlier of start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause.

- Time to second subsequent therapy or death (TSST): Time from randomization until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause.

Other secondary endpoints included safety (reference to Section 3) and patient-reported outcomes (PRO) (reference to Section 4).

The FDA's Position:
The FDA has the following disagreements and clarifications regarding the Applicant's presentation of the SERENA-6 design and endpoints.

- It is unknown whether changing treatment at *ESR1*m detection, prior to radiographic progression, offers long-term benefit to patients. The development program for camizestrant, including SERENA-6, also was not designed to demonstrate whether the experimental strategy of receiving a new treatment at detection of an *ESR1*m is beneficial compared to receiving it at radiographic progression.

- Although FDA did not object to a primary efficacy endpoint of investigator-assessed PFS per RECIST v1.1, FDA cautioned the Applicant that the strategy of switching treatment at detection of *ESR1*m prior to radiographic progression would need justification. The FDA considers the starting point of PFS, after detection of an *ESR1*m, in SERENA-6 to be new. In 1L trials, the PFS starting point is at diagnosis of advanced or metastatic disease and in later line trials, the standard starting point is at radiographic progression. Because of the new PFS starting point, the clinical meaningfulness of a PFS improvement measured from this new starting point is uncertain.

- SERENA-6 did not allow crossover to camizestrant and a CDK4/6 inhibitor after radiographic progression on the control arm.

- Both the PFS and PFS2 analyses result in comparisons where different numbers of new therapies after randomization are received on each arm (i.e., one new therapy versus continuation of a therapy for PFS and two new therapies versus one new therapy for PFS2). This may have the effect of inflating the differences observed in these endpoints without providing long-term benefit for patients who need treatment indefinitely. For the same reason, we disagree with the Applicant's characterization that the therapy on the investigational arm is "first-line therapy" since detecting an *ESR1*m is being treated as a molecular progression event that requires a change in therapy.
- Refer to Section 2.3.3 for more details on FDA concerns regarding PFS2 in SERENA-6.
- Disease progression for STEP 1 was investigator assessed.
- The Guardant360 device is not FDA approved for the detection of *ESR1*m in patients with HR+HER2- ABC who are on treatment with an AI and CDK4/6 inhibitor for ≥ 6 months (as used in SERENA-6). A Premarket Approval (PMA) supplement for the Guardant360 device is under review in CDRH concurrently with the NDA for camizestrant.

2.2.4 Statistical Methodology

The Applicant's Position:

Approximately 300 patients (150 in each arm) were planned to be randomly assigned to study treatment.

The study was powered for both PFS and the key secondary endpoint PFS2.

For PFS, assuming a 2-sided significance level of 0.05, 1:1 randomization, a total of 195 PFS events provides 93% power to detect a treatment effect of an average hazard ratio (HR) of 0.61 in the FAS (translating to an approximate improvement in median PFS over AI + CDK4/6 inhibitor from 7 to 11.5 months).

For PFS2, a total of 158 PFS2 events provides 77% power to detect a treatment effect of an average HR of 0.65 in the FAS (translating to an approximate improvement in median PFS2 over AI + CDK4/6 inhibitor from 15 to 23 months).

PFS was analyzed using a stratified log-rank test adjusting for the stratification factors. The PFS2 and OS endpoints were analyzed using identical methods as for PFS and adjusting for the same set of stratification factors subject to the pooling strategy described in the primary analysis of the primary endpoint.

For all planned analyses of PFS, PFS2, and OS, a multiple testing procedure (MTP) was implemented through a group sequential design and a hierarchical testing procedure to ensure the maintenance of an overall two-sided type I error at a significance level of 0.05 (Appendix 2). The Haybittle-Peto stopping boundary for efficacy was applied, which controlled the type I error

in the strong sense. The significance level for PFS was α = 0.0001 at the interim analysis and approximately 0.05 at the final analysis. No multiplicity adjustment will be applied for other endpoints as other endpoints will be considered supportive endpoints.

This study was planned to have a total of 4 data cut-offs (DCOs) (Table 2). If PFS met statistical significance at DCO1, then PFS2 would be tested and the Haybittle-Peto boundaries would be used. A significance level of 0.0001 was applied for PFS2 at both DCO1 and DCO2 respectively, and a significance level of approximately 0.05 was applied for PFS2 at DCO3.

If PFS2 met statistical significance at DCO1 or DCO2 or DCO3, then OS would be tested and the Haybittle-Peto boundaries would be used. A significance level of 0.0001 was applied for OS at DCO1, DCO2 and DCO3, and a significance level of approximately 0.05 will be applied for OS at DCO4.

Table 2 SERENA-6 DCOs

DCO	Pre-planned analysis per protocol (Trigger)	DCO date	Data maturity and follow-up
DCO1*	PFS interim analysis (135 PFS events)	28 November 2024	**PFS**: 54% (171/315 events); 88% IF (171/195 events) **PFS2**: 27% (85/315 events); 54% IF (85/158 events) **OS**: 12% (39/315 events); 24% IF (39/165 events) **Median duration of follow-up**: 12.6 months
DCO2	Follow-up PFS analysis (195 PFS events)	30 June 2025	**PFS**: 65% (205/315 events) **PFS2**: 42% (133/315 events); 84% IF (133/158 events) **OS**: 22% (69/315 events); 42% IF (69/165 events) **Median duration of follow-up**: 18.7 months
DCO3	PFS2 primary analysis (158 PFS2 events)	02 January 2026	**PFS**: 71% (223/315 events) **PFS2**: 54% (170/315 events) **OS**: 30% (95/315 events); 58% IF (95/165 events) **Median duration of follow-up**: 23.5 months
DCO4	OS primary analysis (165 OS events)	Pending	Pending

*As per study protocol, the DCO1 date was determined once the target number of PFS events was reached, but enrolment, follow-up time after last patient randomized, and time between interim analysis and final analysis were also considered, and the DCO date was scheduled after sufficient data had been collected for all patients
DCO: Data cut-off; PFS: Progression-free survival; PFS2: Second progression-free survival; OS: Overall survival; IF: Information fraction

Three pre-planned analyses have been completed at the date of finalization of the Applicant's sections of this briefing document:

- **PFS Interim Analysis at DCO1 (28 November 2024)**: PFS Interim Analysis was planned to occur when at least 135 events (69% information fraction and 45% maturity) had been observed and at least 1 tumor assessment (at least 2-month follow-up) was performed post-randomization in all randomized patients. Statistical superiority required a p-value of less than the prespecified boundary of 0.0001. At DCO1, a total of 171 PFS events (88% information fraction and 54% maturity) had been observed. PFS2 was tested for statistical

significance since PFS achieved statistical significance. Given that PFS2 p-value did not cross the prespecified boundary of 0.0001, OS was not formally tested for statistical significance.

- **Follow-up PFS analysis at DCO2 (30 June 2025)**: The protocol prespecified a PFS analysis when at least 195 events (65% maturity) had been observed. This follow-up PFS analysis has been conducted based on a total of 205 PFS events (65% maturity). PFS2 was tested for statistical significance at DCO2. Given that PFS2 p-value did not cross the prespecified boundary of 0.0001, OS was not formally tested for statistical significance.
- **PFS2 primary analysis at DCO3 (2 January 2026)**: The protocol prespecified a PFS2 analysis when at least 158 events (53% maturity) had been observed. This analysis has been conducted based on a total of 170 PFS2 events (54% maturity). Given that statistical significance for PFS2 was achieved with a p-value of 0.00373, OS was formally tested. OS p-value did not cross the prespecified boundary of 0.0001.

The final analysis of OS will occur at DCO4 when at least 165 OS events (55% maturity) have been observed.

Major changes to the statistical analysis plan (SAP) are summarized in Appendix 3.

The FDA's Position:

The FDA agrees with the Applicant's description of the statistical analysis plan (SAP) and adds the following clarifications.

- The Applicant fully powered SERENA-6 for PFS and PFS2 only. A demonstrated OS benefit might have mitigated the uncertainty in the long-term benefit of changing treatment at *ESR1*m detection, prior to radiographic progression. For OS, at DCO4 (final analysis of OS), 165 deaths are expected and would provide approximately 63% power to detect a true treatment effect on OS, assuming a hazard ratio of 0.70 and a median OS of 35 months in the AI + CDK4/6 inhibitor arm and 50 months on the camizestrant + CDK4/6 inhibitor arm. Therefore, given the trial is not adequately powered for OS, definitive conclusions about survival benefit may not be able to be drawn from SERENA-6.

- Despite the formal inclusion of PFS2 in the statistical hierarchy, FDA generally does not consider PFS2 acceptable for regulatory decision-making, as communicated to the Applicant in the February 8, 2021, Type C Guidance meeting preliminary comments. In addition, FDA has concerns specific to SERENA-6 regarding PFS2. See Section 2.3 for more details.

- For PFS, the Applicant prespecified a sensitivity analysis based on BICR assessment to evaluate assessment bias. However, BICR assessment for PFS2 was not planned.

- Only PFS, PFS2, and OS were prespecified to be multiplicity-controlled. The remaining endpoints (chemotherapy-free survival, ORR, CBR at Week 24, TFST, and TSST) are exploratory only.

- For efficacy analyses, the same stratification factors used for randomization were

prespecified to be used for the stratified analyses:

- Disease site: visceral disease versus non-visceral disease
- *ESR1*m detectable at first ctDNA test versus subsequent ctDNA tests
- Time from initiation of aromatase inhibitor + CDK4/6 inhibitor to randomization: <18 months versus ≥18 months (<78 weeks versus ≥78 weeks)
- CDK4/6 inhibitor: palbociclib versus abemaciclib versus ribociclib

- The Applicant prespecified a pooling strategy for sparse strata. For the PFS analysis at DCO1 and the PFS2 analysis at DCO3, the CDK4/6 inhibitor strata were excluded from analysis. For the OS analysis at DCO3, the CDK4/6 inhibitor strata and the disease site strata were excluded from analysis.
- In Table 2, the Applicant's definition of data maturity uses the overall population of 315 randomized patients as the denominator. FDA generally considers maturity based on information fraction (also presented in Table 2), which uses as the denominator the target number of events needed for final analysis for a given endpoint.

2.3 Efficacy Summary

2.3.1 SERENA-6 Patient Population

The Applicant's Position:

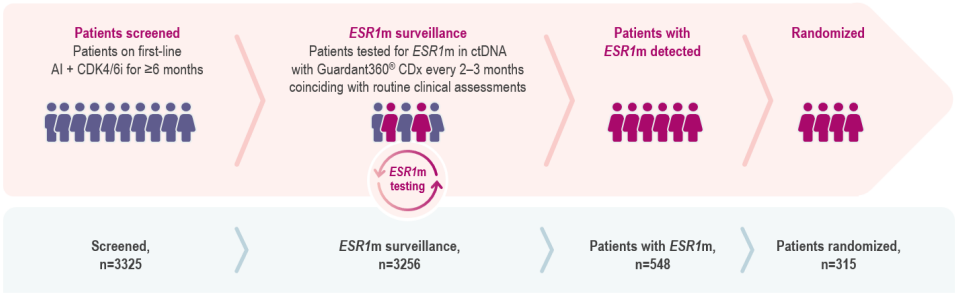
2.3.1.1 Patient Disposition

SERENA-6 is a global, multicenter, randomized, double-blind study.

STEP 1: ESR1m Detection Phase

A total of 3,325 patients were screened across 264 centers in 23 countries worldwide. Of these, 3,256 patients had at least one ctDNA test for *ESR1*m performed. 1,949 patients remained event-free (no *ESR1*m detected and no disease progression) at the time of screening closure, resulting in 1,307 patients with evaluable *ESR1*m status at or before progression. Among these 1,307 patients, 548 (42%) had *ESR1*m detected (Figure 6).

Figure 6 *ESR1*m Surveillance During First-line AI + CDK4/6i



Considering all patients who had an *ESR1*m test, 8.9% had *ESR1*m detected at the first ctDNA test; cumulative incidence reached 19.6% after up to 5 tests. Focusing only on patients who had an *ESR1*m detected, approximately 50% were detected on the first test, and 90% were detected within 5 tests.

STEP2: Randomization Phase

A total of 406 patients consented to participate in STEP 2. Of those, 315 patients met all inclusion criteria and were randomized in a 1:1 ratio to receive the study treatment of either camizestrant + CDK4/6 inhibitor (N = 157) or continue on AI + CDK4/6 inhibitor (N = 158). Main reason for not meeting the STEP 2 eligibility amongst the 91 patients that were not randomized was concurrent radiographic disease progression. More details are presented in Appendix 4.

The first patient was enrolled on 30 June 2021 in the palbociclib cohort. The abemaciclib and ribociclib cohorts were opened in February 2022 and October 2023, respectively, after the Independent Data Monitoring Committee (IDMC) reviewed safety data for these combinations from SERENA-1, and confirmed their acceptability. Overall, the majority of patients continued with palbociclib (~75%), followed by ribociclib (~15%) and abemaciclib (~10%). This is consistent with the real-world usage pattern of CDK4/6 inhibitors at the time of study enrolment (Chamorro et al 2023, Luyendijk et al 2023).

At the time of DCO3, study treatment was ongoing for 29.0% of patients in the camizestrant + CDK4/6 inhibitor arm and 7.7% of patients in the AI + CDK4/6 inhibitor arm. Across both treatment arms, the most common reason for study treatment discontinuation was objective disease progression.

The patient population screened for SERENA-6 is representative of the 1L patient population in the US, and globally. The US contributed the highest number of screening patients in STEP 1, with 427 patients. 47 of those patients had a positive test for an *ESR1*m. The US also had the highest representation in the randomized intent-to-treat (ITT) population, with 45 patients randomized.

2.3.1.2 Demographics and Other Baselines Characteristics

Overall, the screened population was largely representative of patients with HR+/ HER2- ABC receiving 1L treatment (DeMichele et al 2021, Rugo et al 2023, Lloyd et al 2024).

In the randomized patient population, treatment arms were balanced with respect to demographic characteristics, ECOG performance status, prevalence of the most frequent *ESR1*m variants, and the 4 stratification factors (Table 3).

Table 3 Demographic Characteristics and Baseline Characteristics

Characteristic	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range), years	61.0 (29-81)	60.5 (35-89)
Female, n (%)	157 (100)	155 (98)
Male, n (%)	0	3 (2)

Characteristic	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Race, n (%)		
White	97 (62)	102 (65)
Asian	39 (25)	34 (22)
Black or African American	4 (3)	2 (1)
Other/Not reported [a]	17 (11)	20 (13)
Postmenopausal status, n (%)	122 (78)	127 (80)
ECOG performance status score, n (%) [b]		
0	106 (68)	98 (62)
1	49 (31)	56 (35)
Most common *ESR1*m at baseline, n (%) [c]		
D538G	70 (45)	82 (52)
Y537S	61 (39)	60 (38)
Y537N	29 (19)	25 (16)
Region, n (%)		
Asia	40 (25)	39 (25)
Europe	89 (57)	91 (58)
North America	28 (18)	28 (18)
Visceral metastases, n (%)	66 (42)	71 (45)
Time of *ESR1*m detection, n (%)		
At first test	84 (54)	84 (53)
At a subsequent test	73 (47)	74 (47)
Time from initiation of AI + CDK4/6i to randomization, n (%)		
≥18 months	97 (62)	100 (63)
<18 months	60 (38)	58 (37)
Median (range), months	23 (7-96)	23 (6-96)
CDK4/6i continued at randomization, n (%)		
Palbociclib	119 (76)	119 (75)
Ribociclib	24 (15)	23 (15)
Abemaciclib	14 (9)	16 (10)

[a] Other/not reported included Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, other, not reported or missing.

[b] Data missing for 2 patients in the camizestrant + CDK4/6i arm and 3 patients in the AI + CDK4/6i arm. One patient in the AI + CDK4/6i arm had an ECOG performance score of 2, which was a protocol deviation.

[c] The 3 most prevalent *ESR1*m detected of the 11 qualifying mutations. Patients may have had more than one *ESR1*m.

AI, aromatase inhibitor; DCO: 02 January 2026 (DCO3)

Source: DCO3 PSC Table 14.1.2, 14.1.7.1, 14.1.8.1, 14.1.11.2, 14.1.12, 14.1.13, 14.2.21.1

The median time from initiation of treatment with an AI + CDK4/6 inhibitor until randomization was 23.1 months. The median age of the patients was 61 years (range, 29 to 89), 79.0% of the patients were postmenopausal women, 1.0% were men, and 43.5% of the patients had visceral disease. The prevalence of the 3 most frequent *ESR1*m variants was consistent with that

reported in the scientific literature (Rinaldi et al 2020) and was balanced across both treatment arms.

The FDA's Position:
The FDA agrees with the Applicant's assessment that relatively few patients enrolled in STEP 1 of SERENA-6 were randomized in STEP 2; reasons for patients not being randomized in STEP 2 included no detection of an *ESR1*m, no *ESR1*m test available, radiographic progression, lack or withdrawal of patient consent, and not meeting the eligibility criteria for STEP 2. Only 9% (315/3,325) of screened patients underwent randomization in STEP 2.

We also agree that initially only patients receiving palbociclib were allowed to enroll while the IDMC reviewed the safety data from the camizestrant development program. See Section 3.5 on safety for more information about a fatal case of TdP related to camizestrant and ribociclib on SERENA-1.

The FDA agrees with the distribution of CDK4/6 inhibitors on SERENA-6. However, we note that the use of ribociclib is increasing based on an OS benefit in first-line HR+HER2- ABC. We do not find that SERENA-6 represents the current U.S. standard of care regarding the preferred CDK4/6 inhibitor.

Although FDA agrees regarding the number of U.S. patients in SERENA-6, we note that patients in the U.S. made up only 14% of patients enrolled in STEP 2.

We agree with the remainder of the Applicant's description of baseline demographics and disease characteristics. Only 17% of patients on both arms had an *ESR1*m detected after less than 12 months of AI + CDK4/6 inhibitor therapy.

2.3.2 Overview of Efficacy Results

The Applicant's Position:

The efficacy data primarily came from the pre-planned interim analysis of PFS in the SERENA-6 study, based on a DCO of 28 November 2024 (DCO1). At this interim analysis, the IDMC recommended declaring early success for the primary endpoint (PFS), as the observed HR crossed the prespecified efficacy boundary.

At DCO1, the median duration of follow-up was 13.1 months in the camizestrant + CDK4/6 inhibitor arm and 12.1 months in the AI + CDK4/6 inhibitor arm.

At the third prespecified data cut-off (DCO3, 02 January 2026), with longer follow-up (increased to 23.6 and 22.5 months respectively), additional PFS2 and OS events were observed.

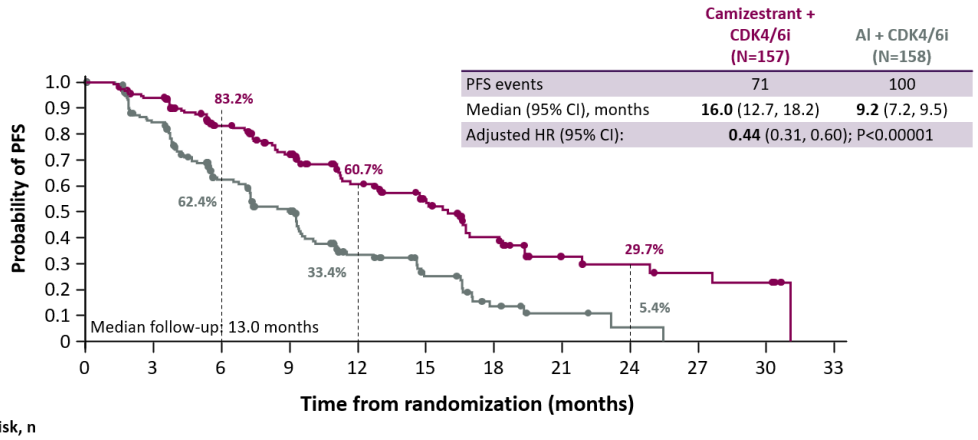
2.3.2.1 Primary Endpoint: PFS

The SERENA-6 study met the primary endpoint of PFS at DCO1. Switching to camizestrant while continuing CDK4/6 inhibition upon the emergence of *ESR1*m demonstrated a statistically

significant and clinically meaningful improvement in investigator-assessed PFS per RECIST 1.1 and reduced the risk of disease progression or death by 56% compared to continued AI + CDK4/6 inhibitor therapy (HR = 0.44; 95% CI: 0.31, 0.60; p < 0.00001). From the time of randomization (switch of therapy), median PFS was 16.0 months in the camizestrant + CDK4/6 inhibitor arm vs 9.2 months in the AI + CDK4/6 inhibitor arm (Figure 7 and Table 4).

This outcome was consistent with Blinded Independent Central Review (BICR)-assessed PFS (HR 0.43; 95% CI: 0.29, 0.63; nominal p = 0.00001).

Figure 7 **PFS Based on Investigator Assessments According to RECIST 1.1, Kaplan-Meier Plot (FAS) – DCO1**



Dots represent censored observations. 2-sided p-value.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
DCO1: 28 November 2024
Reprinted from Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580.
Source: SERENA-6 CSR Figure 14.2.1.2.

With longer follow-up at DCO3, the camizestrant + CDK4/6 inhibitor arm continued to demonstrate a clinically meaningful improvement in PFS over AI + CDK4/6 inhibitor arm (HR = 0.45; 95% CI: 0.34, 0.59; nominal p <0.00001). The median PFS was 16.8 months in the camizestrant + CDK4/6 inhibitor arm and 9.2 months in the AI + CDK4/6 inhibitor arm (Table 4).

The benefit seen with camizestrant + CDK4/6 inhibitor started early and was sustained, with Kaplan-Meier curves diverging from the first tumor assessment at 8 weeks and remaining apart. At 6, 12, 24, and 30 months, a greater proportion of patients in the camizestrant+ CDK4/6 inhibitor arm were estimated to be alive and progression-free compared to those on AI + CDK4/6 inhibitor. This indicates a sustained benefit of early intervention based on *ESR1*m detection by ctDNA prior to radiographic or clinical progression. With longer follow-up at DCO3, the 30-month Kaplan-Meier PFS rate was 30.4% with camizestrant + CDK4/6 inhibitor versus 2.7% with AI + CDK4/6 inhibitor, highlighting durable disease control in a subset of patients who remained progression free for a substantially longer period of time. This temporal pattern was consistent across DCOs (Figure 7 and Table 4).

Table 4 Progression-Free Survival (FAS)

PFS	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO1	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO3
Based on Investigator Assessment		
Total number of patients with events [a], n/N (%)	71/157 (45.2) vs 100/158 (63.3)	99/157 (63.1) vs 124/158 (78.5)
Median, months (95% CI) [b, c]	**15.97 (12.71, 18.23) vs 9.23 (7.23, 9.53)**	**16.76 (14.72, 19.35) vs 9.23 (7.23, 9.66)**
HR (95% CI) [d]	**0.44 (0.31, 0.60)**	**0.45 (0.34, 0.59)**
2-sided p-value [d]	**p < 0.00001**	**nominal p < 0.00001**
PFS rate at 6 months (%) (95% CI)	83.2 (75.9, 88.4) vs 62.4 (53.8, 69.9)	84.1 (77.2, 89.0) vs 62.0 (53.7, 69.2)
PFS rate at 12 months (%) (95% CI)	60.7 (51.1, 69.0) vs 33.4 (24.9, 42.2)	62.2 (53.8, 69.4) vs 35.3 (27.5, 43.0)
PFS rate at 24 months (%) (95% CI)	29.7 (19.0, 41.2) vs 5.4 (0.7, 18.2)	34.9 (26.8, 43.0) vs 14.2 (8.4, 21.4)
PFS rate at 30 months (%) (95% CI)	22.6 (11.8, 35.6) vs 0 (NC, NC)	30.4 (22.2, 39.1) vs 2.7 (0.3, 10.6)
Based on BICR Assessment		
Total number of patients with events, n/N (%)	47/157 (29.9) vs 65/158 (41.1)	-
Median, months (95% CI)	19.25 (15.11, NC) vs 11.50 (7.26, 14.98)	-
HR (95% CI) [e]	0.43 (0.29, 0.63)	-
p-value [e]	nominal p = 0.00001	-

[a] Includes progression events that occur within 2 visits of last valuable assessment.

[b] The calculation is based on the Kaplan-Meier method.

[c] The CI for PFS is derived based on Brookmeyer-Crowley method.

[d] The HR and its CI are estimated using a Cox proportional hazards model stratified by disease site, *ESR1*m status detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization. A HR < 1 favors camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by same stratification factors used for the HR.

[d] The analysis is performed using the BICR data. The p-value (nominal) is based on the stratified log-rank test, stratified by *ESR1*m status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization.

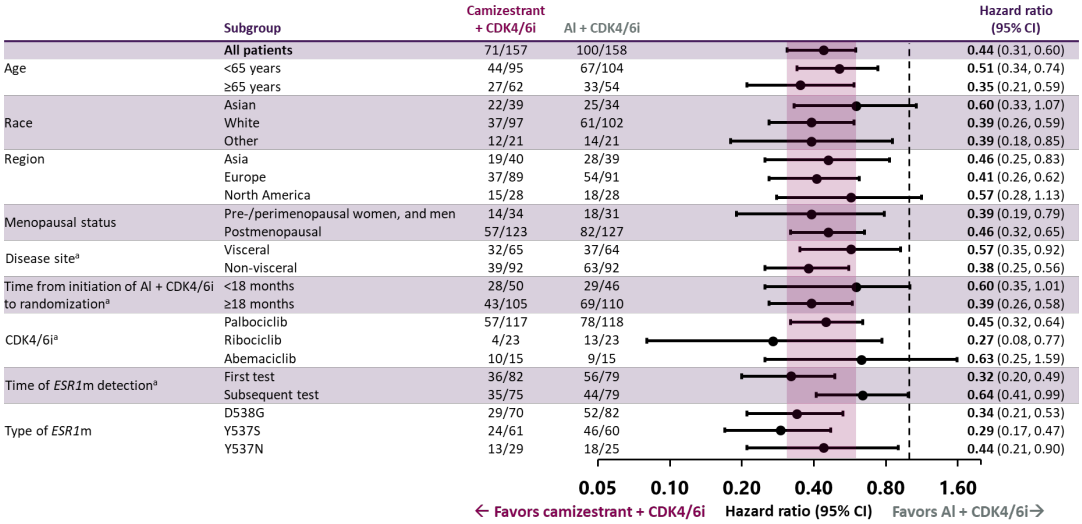
NC: not calculable

DCO1: 28 November 2024; DCO3: 02 January 2026

Source: SERENA-6 CSR Table 14.2.1.1, Table 14.2.1.5.2; DCO3 Table 14.2.1.1

This effect was observed consistently across all prespecified subgroups (Figure 8). A consistent treatment effect (with HR below 1.0) in favor of the camizestrant + CDK4/6 inhibitor arm across all the subgroups was maintained at DCO3 (Appendix 5).

Figure 8 **PFS Based on Investigator Assessment According to RECIST 1.1, Forest Plot by Subgroup (FAS) – DCO1**



[a] Stratification factor.
[b] In follow-up (DCO3) data the upper bound of the 95% CI is now <1.
DCO1: 28 November 2024
Adapted from Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580.
Source: SERENA-6 CSR Table 14.2.1.11, Figure 14.2.1.12.

2.3.2.2 Secondary Endpoints

Results from all secondary endpoints were broadly consistent with the primary PFS analysis, as demonstrated by PFS2, TFST, TSST, chemotherapy-free survival and early OS data.

2.3.2.2.1 Time to second progression or death (PFS2) (*Key Secondary Endpoint*)

PFS2 provides a more comprehensive understanding of both the immediate and the enduring benefit of initial treatment. Therefore, the study was designed with PFS2 as a key secondary endpoint. Published literature suggests that PFS2 results are predictive of OS benefit in HR+/HER2- disease (Woodford et al 2024, Woodford et al 2022, Woodford et al 2021, Mainwaring et al 2019, Filis et al 2026).

PFS2 is defined as the time from randomization to the earliest of second disease progression (after the first objective disease progression and after starting the next therapy) or death. This definition is consistent with regulatory guidance (EMA Guideline 2013).

Because PFS2 data capture has historically been challenging, multiple measures to strengthen the quality of the PFS2 assessment were implemented in SERENA-6. The protocol required investigators to follow the most recent NCCN, ESMO, Pan-Asian adapted ESMO, or other internationally recognized guidelines when selecting subsequent lines of therapy to ensure appropriate treatment, with the possibility of unblinding to allocated study therapy upon request, after progression, and to carefully document treatment options, progression type, and RECIST 1.1 measurements at each assessment visit for PFS2.

Treatment options broadly fell into 2 therapeutic classes: cytotoxic therapies (chemotherapy

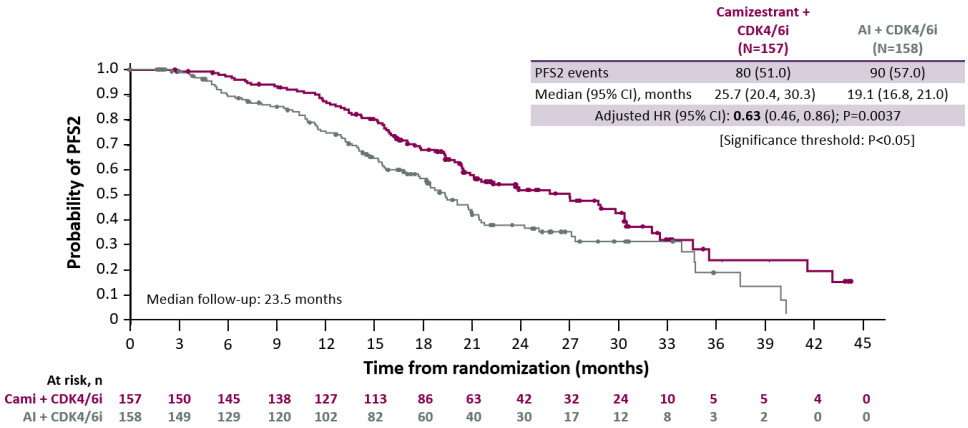
and ADCs) and ET with or without targeted agents. (see Section 2.3.2.2.2 for details).

The investigator's assessment of the date of second progression was the primary measure of PFS2. The date of second progression was defined according to local standard clinical practice and could be clinical or radiological (per RECIST 1.1 using CT or MRI if CT was not possible, or radiological progression per clinical practice imaging modalities beyond CT/MRI). The evaluation of PFS2 per RECIST 1.1 was also prespecified, and a supplementary analysis among patients whose PFS2 events met RECIST 1.1 criteria was conducted.

Per protocol, assessments were requested every 8 to 12 weeks after the start of subsequent anticancer therapy until second progression. Data collected in SERENA-6 show that the median interval between PFS2 assessments was comparable across arms.

At DCO3, with 170 PFS2 events observed, the key secondary endpoint of PFS2 was met, demonstrating a persistent benefit in favor of the camizestrant + CDK4/6 inhibitor arm (25.7 months vs 19.1 months; HR: 0.63; 95% CI: 0.46, 0.86; p = 0.00373), with a difference of 6.6 months. These results indicate that the PFS benefit carries forward beyond initial progression, reflecting sustained efficacy in the post-progression period (Figure 9 and Table 5).

Figure 9 **Time to second progression or death (PFS2), Kaplan-Meier plot (FAS) – DCO3**



Dots represent censored observations. The p-value is based on the stratified log-rank test, stratified by disease site, *ESR1*m detectable at first versus subsequent ctDNA and time from initiation of AI + CDK4/6 inhibitor to randomization.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
Source: DCO3 Figure 14.2.2.2.

A supplementary analysis of PFS2 events assessed by RECIST 1.1 criteria (>80% patients qualified for PFS2 RECIST criteria event) was consistent with the primary analysis of PFS2, using PFS2 events per local practice. This further substantiated the robustness of the PFS2 result (Table 5).

Table 5 **Time to Second Progression or Death (PFS2) (FAS) – DCO3**

PFS2	**Camizestrant + CDK4/6i vs AI + CDK4/6i**
Total number of patients with events, n/N (%)	**80/157 (51.0) vs 90/158 (57.0)**
Median, months (95% CI) [a, b]	25.72 (20.40, 30.32) vs 19.06 (16.82, 21.03)
HR (95% CI) [c]	0.63 (0.46, 0.86)

PFS2	Camizestrant + CDK4/6i vs AI + CDK4/6i
2-sided p-value [c]	p = 0.00373
Supplementary analysis based on RECIST 1.1 [d]	
Number of patients with events, n/N (%)	69/157 (43.9) vs 78/158 (49.4)
Median, months (95% CI)	27.73 (22.31, 30.46) vs 20.76 (17.68, 25.10)
HR (95% CI)	0.64 (0.46, 0.90)
p-value	nominal p = 0.00939

[a] The calculation is based on the Kaplan-Meier method.

[b] The CI for PFS2 is derived based on Brookmeyer-Crowley method.

[c] The HR and its CI are estimated using a stratified Cox proportional hazards model stratified by *ESR1*m detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization. The same patient may have more than one type of progression event. A HR < 1 favors camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by disease site, *ESR1*m detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization.

[d] The analysis is a repeat of the primary PFS2 analysis but the determination of second progression is assessed by investigator based on RECIST 1.1 . A HR < 1 favors camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by *ESR1*m status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization.

DCO3: 02 January 2026

Source: DCO3 Table 14.2.2.1, Table 14.2.2.3.

2.3.2.2.2 Subsequent Therapy

Subsequent therapy provided further insights into the PFS2 results and support the risk-benefit assessment for camizestrant. Of the 110 patients who discontinued camizestrant + CDK4/6 inhibitor, 87 (79.1%) received subsequent therapy. In the AI + CDK4/6 inhibitor group, 117 of 143 patients (81.8%) who discontinued treatment received subsequent therapy.

Details of first subsequent anticancer regimens are presented in Table 6. Overall, the regimens used in SERENA-6 are highly concordant with NCCN and ESMO treatment guidelines, as shown in the right-hand columns of Table 6.

Table 6 Summary of First Subsequent Anticancer Regimen in SERENA-6 – DCO3

Subsequent regimen	Camizestrant + CDK4/6i N = 87, n (%)	AI + CDK4/6i N = 117, n (%)	Align with current NCCN treatment guidelines (Y/N)	Align with current ESMO treatment guidelines (Y/N)
Cytotoxic therapy	**38 (43.7)**	**36 (30.8)**	-	-
ADC-based regimen	**2 (2.3)**	**10 (8.5)**	-	-
Datopotamab deruxtecan	0	1 (0.9)	Y	Y
DB1303 [a]	1 (1.1)	0	Y [e] (trial participation)	Y [e] (trial participation)
Sacituzumab govitecan	0	1 (0.9)	Y	Y
Sacituzumab tirumotecan	1 (1.1)	1 (0.9)	Y [e]	Y [e]
Trastuzumab deruxtecan	0	7 (6.0)	Y	Y
Chemotherapy-based regimen	**36 (41.4)**	**26 (22.2)**	-	-
Anthracycline based regimen	2 (2.3)	5 (4.3)	Y	Y

Subsequent regimen	Camizestrant + CDK4/6i N = 87, n (%)	AI + CDK4/6i N = 117, n (%)	Align with current NCCN treatment guidelines (Y/N)	Align with current ESMO treatment guidelines (Y/N)
Pyrimidine based regimen	21 (24.1)	14 (12.0)	Y	Y
Taxane based regimen	12 (13.8)	7 (6.0)	Y	Y
Other antineoplastic agent	1 (1.3)	0	Y	Y
Endocrine-based therapy	**48 (55.1)**	**78 (66.7)**	-	-
Endocrine + targeted therapy	**35 (40.2)**	**54 (46.2)**	-	-
AI + CDK4/6i	8 (9.2)	7 (6.0)	Y	Y
ET + mTORi	14 (16.1)	18 (15.4)	Y	Y
Fulvestrant + CDK4/6i	6 (6.9)	9 (7.7)	Y	Y
Fulvestrant + CDK4/6i + KRASi	1 (1.1)	0	Y [e]	Y [e]
Fulvestrant + PIK3CAi or AKTi	5 (5.7)	13 (11.1)	Y	Y
Fulvestrant + PIK3CAi or AKTi + CDK4/6i	0	2 (1.7)	Y	Y
Novel ET [b] + targeted therapy	1 (1.1)	5 (4.2)	Y [e]	Y [e]
Novel ET [b] + CDK4/6i	0	4 (3.4)	Y [e]	Y [e]
Novel ET [b] + PARPi	1 (1.1)	1 (0.9)	Y [e]	Y [e]
Endocrine monotherapy	**13 (14.9)**	**24 (20.5)**	-	-
Anti-estrogens [c]	0	0	Y	Y
AI	3 (3.4)	0	Y	Y
Fulvestrant	8 (9.2)	14 (12.0)	Y	Y
Novel ET [b]	1 (1.1)	10 (8.5)	Y [e]	Y [e]
Tamoxifen	1 (1.3)	0	Y	Y
Others [d]	**1 (1.3)**	**3 (2.8)**	-	-
Androgen receptor modulator	1 (1.3)	0	Y [e]	Y [e]
PARPi	0	3 (2.8)	Y	Y

[a] Topoisomerase-1 inhibitor-based ADC targeting HER2.

[b] "Novel ET" subgroup includes the following terms – elacestrant, imlunestrant, camizestrant, vepdegestrant, lasofoxifene, and palazestrant.

[c] Anti-estrogen was the coded term for "ER antagonist and selective ER degrader". No specific compound name was available at time of DCO.

[d] Others included PARPi (olaparib, talazoparib) or androgen receptor modulator (enobosarm).

[e] Clinical trials are encouraged when applicable and available in each line of therapy, as per NCCN and ESMO guidelines.

The percentages are based on the number of patients who received a subsequent line of therapy.
Y = yes; N = no.
DCO3: 02 January 2026
Source: DCO3 IEMT000177, IEMT 000279; NCCN 2026, Trapani et al 2025.

Overall, more than 50% of patients in the camizestrant + CDK4/6i arm received endocrine-based therapy as subsequent treatment. The use of chemotherapy/ADC appears to be multifactorial, potentially reflecting local availability of treatment options and molecular testing, patient preference, and site-level practice patterns (see Appendix 6 for further details). There was no evidence of increased use of cytotoxic agents in the camizestrant arm among US patients (Appendix 7). Greater ADC usage was observed in the AI arm (2 patients in the

camizestrant arm vs 10 patients in the AI arm). In addition, among patients who experienced disease progression, the patterns of progression were similar across arms, with no differences observed in visceral progression rates, suggesting the rate of chemotherapy use in the camizestrant arm was not reflective of the nature of the disease progression.

Importantly, switching to camizestrant before radiological progression led to extended time on 1L endocrine-based therapy and delayed the need for chemotherapy as evidenced by the results of chemotherapy-free survival in favor of the camizestrant arm (see Section 2.3.2.2.3).

In summary, these data further contextualize the PFS2 findings in Section 2.3.2.2.1). Patients in SERENA-6 received appropriate subsequent therapy, demonstrated by high concordance with the latest treatment guidelines. Additionally, when considered alongside TSST and chemotherapy-free survival (see Section 2.3.2.2.3), the data indicate that switching to camizestrant does not compromise the efficacy of the next line of therapy.

2.3.2.2.3 Chemotherapy/ADC -free Survival, TFST, and TSST

At DCO3, chemotherapy/ADC-free survival favored the camizestrant + CDK4/6 inhibitor arm (HR = 0.64) (Table 7). These data suggest that switching to camizestrant delays the need for cytotoxic therapy. Furthermore, TFST (HR = 0.43) and TSST (HR = 0.59) also indicate the maintenance of benefit with camizestrant.

Table 7 Other Secondary Efficacy Results (FAS) – DCO3

Secondary Endpoint	Camizestrant + CDK4/6i vs AI + CDK4/6i
Chemo/ADC-free survival [a]	
Events, n/N (%)	85/157 (54.1) vs 98/158 (62.0)
Median, months (95% CI) [b,c]	22.6 (19.3, 30.9) vs 18.7 (15.8, 22.1)
HR (95% CI) [d]	**0.64** (0.47, 0.87)
Time to first subsequent therapy (TFST)	
Events, n/N (%)	101/157 (64.3) vs 131/158 (82.9)
Median, months (95% CI) [b,c]	17.0 (15.8, 20.4) vs 9.6 (7.6, 11.5)
HR (95% CI) [d]	**0.43** (0.33, 0.57)
Time to second subsequent therapy (TSST)	
Events, n/N (%)	81/157 (51.6) vs 99/158 (62.7)
Median, months (95% CI) [b,c]	21.7 (20.4, 31.5) vs 18.7 (15.9, 20.0)
HR (95% CI) [d]	**0.59** (0.43, 0.80)

[a] Antibody-drug conjugates and chemotherapies were included in the chemotherapy-free survival analysis

[b] The calculation is based on the Kaplan-Meier method.

[c] The CI is derived based on Brookmeyer-Crowley method.

[d] The HR and its CI are estimated using a stratified Cox proportional hazards model stratified by disease site, *ESR1*m detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomization. A HR < 1 favors camizestrant + CDK4/6 inhibitor.

DCO3: 02 January 2026

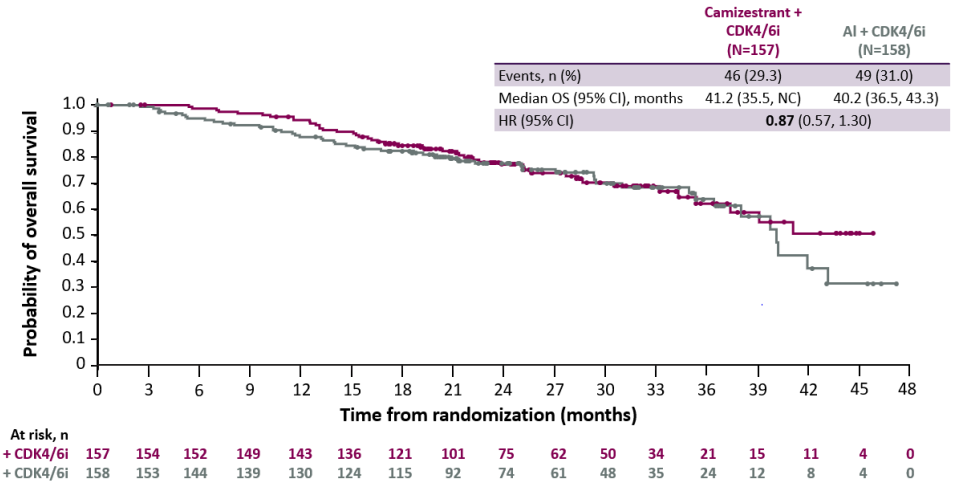
Source: DCO3 Table 14.2.9.1, Table 14.2.10.1, and Table 14.2.8.3.IEMT

2.3.2.2.4 Overall Survival (*Key Secondary Endpoint*)

At DCO3 there is no evidence of detriment in OS (HR: 0.87; 95% CI: 0.57, 1.30), with a median

duration of follow-up of 23.5 months and maturity of 30% (95/315) (Figure 10 and Appendix 8).

Figure 10 Overall Survival, Kaplan-Meier Plot (FAS) – DCO3

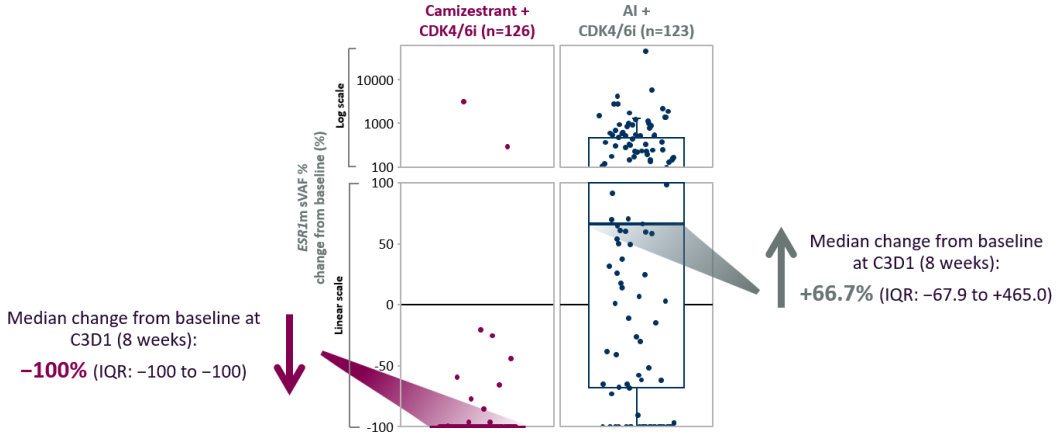


Dots represent censored observations.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
DCO3: 02 January 2026
Source: DCO3 Figure 14.2.3.2.

2.3.2.2.5 Changes in *ESR1*m ctDNA Levels (*Exploratory Endpoint*)

Descriptive analysis of the change in *ESR1*m ctDNA variant allele frequency (VAF) across arms has been performed, investigating the effect of switching from AI to camizestrant while maintaining CDK4/6 inhibitor treatment. These data demonstrate a profound reduction in *ESR1*m ctDNA in patients who switch to camizestrant (median change in *ESR1*m summed VAF of -100% [IQR -100% to -100%]), while levels continue to rise in patients on the AI arm (increase of 66.7% [IQR -67.9% to 465.0%]) (Figure 11) (Bidard et al 2026).

Figure 11 Change in *ESR1*m ctDNA Levels



IQR=interquartile range; sVAF=summed variant allele fraction; C3D1=Cycle 3, Day 1.
Percentage change in *ESR1*m summed VAF detected in plasma from screening to Cycle 3 Day 1 in the AI + CDK4/6 inhibitor arm or the Camizestrant + CDK4/6 inhibitor arm of SERENA-6.
DCO2: June 30, 2025
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.

Source: SERENA-6 Biomarker Report Figure 2.

2.3.3 Efficacy Conclusions

The Applicant's Position:

The SERENA-6 study was innovatively and robustly designed to test the hypothesis that switching to camizestrant upon detection of an *ESR1* mutation by ctDNA in blood, prior to radiographic or clinical progression, would extend the duration of 1L ET + CDK4/6 inhibitor therapy and improve patient outcomes.

SERENA-6 met its primary endpoint of PFS at the interim analysis, demonstrating a statistically significant and clinically meaningful 56% reduction in the risk of progression or death when switching to camizestrant compared to continuing on AI (HR = 0.44). The benefit of camizestrant + CDK4/6 inhibitor was both early and sustained, and was consistently observed across all prespecified patient subgroups. Notably, the PFS advantage persisted through subsequent lines of therapy, and was maintained through PFS2. There is no evidence of detriment in OS. Additional secondary endpoints such as chemotherapy/ADC-free survival further support the benefit of switching to camizestrant. A profound reduction of *ESR1*m ctDNA levels was also observed following the switch to camizestrant, confirming the targeted biological effect of camizestrant on *ESR1*m.

The totality of data from SERENA-6 demonstrates the benefit of an early, ctDNA-guided switch from AI to camizestrant in patients on 1L treatment with a CDK4/6 inhibitor, at emergence of *ESR1*m.

The FDA's Position:

The FDA is uncertain whether SERENA-6 has demonstrated a clinically meaningful benefit for camizestrant in patients with HR+HER2- ABC upon detection of an *ESR1*m, prior to radiographic progression. We agree with the Applicant that SERENA-6 achieved a statistically significant result for PFS and PFS2; however, these results are difficult to interpret due to the following issues:

1. Trial Design does not Assess Early Switch Strategy

- The Applicant's proposed indication represents a new treatment paradigm which intertwines the treatment effect of camizestrant with an experimental treatment strategy that is not proven to have long-term clinical benefit.
- The FDA remains uncertain as to whether the intended patients would benefit from the proposed experimental strategy of receiving a new treatment (i.e., camizestrant) at detection of an *ESR1*m compared to receiving it at radiographic progression as SERENA-6 was not designed to assess this and FDA is not aware of any external data to support this either. Thus, it is unclear whether the experimental treatment strategy would result in long-term benefit for patients in this incurable disease setting.

2. PFS

- Measurement of PFS in SERENA-6 starts at a new time point, upon detection of an *ESR1*m, which initiates randomization. This is not the same PFS starting point (e.g., diagnosis for first-line trials or radiographic progression for second-line trials) that has been used to support the clinical benefit of other drugs for patients with HR+HER2- ABC. Consequently, the FDA is uncertain whether the observed improvement in PFS in this trial is clinically meaningful. By switching therapy early, patients may not be maximizing the benefit of each line of therapy—as evidenced by the estimated 9.2-month (95% CI: 7.2, 9.5) median PFS experienced by patients on the control arm.

- The FDA acknowledges that the Applicant has presented Kaplan-Meier estimates of PFS rates at various landmark time points (for DCO1 and DCO3). However, the landmark PFS rates do not resolve the issue of a new starting point that complicates interpretation. Furthermore, even when defined using a conventional starting point, FDA generally interprets landmark analyses with caution, because they may misrepresent clinical benefit by focusing on specific timepoints rather than the full time-to-event distribution. The estimates of PFS rates at any given time point would also be impacted by censoring and duration of follow-up and may not be robust at later time points. We do not agree with the Applicant's assertion that the 30-month PFS rate at DCO3 supports durable disease control. In the DCO3 PFS analysis, only 18 patients across both arms remained at risk at Month 30. In addition, because the primary endpoint of PFS was met at DCO1, the updated results of PFS at DCO3 are considered exploratory only.

3. PFS2

- FDA does not believe that PFS2 is interpretable as a measure of clinical benefit, and this was communicated to the Applicant in preliminary comments to a Type C meeting request on November 4, 2024. In general, PFS2 does not isolate the effect of the investigational drug since it evaluates the combined effect of the randomized treatment and subsequent therapy, rather than the effect of the initially randomized treatment. Consequently, any observed difference in PFS2 between the treatment arms cannot be attributed to a specific treatment component, as the endpoint definition does not allow the effect of any individual therapy to be isolated.

- At PFS2, patients have received different numbers of new therapies after randomization between the two arms (i.e., two new therapies on the camizestrant arm and one new therapy on the AI arm). However, PFS2 in SERENA-6 does not address whether there is benefit in switching treatment at detection of *ESR1*m rather than at radiographic progression because the trial was not designed to do so.

- SERENA-6 did not allow crossover to camizestrant and a CDK4/6 inhibitor after radiographic progression on the control arm. For subsequent therapy, the timing and choice was at the investigator's discretion. The SERENA-6 protocol instructed investigators to follow the most recent version of several different internationally recognized guidelines. However, variability in regional availability of drugs and local standards created heterogeneity in subsequent therapy with patients receiving one of

more than 15 different treatment regimens, which further impacts the interpretability of the results. A larger proportion of patients on the investigational arm of SERENA-6 (44%) received chemotherapy or an ADC (versus 31% on the control arm) as their first subsequent therapy. Despite the whole population having tumors with an *ESR1*m, relatively few patients on either arm received an oral estrogen receptor antagonist in combinations or as monotherapy (2.2% on the investigational arm versus 13% on the control arm).

- In SERENA-6, investigators were allowed to determine a PFS2 event by one or more of the following: clinical progression, unequivocal radiological progression, and RECIST v1.1 progression (see FDA Table below). FDA sent an information request to the Applicant on March 31, 2026, seeking clarification on what constituted clinical progression and unequivocal radiological progression. According to the Applicant response, an investigator could determine clinical progression based on subjective disease progression considering symptomatic deterioration and clinical context. Unequivocal progression was assessed by investigator based on overall impression of the radiological assessment without a need to follow RECIST v1.1. Clinicians were also allowed to use imaging modalities other than CT or MRI based on local practice, further increasing heterogeneity and uncertainty around this endpoint. These options for determining a PFS2 event introduce subjectivity to the PFS2 determination and make the PFS2 results more unreliable. There was no BICR sensitivity analysis for PFS2.

FDA Table. PFS2 Event Description (DCO3) – FAS[1]

Event Description	camizestrant + CDK4/6i, n (%)	aromatase inhibitor + CDK4/6i, n (%)
Censored due to no event	77 (49)	68 (43)
Death	22 (14)	27 (17)
Progression	58 (37)	63 (40)
RECIST progression[†]	33 (21)	38 (24)
Non-RECIST progression	25 (16)	25 (16)

[1] Full analysis set, defined as all randomized patients
[†] Patients who had RECIST progression could also have clinical progression and/or unequivocal radiological progression.
The percentages were calculated based on the FAS.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; DCO, data cutoff; FAS, full analysis set; n, number of patients in the category; RECIST, Response Evaluation Criteria in Solid Tumors

- FDA disagrees with the Applicant's assertion that PFS2 has been established to be predictive of OS benefit in HR+HER2- ABC. Traditional early endpoints, such as PFS and ORR, have been shown to be discordant with OS in some trials, including in trials supporting FDA approval. Several reasons for the discordance include trial designs, modest effect sizes, toxicity, and adverse events that can impact the patient's ability to be exposed to the entire treatment regimen or receive subsequent therapy (Merino et al 2023). PFS2 is a complex endpoint with added uncertainty due to subjectivity,

analytical challenges, and difficulties in maintaining adequate follow-up for regulatory decision-making (Fiero et al 2026). OS remains an important endpoint for both safety and efficacy. Additionally, FDA is aware of instances in other diseases where a trial showed a favorable PFS2 trend yet a potential detrimental effect on OS.

4. OS

- The FDA agrees that the current OS data at DCO3 are immature at 58% information fraction (with 95 of the 165 OS events required for final analysis observed) and have not achieved statistical significance. Final OS results are not expected until 2028 (as communicated by the Applicant to FDA in an information request response on March 30, 2026).

- The FDA does not typically require demonstration of a statistically significant OS improvement for approvals in HR+HER2- ABC. However, in this case, achieving a statistically significant improvement in OS could overcome some of the uncertainties with the SERENA-6 trial design and clinical meaningfulness of the PFS result. As SERENA-6 was not fully powered to detect an effect on OS, with a target power of 63% at the final analysis, FDA is concerned that statistical significance for OS may not be reached. Also, multiple subsequent therapies and improved baseline survival for patients with HR+HER2- ABC will make achieving statistical significance for OS difficult in this setting.

5. Other Exploratory Analyses

- The FDA does not agree with the Applicant that other exploratory analyses, including chemotherapy/ADC-free survival, time to first subsequent therapy, and time to second subsequent therapy, provide evidence of clinical benefit. FDA acknowledges that the transition from endocrine therapy to chemotherapy may be clinically important in an individual patient's disease course. However, FDA does not consider chemotherapy/ADC-free survival suitable for evaluating clinical benefit to support regulatory decision-making. Chemotherapy/ADC-free survival is defined as time from randomization until chemotherapy or ADC initiation, which reflects a clinical decision rather than a direct assessment of disease status or patient benefit. Furthermore, the decision to initiate chemotherapy or an ADC may vary based on drug availability, clinician and patient preference, and clinical setting, which introduces heterogeneity into the endpoint and complicates attribution of any improvement in this endpoint to the drug. Additionally, FDA notes that more patients receiving chemotherapy or an ADC as subsequent therapy on the camizestrant arm than the AI arm (44% versus 31%).

- FDA does not agree that the exploratory analysis of ctDNA change from baseline to cycle 3 day 1 constitutes evidence of clinical benefit. This is due to the fact that the relevance of the Cycle 3 Day 1 timepoint, the acceptability of the ctDNA assessment methods, and association of clearing *ESR1*m in ctDNA with outcomes such as PFS and OS have yet to be replicated in more patients and across trials. The Applicant's analysis only accounts for *ESR1*m, which may obscure the overall benefit of a therapy. FDA also notes that not

all patients had Cycle 3 Day 1 ctDNA results with 21% missing on the investigational arm and 19% missing on the control arm, which further limits the reliability of these results. Finally, some patients in the control arm also cleared *ESR1*m in ctDNA.

Overall Conclusion: FDA remains uncertain regarding the clinical meaningfulness of the SERENA-6 results because of lack of evidence that switching at *ESR1*m detection is better than at radiographic progression, the new PFS starting point, and the immature OS results that may not achieve statistical significance.

To help establish evidence of benefit for the early treatment-switching strategy, an adequately designed trial would demonstrate that switching treatment at *ESR1*m detection is beneficial compared to switching at radiographic progression. For example, such a trial design could include a randomized treatment arm with a pre-specified treatment sequence where patients continue 1L therapy until radiographic progression and then switch to a pre-defined 2L regimen.

3. Safety

The Applicant's Position:

The safety profile of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) in SERENA-6 is consistent with clinical experience of camizestrant to date and the known safety profile of each CDK4/6 inhibitor. A robust safety pool of 380 patients from completed trials, including SERENA-6, supports the tolerability of camizestrant both as monotherapy and in combination. Across the program, including ongoing blinded trials in early and metastatic breast cancer, over 6,000 patients have been exposed to camizestrant with more than 1,000 treated for over one year, and some for more than 4 years. There are no indications of clinically significant overlapping toxicity or additive toxicities between camizestrant and the CDK4/6 inhibitor with which it is combined. The combination of camizestrant with a CDK4/6 inhibitor was well tolerated, with no compromise in the delivery of either agent.

The safety data presented herein are from DCO1. Safety data from DCO3 on 02 January 2026, corresponding to approximately 13 months of additional study follow-up since DCO1, indicated no change in the overall safety profile of camizestrant in combination with a CDK4/6 inhibitor.

The FDA's Position:

The FDA agrees with the size of the presented safety pool for camizestrant; however, only a limited number of patients on the camizestrant and CDK4/6 inhibitor arm were treated with camizestrant in combination with either ribociclib (23 patients or 15%) or abemaciclib (15 patients or 10%). Therefore, although the safety profile for each of these combinations appears similar to the known safety profile for each individual CDK4/6 inhibitor, these combinations were not extensively evaluated in SERENA-6. In addition, there is concern for an additive and

overlapping risk of cardiotoxicity when camizestrant is administered in combination with ribociclib, as further discussed in Section 3.5.

3.1 Overall Extent of Exposure

Consistent with the longer PFS, the median exposure in the camizestrant + CDK4/6 inhibitor arm was 10.1 and 9.8 months respectively compared to 6.3 and 6.1 months respectively in the AI + CDK4/6 inhibitor arm.

Relative dose intensity was uniformly high: 99.6% for camizestrant in combination therapy and 99.7% for AI, with comparable dose intensity observed for all CDK4/6 inhibitors, LHRH agonists, across both arms. This demonstrates that camizestrant plus a CDK4/6 inhibitor allows for maintenance of an optimal dose of CDK4/6 inhibitor throughout treatment, allowing for 60% longer exposure with no impact on treatment adherence.

The FDA's Position:
The FDA agrees that patients on the camizestrant arm had a longer median exposure to camizestrant + CDK4/6 inhibitor than patients on the AI arm had to AI + CDK4/6 inhibitor.

3.2 Overview of Adverse Events

The overall safety profile of camizestrant + CDK4/6 inhibitor in SERENA-6 was consistent with the camizestrant clinical experience to date and with the known safety profiles of each CDK4/6 inhibitor (palbociclib, ribociclib and abemaciclib) (Table 8). Camizestrant + CDK4/6 inhibitor had a low discontinuation rate (1.3%) due to adverse events (AEs), demonstrating that camizestrant is well tolerated in combination with CDK4/6 inhibitor. There were 5.8% dose reductions, and dose interruptions to manage AEs lasted one week on average.

AEs (all grades and regardless of causality) were reported in 93.5% of patients in the camizestrant + CDK4/6 inhibitor arm and 87.1% of patients in the AI + CDK4/6 inhibitor arm. Serious AEs (SAEs) were balanced across arms (10.3% vs 12.3%), with outcome of death in 1.9% vs 0% respectively (see Section 3.3 for details). There was a numerical increase in CTCAE Grade ≥3 AEs in the camizestrant + CDK4/6 inhibitor arm vs the AI + CKD4/6 inhibitor arm (60.0% vs 45.8%, respectively), which is driven by CDK4/6 inhibitor-related hematological AEs.

The most commonly reported AEs (shown in Figure 12 and Figure 13) were hematologic (neutropenia, anemia, and leukopenia). Commonly reported non-hematologic AEs included photopsia, arthralgia, and fatigue. There are very few CTCAE Grade 3 non-hematological AEs, with the majority of those events reported as CTCAE Grade 1 or 2. After adjustment for duration of exposure, the frequency of the most commonly reported AEs, particularly Grade ≥3 hematologic AEs, was generally balanced between treatment arms (Figure 13), demonstrating that there is no addition to the CDK4/6 inhibitor toxicity in combination with camizestrant. Of

note, exposure-adjusted AEs for fatigue, pain (e.g., arthralgia, back pain, headache), and gastrointestinal AEs (e.g., nausea, vomiting, diarrhea) were lower on the camizestrant + CDK4/6 inhibitor arm, indicating a favorable toxicity profile of camizestrant.

Table 8 Overview of Safety Profile in SERENA-6 (Safety Analysis Set)

Event	Camizestrant + CDK4/6i (N = 155) Patients, n (%) [a]	AI + CDK4/6i (N = 155) Patients, n (%) [a]
Any AE	145 (93.5)	135 (87.1)
Any AE possibly related to camizestrant/AI [b]	96 (61.9)	63 (40.6)
Any AE possibly related to CDK4/6i [c]	113 (72.9)	96 (61.9)
Any AE of CTCAE Grade 3 or higher [d]	93 (60.0)	71 (45.8)
Any AE of CTCAE Grade 3 or higher, possibly related to camizestrant/AI [b, d]	11 (7.1)	8 (5.2)
Any AE of CTCAE Grade 3 or higher, possibly related to CDK4/6i [c, d]	79 (51.0)	55 (35.5)
Any SAE (including events with outcome of death)	16 (10.3)	19 (12.3)
Any SAE (including events with outcome of death), possibly related to camizestrant/AI [b]	1 (0.6)	5 (3.2)
Any SAE (including events with outcome of death), leading to discontinuation of camizestrant/AI	0	2 (1.3)
Any SAE with outcome of death	3 (1.9) [e]	0
Any SAE with outcome of death, possibly related to camizestrant/AI [b]	1 (0.6)	0
Any SAE with outcome of death possibly related to camizestrant/AI reported beyond 28 days of study treatment administration [f]	0	1 (0.6)
Any AE leading to discontinuation of camizestrant/AI	2 (1.3)	3 (1.9)
Any AE leading to dose interruption of camizestrant/AI	34 (21.9)	22 (14.2)
Any AE leading to dose reduction of camizestrant/AI	9 (5.8)	2 (1.3) [g]

[a] Percentages are based on N, apart from AEs involving CDK4/6 inhibitors or LHRH respectively, where the percentages are based on the number of patients receiving at least one dose of CDK4/6 inhibitor or LHRH respectively.

[b] Possibly related to camizestrant/AI, as assessed by the investigator.

[c] Possibly related to CDK4/6 inhibitor, as assessed by the investigator.

[d] Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal.

[e] A Grade 5 AE of anemia was deleted by the investigator after DCO1 and confirmed as unequivocally due to disease progression.

[f] Post treatment included AEs with an onset date more than 28 days after last dose of study treatment or once subsequent cancer therapy started, whichever came first.

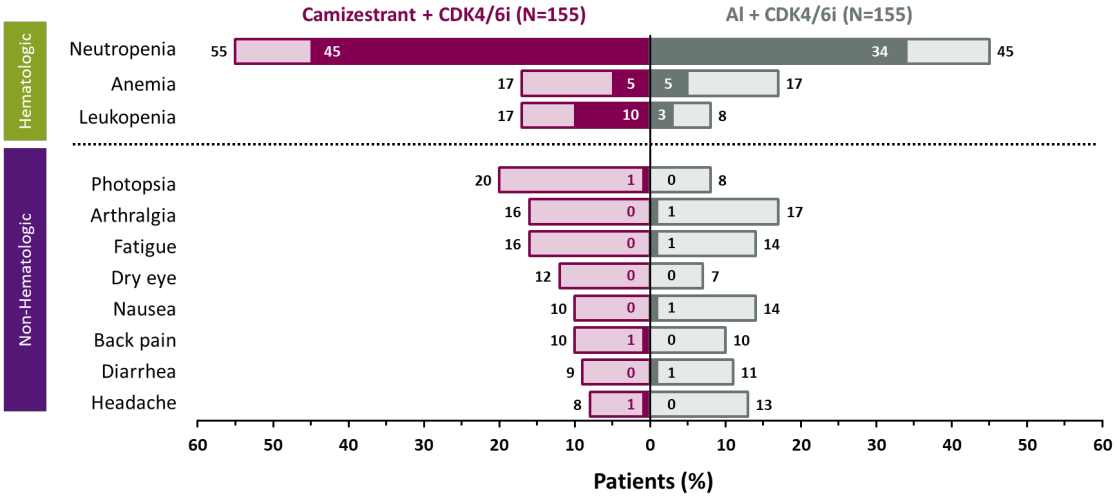
[g] At the time of DCO1, one patient with an AE of thrombocytopenia was reported with an action taken of 'dose reduction'. At the Day 90 Safety Update DCO, the action taken was updated by the investigator to 'drug interrupted'.

Patients with events in more than one category are counted once in each of those categories.

Note: This table includes AEs with an onset date or that worsen on or after the date of first dose of study treatment up to and including 28 days following the date of last dose of study treatment and prior to the start of any subsequent cancer therapy.

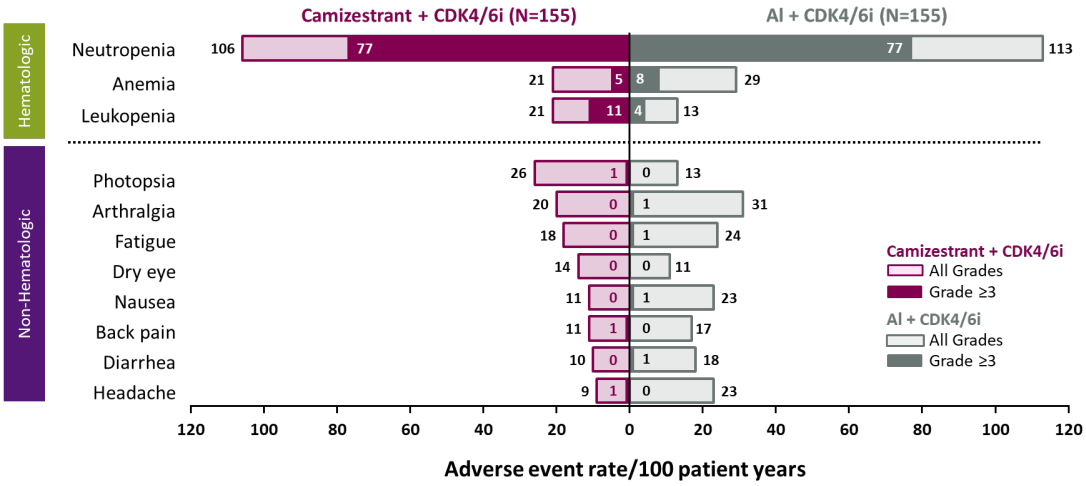
CTCAE version 5.0 in SERENA-6.
DCO: 28 November 2024 (DCO1)
Source: SERENA-6 CSR Table 14.3.2.1 and Table 14.3.3.1.1.

Figure 12 Most Common AEs (≥10% of Patients) by Grade in SERENA-6



DCO: 28 November 2024 (DCO1)
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
Data from Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580.
Source: SERENA-6 CSR Table 23, IEMT 000093 Table 1b, IEMT 000093 Table 2b

Figure 13 Exposure-Adjusted Incidence of AEs by Grade in SERENA-6



Exposure-adjusted incidence rates were calculated as the total number of patients who had an AE reported, divided by the total number of days at risk for AEs across all subjects in each arm, multiplied by 365.25 and then by 100.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
DCO: 28 November 2024 (DCO1)
Source: SERENA-6 CSR Table 23, IEMT 000093 Table 1b, IEMT 000093 Table 2b, IEMT 000093 Table 4b, IEMT 000093 Table 5b

The FDA's Position:

In general, the FDA agrees with the safety profile provided in Table 8. However, we do not typically review adverse events based on attribution as highlighted in specific rows of Table 8 with footnotes (b) and (c), as attribution can be subjective and prone to bias. Therefore, our

assessment of toxicity is based on all treatment- emergent adverse events (TEAEs). Furthermore, the FDA does not typically conduct analyses for exposure-adjusted incidence of AEs by grade (as shown in Figure 13). Although the incidence of certain AEs may be higher on the camizestrant arm due to longer treatment exposure, ultimately, this cumulative toxicity is what is experienced by patients and should be considered in totality without diminishing it based on exposure. For more discussion of visual disturbances, refer to Section 3.4.

3.3 Adverse Events with Outcome of Death

The number of patients who died due to any cause was comparable between the 2 treatment arms, with 20 patients (12.9%) in camizestrant + CDK4/6 inhibitor arm and 18 patients (11.6%) in AI + CDK4/6 inhibitor arm at DCO1. The majority of reported deaths were attributed to progression of disease (Appendix 9).

AEs leading to death were reported in 2 patients (1.3%) in the camizestrant + CDK4/6 inhibitor arm and 1 patient (0.6%) in the AI + CDK4/6 inhibitor arm. One patient randomized to receive AI + CDK4/6 inhibitor died prior to receiving study treatment and hence was counted as a death occurring in the AI + CDK4/6 inhibitor arm in the FAS and not in the safety analysis set.

At DCO1, there were 3 SAEs with fatal outcome in the camizestrant arm and included acute respiratory distress syndrome (which was considered by the investigator to be unrelated to camizestrant), anemia (SAE deleted by the investigator after DCO1, confirmed as unequivocally due to disease progression), and sudden death (which was considered by the trial investigator to be possibly related to camizestrant, occurring on Day 459 of study treatment with an unknown cause as the patient died at home). This death was preceded by an Emergency Department attendance with thoracic back pain. No autopsy was performed, and no death certificate is available). One patient in the AI arm died from a SAE (ileus) that was considered by the investigator to be possibly related to AI.

The FDA's Position:
The FDA agrees with the assessment of deaths on the SERENA-6 trial at data cutoff 1 (DCO1).

3.4 Identified Adverse Drug Reactions for Camizestrant

Visual effects and bradycardia are recognized Adverse Drug Reactions (ADRs) for camizestrant and classified as adverse events of special interests (AESIs) for further risk characterization purposes. A summary of these ADRs by grouped term and preferred term are presented in Table 9. These were characterized as being predominantly CTCAE Grade 1 or 2 and reversible. There were no SAEs, and no events leading to treatment discontinuation.

Visual Effects

Visual effects were reported in 31.6% of patients in the camizestrant + CDK4/6 inhibitor arm

and, notably, 16.1% of patients in the AI + CDK4/6 inhibitor arm. The dominant preferred term reported (in both arms) was photopsia, with fewer than 10% reports of other preferred terms, including vision blurred and diplopia with similar incidences in both arms. Photopsia presents as transient flashes of light in the peripheral vision. There were no SAEs and very few treatment interruptions were required for any visual effect AE. These events usually exhibited an early onset (median 8 days) and resolved upon cessation of treatment. Importantly, comprehensive ocular exams showed no evidence of structural effects in the eye, no change in visual acuity, visual fields, no sequalae, and no long-term effects. This is consistent with our understanding (Hamm et al 2025) of this non-structural effect on retinal signaling. Patient-reported outcome data indicate that these events happened at times of changing light (morning and evening), intermittently, less than one minute at a time, on 3 or fewer days per week, with no/minimal impact on patients daily living, similar to the control arm patients – see Section 4 for more detail.

Bradycardia

Bradycardia AEs were reported in 7.7% of patients in the camizestrant + CDK4/6 inhibitor arm. Six patients had max CTCAE Grade 1 (asymptomatic) events reported; 6 patients had max Grade 2 AEs reported, with dizziness as main symptom recorded, including 1 patient with flu-like symptoms. None of the bradycardia events were SAEs or resulted in syncope, heart failure, treatment discontinuation or need for implantation of a pacemaker. Seventy-five percent of those patients had an outcome of event reported as recovered at DCO1. There was a decrease of 14 bpm in median heart rate on Day 15 (from median 73 bpm at baseline), reaching a stable nadir at that time, followed by recovery to baseline at safety follow-up. Heart rate decreases were broadly proportional to baseline heart rate, with patients with a high baseline heart rate having larger decreases on treatment, and patients with lower baseline heart rate having smaller decreases on treatment. There were no notable changes in heart rate in the AI + CDK4/6 inhibitor arm.

There were no notable changes in blood pressure, on either arm.

These data are consistent with our understanding of the effect of camizestrant on the HCN4 “pacemaker channel”.

Table 9 ADRs by Grouped Term and Preferred Term in SERENA-6 (Safety Analysis Set)

Grouped term / Preferred Term (MedDRA version 27.1)	Camizestrant + CDK4/6i N = 155, n (%)	AI + CDK4/6i N = 155, n (%)
Visual effects (grouped term)	**49 (31.6)**	**25 (16.1)**
Photopsia	31 (20.0)	12 (7.7)
Vision blurred	11 (7.1)	11 (7.1)
Visual impairment	6 (3.9)	3 (1.9)
Diplopia	3 (1.9)	2 (1.3)
Photophobia	3 (1.9)	0
Visual perseveration	2 (1.3)	0
Bradycardia (grouped term)	**12 (7.7)**	**0**

Grouped term / Preferred Term (MedDRA version 27.1)	Camizestrant + CDK4/6i N = 155, n (%)	AI + CDK4/6i N = 155, n (%)
Bradycardia [a]	8 (5.2)	0
Sinus bradycardia [a]	4 (2.6)	0

[a] MedDRA coded preferred term from verbatim Investigator reported term

The table includes ADRs with an onset date or that worsened on or after the date of first dose of study treatment up to and including 28 days following the date of last dose of study treatment and prior to the start of any subsequent cancer therapy.

Patients with multiple occurrences were counted once per category regardless of the number of occurrences.

Table was sorted by descending frequency in the camizestrant + CDK4/6 inhibitor group.

DCO: 28 November 2024 (DCO1)

Source: SERENA-6 CSR Table 14.3.6.1.

The FDA's Position:

The FDA agrees that visual effects (grouped term- GT) and bradycardia (GT) are the two adverse events of special interest (AESIs) identified by the Applicant. FDA prefers use of visual disturbances as the GT rather than visual effects since it better characterizes the individual preferred terms (PT). QT prolongation is an additional important safety topic and is discussed in Section 3.5.

For visual disturbances, in addition to the Applicant's grouping, the FDA included the PTs visual field defect (1.9%) and visual acuity decreased (1.3%) in the visual disturbances GT, resulting in 34% of patients on the camizestrant + CDK4/6 inhibitor arm compared to 16% on the AI + CDK4/6 inhibitor arm experiencing visual disturbances of any grade. The FDA agrees that the most common PT under visual disturbances was photopsia (20% in the camizestrant and CDK4/6 inhibitor arm and 8% in the AI and CDK4/6 inhibitor arm). All cases of visual disturbances (GT) were Grade 1 and 2, except for one case of Grade 3 photopsia. The visual PROs are further discussed in Section 4.

Regarding bradycardia, FDA acknowledges the Applicant's assessment. The FDA agrees that *in vitro* data indicated inhibition of HCN4 by camizestrant. Regarding clinical data, while there were no cases of bradycardia associated with severe AEs (e.g., syncope) in SERENA-6, the heart rate lowering effect (14 bpm median decrease) with use of camizestrant may increase the risk of clinically significant bradycardia, particularly for patients with low baseline heart rate. Bradycardia is a risk factor for development of TdP (Roden 2004). This is particularly concerning because camizestrant may also have a QT interval-prolonging effect and may be administered concomitantly with other QT interval-prolonging drugs such as ribociclib, increasing cardiac risk. Of note, although there were no cases of bradycardia associated with syncope in SERENA-6, there was one case of syncope for a patient on SERENA-1 who developed bradycardia and QT prolongation, resulting in TdP, as discussed in Section 3.5 and Appendix 10.

3.5 Other Safety Topics of Interest

Based on non-clinical data, QT prolongation was assessed in the clinical program as a potential

risk. A QTc study was performed in the SERENA-1 Phase I first-in-human study, obtaining high-quality digital ECGs from 24-hr Holter monitoring in 31 patients, analyzed by an ECG core laboratory. Clinical data obtained following international guidance (ICH E14, Garnett et al 2012) demonstrate that camizestrant does not have a significant effect on QTc prolongation, with no evidence of a proarrhythmic effect. This conclusion was based on:

a) QTcI analysis (to remove heart rate dependence of correction, per ICH E14 guidance) results confirmed that, at clinically relevant concentrations, the upper bound of the 90% CI of the change in QTcI excludes 10 ms, confirming no clinically relevant effect of camizestrant on the QTc interval, with no negative impact on the conduction system or ECG morphology.

b) Analysis of QTcF thresholds shows no patients in SERENA-6 with QTcF >500 ms, or QTcF increases >60 ms from baseline and QTcF >480 ms (based on mean of centrally read triplicate ECGs). Per local assessment, QT prolongation AEs were reported in 4 patients in the camizestrant arm vs 2 patients in the AI arm (notably 2 patients in each arm in combination with ribociclib).

c) Evaluation of clinical AEs, with no QT-induced arrhythmias reported in SERENA-6.

   There is no evidence of a pro-arrhythmic effect of camizestrant across the program.

   One patient in SERENA-1 for treatment with 75 mg camizestrant + 600 mg ribociclib had a Grade 4 QT Prolongation AE reported on Day 15. A comprehensive analysis of this event revealed confounding factors including cardiovascular medical history; concurrent events of nausea, vomiting and diarrhea; electrolyte disturbances; concomitant medications known to increase QT prolongation; and a QTcF on Day 8 of >560ms (centrally read, triplicate ECG, HR = 55bpm) with no action taken on ribociclib (as required in ribociclib label). See Appendix 10 for the patient's narrative.

Overall, the totality of the data show no significant impact of camizestrant on QT prolongation, and no evidence of a pro-arrhythmic effect.

The FDA's Position:

The FDA disagrees with the Applicant's conclusions. The FDA considers the current data insufficient to characterize camizestrant's QT prolongation effect, particularly in the setting of camizestrant's concomitant heart rate lowering effect. The FDA is concerned about the proarrhythmic potential of camizestrant arising from the combination of bradycardia and QT prolongation, especially when combined with other drugs that have QT prolonging effects and/or that may increase camizestrant exposure. A life-threatening serious adverse event (TdP) was observed in SERENA-1 with use of the combination of camizestrant and ribociclib. Ribociclib has known QT prolongation effects and increases the exposure of camizestrant when co-administered. The FDA's assessment is based on the following considerations.

- Nonclinical assays and evaluations in dogs demonstrated camizestrant's concentration-dependent potential for QT prolongation.
- In the phase 1 trial SERENA-1, the Applicant demonstrated concentration-dependent QT interval prolongation using both QTcI (individually corrected QT) and QTcF (Fridericia-corrected QT) analyses over the camizestrant dose range of 75 mg to 300 mg QD. Notably, the Applicant's exposure-response analyses gave conflicting results depending on the QTc correction method employed: the estimated increase in the QTc interval from baseline at mean steady-state C_{max} for camizestrant 75 mg QD monotherapy (proposed dose) was 3.0 msec for QTcI and 16 msec for QTcF.
- FDA identified concerns with reliance on the individual QT correction methodology (QTcI) when used in the setting of a drug that causes large reductions in heart rate. Therefore, FDA believes these data are insufficient to characterize the QT prolongation effect, and that the QTcI method may underestimate the true QT interval effect of camizestrant.
- FDA considers that any increase in QT interval warrants careful evaluation, particularly in the presence of concomitant bradycardia as is the case with camizestrant. Bradycardia represents a well-established risk factor for TdP. The combination of QT prolongation and bradycardia synergistically increases the risk of drug-induced TdP, as bradycardia prolongs ventricular repolarization and increases the likelihood of early afterdepolarizations that can trigger ventricular arrhythmias.
- FDA is particularly concerned about coadministration of camizestrant with ribociclib, due to both pharmacokinetic (PK) and pharmacodynamic (PD) interactions that increase the risk of QTc prolongation and TdP. From a PK perspective, co-administration of camizestrant 75 mg QD with ribociclib 600 mg QD (dosing regimen in SERENA-6) increases camizestrant exposure; camizestrant steady-state exposure was approximately 2-fold higher for the combination compared with camizestrant 75 mg monotherapy. From a PD perspective, the combination creates additive QT prolongation effects as ribociclib itself causes concentration-dependent increases in QTcF with a mean increase of around 20 msec (Ribociclib USPI).
- In SERENA-1, two cohorts investigated camizestrant 75 mg QD co-administered with ribociclib at two dose levels (400 mg or 600 mg QD). Investigators reported TEAEs of ECG QT prolongation in 6 out of 28 patients (21%) receiving camizestrant 75 mg + ribociclib 400 mg and 5 out of 32 patients (16%) receiving camizestrant 75 mg + ribociclib 600 mg. Two patients had a reported QTcF >500 msec with change from baseline >60 msec.
- Most critically, one patient receiving camizestrant 75 mg + ribociclib 600 mg experienced Grade 3 syncope followed by ventricular fibrillation (Grade 4) and a serious adverse event of ECG QT prolongation (Grade 4) one week after a reported QTcF >500 msec. FDA reviewed the ECG waveforms for this patient and confirmed significant QTc prolongation, bradycardia, and ultimately TdP. The FDA review team disagrees with the

Applicant's assessment and considers both events (QT prolongation and ventricular fibrillation/TdP) to be drug related.

In conclusion, camizestrant has dose dependent heart rate lowering and QT prolonging effects, both of which synergistically increase proarrhythmic risk. Coadministration of camizestrant with ribociclib, itself a known QT prolonging drug with dose-dependent effects, further increases the risk of bradycardia and QT prolonging potential. Furthermore, one patient in SERENA-1 who received camizestrant and ribociclib at the doses used in SERENA-6 experienced QT prolongation and life-threatening arrhythmia (TdP). Only 23 patients enrolled to SERENA-6 received camizestrant and ribociclib, limiting further evaluation of the cardiac safety for this combination.

3.6 Safety Conclusions

Overall, SERENA-6 demonstrates that camizestrant plus a CDK4/6 inhibitor has a well-tolerated safety profile. The most frequently reported AEs are consistent with the clinical experience of camizestrant to date and the known safety profile of each CDK4/6 inhibitor. The most commonly reported AEs in both arms were hematological toxicities, known to be related to CDK4/6 inhibitor treatment, and balanced across arms when adjusting for the 60% increase in median exposure in the camizestrant + CDK4/6 inhibitor arm compared to the AI + CDK4/6 inhibitor arm. The high relative dose intensity and low discontinuation rate due to AEs allows for a seamless transition in the switch of endocrine backbone while on 1L treatment.

Treatment-related visual effects were mostly reported as low-grade photopsia, which presents as transient flashes of light in the peripheral vision. These are reversible, with no evidence of structural effects, effects on visual acuity, sequelae, or long-term toxicity. This is consistent with our understanding of non-structural effect of camizestrant on retinal signaling in changing light conditions.

Bradycardia events generally present as asymptomatic heart rate decreases, with ECG assessments showing a gradual decrease in heart rate of about 14 bpm, from baseline to Day 15, reaching a stable nadir at that time, returning to baseline after cessation of treatment. This is consistent with our understanding of the effect of camizestrant on the HCN4 "pacemaker channel".

Overall, camizestrant + CDK4/6 inhibitor is well tolerated, allowing for optimal dose of ET + CDK4/6 inhibitor treatment, with no impact on treatment adherence.

<u>The FDA's Position:</u>
Although the safety profile for camizestrant and CDK4/6 inhibitor was generally as expected for an ET combined with CDK4/6 inhibitor, camizestrant was associated with the additional toxicities of bradycardia, QT prolongation, and visual disturbances. FDA's safety review focused on better understanding these additional toxicities.

FDA disagrees with the Applicant's characterization of cardiac risk and is concerned about the potential for camizestrant to cause life-threatening arrhythmias, particularly when administered with other drugs that have QT interval prolonging effects and/or that may increase camizestrant exposure. Camizestrant is associated with a heart rate lowering effect (14 bpm median decrease) which may increase the risk of clinically significant bradycardia, particularly for patients with a low heart rate at baseline. Bradycardia is a risk factor for development of clinically significant arrhythmias such as ventricular fibrillation or TdP. Camizestrant also has dose-dependent QT prolonging effects, and when bradycardia and QT prolongation are combined, this synergistically increases proarrhythmic risk.

When camizestrant is co-administered with other drugs that have QT prolonging effects, such as ribociclib, this further increases the risk of developing a life-threatening arrhythmia. Ribociclib also increases the exposure of camizestrant, which could further potentiate camizestrant's heart rate lowering and QT prolonging effects. One patient enrolled in the phase 1 trial SERENA-1 received camizestrant and ribociclib at the doses used in SERENA-6 and experienced bradycardia, QT prolongation and life-threatening arrhythmia (TdP). Only 23 patients enrolled to SERENA-6 received camizestrant and ribociclib, limiting further evaluation of the cardiac safety for this combination.

Otherwise, regarding visual disturbances, the FDA generally agrees with the Applicant's characterization. Visual disturbances were generally low grade, with the most common TEAE being photopsia. Photopsia cases were reported as brief periods (<1 min/episode) of flashing lights that were reversible and not associated with structural findings on ophthalmic examination. The PRO data discussed in Section 4 support clinician reported observations that these events were not severe, of short duration, and had minimal impact on daily living.

The other toxicities observed, including arthralgia, fatigue, and hematologic toxicities such as neutropenia, were generally as expected for an endocrine therapy and CDK4/6 inhibitor. The most common adverse events that occurred in both treatment arms of SERENA-6 were hematologic toxicities.

4. Clinical Outcome Assessment Analyses

The Applicant's Position:

PROs were prespecified as secondary and exploratory endpoints and were selected to align with FDA guidance (FDA Guidance 2024) and best practice to ensure scientific rigor. The PRO endpoints were not alpha-controlled or powered for formal statistical comparison in the study, and intended to help inform the overall benefit-risk assessment.

All PRO assessments were collected electronically. For EORTC QLQ-C30 and BR23, the compliance rates were ~70% at baseline; they went up to ~ 80% at Week 4, were broadly

similar between both arms, and were consistent with rates reported in other studies using electronic questionnaires (Hu et al 2025). *Post hoc* analysis of the baseline characteristics of patients who completed at least one item on the EORTC QLQ-C30 suggests that these patients were representative of the overall study population, supporting that missing data is unlikely to bias findings (Mayer et al 2026).

Time to deterioration (TTD) is frequently used in cancer clinical trials, although this type of endpoint and analysis has its limitations as highlighted by Fiero et al 2022. The following approaches were considered for the TTD analyses:

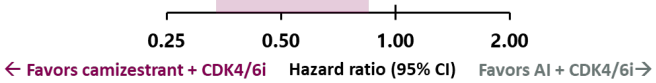
- Per FDA guidance (FDA Guidance 2024), the meaningful change thresholds for the selected EORTC subscales were derived based on the blinded data from SERENA-6 (Arizmendi et al 2025). The prespecified analyses of TTD used these trial-specific thresholds for deterioration, better reflecting a meaningful change in the targeted patient population. Sensitivity analyses using the traditional 10-point threshold to define deterioration were conducted.

- Confirmed TTD was prespecified. Specifically, the TTD was defined as the time from randomization until the first deterioration that was confirmed at a subsequent timepoint after the initial deterioration. Sensitivity analyses including the intercurrent events (i.e., death, progression) as a deterioration event were performed (Appendix 11).

The prespecified, secondary PRO endpoints of TTD in pain, breast symptoms, arm symptoms, and physical functioning, as measured by EORTC QLQ-C30 and breast cancer module QLQ-BR23, numerically favored the camizestrant + CDK4/6 inhibitor arm compared to the AI + CDK4/6 inhibitor arm (Figure 14). Switching from AI to camizestrant during 1L resulted in a meaningful delay in TTD of global health status (GHS)/QoL, a prespecified exploratory endpoint, compared with continuing AI + CDK4/6 inhibitor therapy, with consistent benefit observed across other prespecified exploratory PRO endpoints of TTD in cancer symptoms (e.g., fatigue) and other functioning (e.g., role, cognitive, emotional, social) (Figure 14).

Figure 14 **TTD in Patient-Reported Breast Cancer Symptoms, Functioning, and GHS/QoL**

	n/N events		Median Time To Deterioration, months		
	Camizestrant + CDK4/6i	AI + CDK4/6i	Camizestrant + CDK4/6i	AI + CDK4/6i	Hazard ratio (HR) (95% CI)
GHS/QoL	**37/107**	**49/95**	**20.96**	**6.37**	**0.54 (0.34, 0.84)**
Breast cancer symptoms					
Pain[a]	42/106	49/94	16.56	6.47	0.57 (0.37, 0.86)
Fatigue	34/104	33/91	NR	13.77	0.75 (0.46, 1.24)
Breast symptoms[a]	13/102	16/92	NR	NR	0.59 (0.28, 1.24)
Arm symptoms[a]	15/100	18/90	NR	NR	0.69 (0.34, 1.39)
Functioning					
Physical[a]	33/108	29/95	23.03	15.67	0.74 (0.44, 1.24)
Role	48/108	47/94	15.57	8.21	0.73 (0.48, 1.10)
Cognitive	38/107	31/95	23.03	NR	0.92 (0.57, 1.50)
Emotional	25/107	32/95	NR	13.73	0.51 (0.29, 0.87)
Social	39/107	35/95	34.10	15.87	0.80 (0.50, 1.28)



[a] TTD in pain, breast symptoms, arm symptoms and physical functioning are secondary endpoints, the others are exploratory endpoints.

NR: not reached. HR<1 favoring camizestrant vs AI.

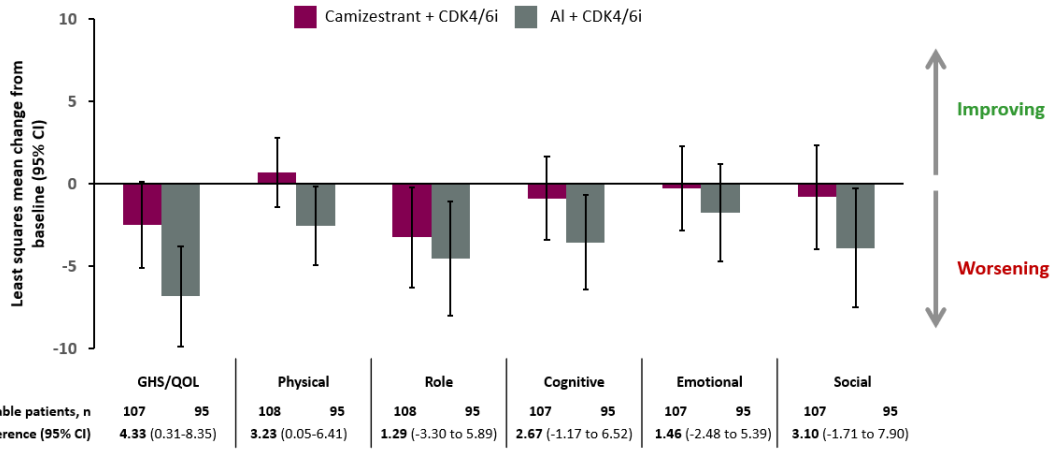
Source: SERENA-6 CSR Table 14.2.11.5, Table 14.2.12.5

Results from the *post hoc* sensitivity analyses of TTD using a 10-point meaningful change threshold and the sensitivity analysis including death or death/progression as a deterioration event were consistent with findings from the prespecified analysis (Appendix 11).

Furthermore, the change from baseline in symptoms, functioning and GHS/QoL, as measured by the EORTC QLQ-C30 and breast cancer module QLQ-BR23, were also prespecified, exploratory endpoints. The model-adjusted mean change from baseline results numerically favored the camizestrant + CDK4/6 inhibitor arm compared to the AI + CDK4/6 inhibitor arm (Figure 15 and Figure 16). These results were in line with TTD results, providing additional support to the observed advantage of camizestrant over AI.

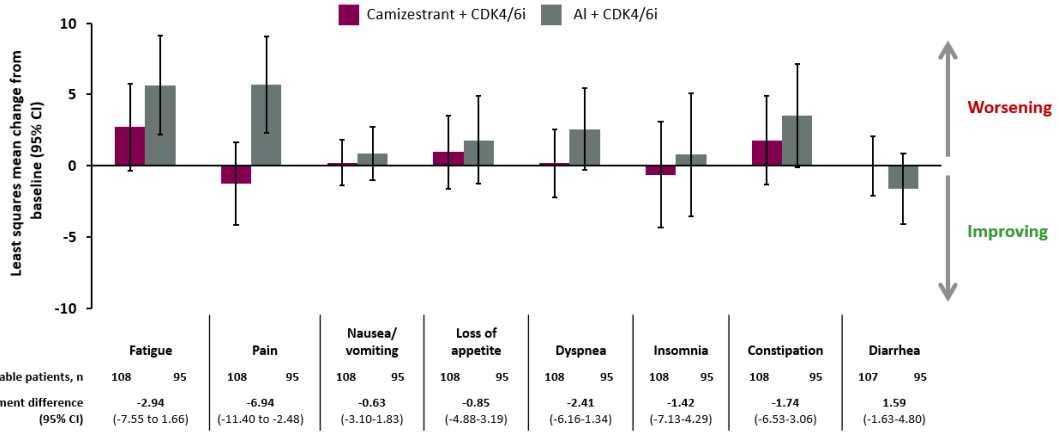
Mean change from baseline in pain and physical functioning showed numerical improvement in the camizestrant + CDK4/6 inhibitor arm compared with worsening in the AI + CDK4/6 inhibitor arm. All other EORTC QLQ-C30 functional and symptom scales numerically favored camizestrant + CDK4/6 inhibitor compared with AI + CDK4/6 inhibitor, except for diarrhea. Mean change from baseline in EORTC QLQ-BR23 scales was comparable between treatment arms.

Figure 15 **Model-Adjusted Mean Change from Baseline in EORTC QLQ-C30 GHS/QoL and Functioning Over First 28 Weeks[a]**



[a] 28-week timepoint was prespecified in the SAP based on estimated PFS for control arm.
Estimates were obtained using a mixed model repeated measures (MMRM) analysis, including treatment, visit, and treatment-by-visit interaction as explanatory variables and the baseline score and the baseline score by visit interaction as covariates.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
Source: Mayer et al 2026

Figure 16 **Model-Adjusted Mean Change from Baseline in EORTC QLQ-C30 Symptoms Over First 28 Weeks[a]**



[a] 28-week timepoint was prespecified in the SAP based on estimated PFS for control arm.
Estimates were obtained using an MMRM analysis, including treatment, visit, and treatment-by-visit interaction as explanatory variables and the baseline score and the baseline score by visit interaction as covariates.
The camizestrant arm is depicted in purple; the AI arm is depicted in gray.
Source: Mayer et al 2026

For visual symptoms:

Patient-reported visual effects (measured by Visual Symptom Assessment Questionnaire [VSAQ]) with camizestrant + CDK4/6 inhibitor occurred mostly in the morning or evening (in the first 6 weeks of study treatment), were typically brief (< 1 minute/episode), and intermittent/infrequent (occurring ≤ 3 days per week). Patients reported that visual effects had no or a low degree of bother and no or minimal impact on activities of daily living. Similar

results were observed in the AI + CDK4/6 inhibitor arm, with the exception that visual effects occurred at a similar frequency throughout the day (morning, afternoon, and evening) (Park et al 2025). Patient-reported vision-related health status as measured by the composite and subscale scores (difficulty in driving, performing near activities, and role functioning) of the National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25), a validated questionnaire, were stable over time and comparable between treatment arms (Brufsky et al 2026).

In conclusion, the PRO assessments helped to document the patient experience, providing a more complete understanding on the impact of switching to camizestrant on symptoms, functioning, and HRQoL and informing the overall benefit-risk assessment. The PRO results further supported camizestrant + CDK4/6 inhibitor as a potential new treatment strategy to optimize and improve outcomes in patients with HR+, HER2- ABC and emergence of *ESR1*m, ahead of clinical disease progression, during 1L AI + CDK4/6 inhibitor treatment.

The FDA's Position:

FDA disagrees with the Applicant's assertion that the patient-reported outcome (PRO) results from SERENA-6 support a benefit in terms of symptoms and functioning. However, FDA agrees with the Applicant description of visual symptom PROs. Overall, the PRO data from SERENA-6 do not provide support for switching to camizestrant prior to radiographic disease progression for the following reasons:

1. Use of TTD analyses for PRO data: FDA agrees with the Applicant that PRO TTD analyses have substantial limitations. Beyond those noted by the Applicant, interpretation of TTD endpoint results from SERENA-6 are further constrained by the following:
    a. Low Event Rates: Deterioration events occurred in less than half of each trial arm for most PRO domains, limiting the interpretability of the hazard ratios. For example, in the primary TTD analysis for physical functioning (Figure 14), only 33 patients (31%) in the camizestrant and CDK4/6 inhibitor arm and 29 patients (31%) in the AI and CDK4/6 inhibitor arm experienced deterioration events. Similarly low event rates were observed across other domains including role functioning, breast symptoms, and arm symptoms.

    b. Data Quality Issues: PRO data quality dropped substantially after Week 20, with less than 55% PRO compliance (defined as the proportion of patients who completed a PRO out of those eligible to complete a PRO) rate in the control arm after this timepoint. The high rate of missing data undermines the reliability of TTD estimates, particularly for later timepoints where the Kaplan-Meier curves may be driven by a small number of patients remaining at risk.

    c. Sparse Assessment Frequency: PRO assessment frequency was sparse after Week 12, occurring only every 8 weeks. An infrequent assessment schedule makes capture of deterioration events challenging and the results less reliable.

2. PRO baseline assessment timing: In SERENA-6, the baseline assessment occurs at *ESR1*m detection, which represents a molecular event rather than clinical or radiographic disease progression. For both TTD and change from baseline PRO analyses, a baseline assessment is an important relative milestone. Usually, this baseline assessment occurs at a time of disease progression or before initiation of a new therapy with the expectation that improvements in disease symptoms will occur and patient's functioning will change due to the treatment being studied. In SERENA-6, baseline at *ESR1*m detection is not at a timepoint of disease progression and makes any PRO result relative to baseline difficult to interpret. Patients may also have varying underlying symptoms from ongoing treatment, making this even more unreliable and heterogenous.

3. Marginal Magnitude of Change from Baseline Analyses: Despite the arbitrary nature of the baseline timepoint assessment as described above, FDA examined whether there was improvement in PRO scores to support the Applicant's claims. For physical functioning, the mean change from baseline at Week 28 was -0.18 in the camizestrant and CDK4/6 inhibitor arm versus -2.95 in the AI and CDK4/6 inhibitor arm—a difference of smaller than 3 points on a 100-point scale. For pain, the mean change from baseline at Week 28 was 0.67 in the camizestrant and CDK4/6 inhibitor arm versus 6.59 in the AI and CDK4/6 inhibitor arm. While these numerical differences favor camizestrant, the magnitude of difference is small and of uncertain clinical meaningfulness. Furthermore, these analyses are compromised by differential missing data between arms, with consistently lower completion rates in the control arm at later timepoints. The analysis assumes data are missing at random, which is not supported by the differential disease progression rates between arms, potentially biasing results.

4. Although the Applicant considered some PRO endpoints as secondary endpoints, FDA considered all PRO endpoints as exploratory as they were not controlled for multiplicity. Without appropriate control for multiple comparisons, the observed numerical trends cannot be considered evidence of benefit.

FDA does not consider the SERENA-6 PRO results as evidence in support of clinical benefit. The TTD endpoint results are unreliable for the reasons discussed above, and the change from baseline improvements are marginal and of uncertain clinical significance especially relative to a baseline assessment triggered by *ESR1*m detection. These limitations, combined with the lack of multiplicity control, preclude the use of these PRO data to support a claim of clinical benefit for camizestrant.

5. Points for the Advisory Committee to Consider

The Applicant's Position:

Despite the proven efficacy of 1L ET + CDK4/6 inhibitor for newly diagnosed patients with HR+/HER2- ABC, inevitable disease progression following therapeutic resistance is associated

with increased tumor burden, worsening symptoms and QoL, and greater genomic complexity of the tumor with relative loss of ER-signaling dependency, which limits the effectiveness of subsequent endocrine-based therapies.

Activating *ESR1*m represent a major mechanism of resistance to current endocrine-based therapies, emerging under selective pressure on 1L AI + CDK4/6 inhibitor treatment in up to 40% of patients with HR+/HER2- ABC. *ESR1*m cancers have a more aggressive biology with poor PFS and OS. For patients with *ESR1*m, the optimal subsequent treatment strategy after disease progression on 1L AI + CDK4/6 inhibitor remains to be defined, and there is no clearly defined SoC. Monotherapy regimens, including novel SERDs such as elacestrant and imlunestrant, show limited efficacy (~60% of patients have disease progression within 6 months of treatment, with the majority of those demonstrating no disease control at all, with progression at the first scan). Of note, the 2L monotherapy trials were conducted in patients for whom fulvestrant monotherapy in the control arm was considered acceptable by the investigator and therefore the trials enrolled a selected subpopulation of patients, excluding those for whom combination therapy or chemotherapy was a preferred option. By contrast, the population eligible for ctDNA monitoring during 1L treatment is much broader. Therefore, the SERENA-6 approach has the potential to benefit more patients than the smaller second-line population suitable for treatment with a monotherapy oral SERD.

Although approved combination regimens achieve greater activity than monotherapies, their overall efficacy remains moderate (median PFS is typically less than 6 months following progression on 1L AI + CDK4/6 inhibitor). Currently, there are no therapies specifically approved for the 1L treatment of patients with HR+/HER2- ABC with emergent *ESR1*m prior to radiographic or clinical progression, and delaying progression for these patients on 1L ET + CDK4/6 inhibitor remains a significant unmet clinical need.

It was hypothesized that intercepting *ESR1*m would maximize the duration of benefit of 1L ET + CDK4/6 inhibitor therapy, prior to progression to a disease that is often independent of ER-signaling, exhibits increased tumor heterogeneity, and is characterized by poorer QoL and clinical outcomes for patients. The SERENA-6 Phase III double-blind clinical trial was robustly designed to test if the replacement of a failing ET backbone (AI) with a potent therapy against *ESR1*m (camizestrant), at emergence of an *ESR1*m detected in ctDNA, prior to clinical or radiographic progression, would extend the clinical benefit of 1L CDK4/6 inhibitor-based therapy with a well-tolerated regimen.

The replacement of AI with camizestrant at detection of *ESR1*m demonstrated a statistically significant and clinically meaningful 56% reduction in the risk of progression or death (HR = 0.44; 95% CI: 0.31, 0.60; $p < 0.00001$), delaying disease progression by ~7 months. At DCO1, the 24-month Kaplan-Meier PFS rate was 29.7% with camizestrant + CDK4/6 inhibitor vs 5.4% with AI + CDK4/6 inhibitor. With longer follow-up at DCO3, benefit persisted: 24-month PFS rate was 34.9% vs 14.2%, and 30-month PFS rate was 30.4% vs 2.7%, highlighting durable disease control in a subset of patients who remained progression free for a substantially longer period of time.

This benefit was maintained through subsequent therapies, as demonstrated by a statistically

significant and clinically meaningful prolongation of PFS2, providing patients the opportunity to receive a 2L endocrine-based therapy, extending overall time on ET and delaying time to cytotoxic treatments (HR = 0.64; 95% CI: 0.47, 0.87), with no adverse impact on OS. A profound reduction of *ESR1*m ctDNA levels was also observed following the switch to camizestrant, confirming the targeted biological effect of camizestrant on *ESR1*m.

Importantly, patients experienced a delay in median TTD of GHS/QoL by more than 1 year after switching from AI to camizestrant (HR = 0.54; 95% CI: 0.34, 0.84). The risk of clinically meaningful deterioration in patient-reported cancer symptoms was reduced, including pain, shortness of breath, and fatigue. There was also delayed deterioration in functional domains, including physical and role functioning as well as emotional scores. Additionally, the combination of camizestrant with a CDK4/6 inhibitor is well tolerated, with a low rate of discontinuation. AEs were not considered bothersome, had no effect on activities of daily living, and were consistent with the known safety profiles of both camizestrant and the respective CDK4/6 inhibitor. This confirms the patient experience of a favorable safety profile, supporting a seamless replacement of the endocrine backbone during 1L treatment.

In conclusion, the sponsor considers that the proposed improvement in the treatment paradigm, replacing AI with camizestrant while maintaining the same CDK4/6 inhibitor partner, at earliest detection of *ESR1*m in ctDNA during first-line treatment, ahead of radiographic or clinical disease progression, provides an overall positive benefit-risk for camizestrant in the proposed indication, optimizing the overall endocrine-based treatment journey and delaying the time to chemotherapy, for patients with *ESR1*m/HR+/HER2- ABC.

The results from SERENA-6 suggest a potential new and improved treatment option that can empower patients with *ESR1*m/HR+/HER2- ABC and their healthcare providers to take charge of the disease in a patient-centric way, leveraging molecular monitoring in routine blood tests, to guide timely and targeted treatment adaptation.

The FDA's Position:

The FDA has uncertainty about whether the results of SERENA-6 demonstrate an overall favorable benefit-risk assessment for camizestrant in patients with ER+HER2- ABC upon detection of an *ESR1*m. Our review has focused on the primary and key secondary endpoints of PFS and OS within the context of the trial design, as these are suitable for regulatory decision-making. We do not find that the other analyses and data, including PFS2, proposed by the Applicant are suitable to establish clinical benefit. We have the following considerations for the Committee:

1. **Key Efficacy Issues**
    a. **Trial Design:** SERENA-6 was not designed to demonstrate the clinical benefit of an experimental strategy in which patients receive a new therapy at *ESR1*m detection rather than at radiographic progression. There is also no external evidence which can support the early switch strategy. It is unclear if the experimental strategy of earlier intervention meaningfully improves long-term outcomes (extends patients' lives). We disagree that the observed median PFS

results from other monotherapy trials of oral estrogen receptor antagonists can be used to support the benefit for this new experimental strategy both because cross trial comparisons are uninterpretable due to confounding factors and they ignore any contribution of a CDK4/6 inhibitor. Furthermore, in SERENA-6 both PFS and PFS2 involve imbalanced comparisons in the number of new treatment regimens patients received on the two arms without assessing whether the therapy switch at *ESR1*m detection is beneficial compared to switching at radiographic progression. Refer to Section 2.3.3.

b. **PFS:** Although SERENA-6 met its PFS endpoint, the FDA disagrees with the Applicant's assertion that PFS in SERENA-6 is like PFS in other trials for HR+HER2- ABC, where a statistically significant improvement supported approval. SERENA-6 used a new start time for PFS and did not test the switch strategy at detection of an *ESR1*m versus at radiographic progression. Together these differences raise uncertainty about the clinical meaningfulness of the observed PFS results for the intended patients. Rather, patients may be stopping a well-tolerated therapy early and not maximizing the benefit they could receive from each line of treatment. Refer to Section 2.3.3.

c. **OS:** Although FDA does not typically require a statistically significant improvement in OS for HR+HER2- ABC, a statistically significant improvement for OS in SERENA-6 could help to overcome some of the uncertainties with whether the new experimental strategy of switching therapy at detection of *ESR1*m prior to radiographic progression benefits patients. However, the current OS results are immature with final OS not anticipated until sometime in 2028. Also, given that the trial was also not fully powered (target power for final OS analysis is 63%) to detect an effect on OS, FDA is concerned that SERENA-6 may not reach statistical significance for OS. Refer to Section 2.3.3.

d. **Future Considerations:** The FDA is concerned that future drug development in ABC and other cancers will adopt SERENA-6 as a new paradigm for clinical trial design despite the trial's inability to demonstrate a clinical benefit for the experimental strategy of switching at biomarker detection and before radiographic progression. We anticipate that this could include introducing more toxic therapies in an early treatment switch prior to radiographic progression without evidence that such an approach benefits patients and extends life.

2. Other Efficacy Issues

a. **PFS2:** The FDA does not believe PFS2 to be interpretable as a measure of clinical benefit. PFS2 does not isolate the investigational drug's treatment effect because patients received therapies in addition to camizestrant. In SERENA-6, PFS2 also does not assess the benefit of switching treatment at *ESR1*m detection versus at radiographic progression. Heterogeneity in timing and choice of subsequent therapies created additional interpretability challenges. Additionally,

the inclusion of clinical progression and radiographic progression not according to RECIST v.1.1 as event criteria introduces inappropriate subjectivity into the assessment. Refer to Section 2.3.3.

b. **PROs (Time to Deterioration):** FDA does not consider the SERENA-6 PRO results as supportive of clinical benefit. The TTD endpoint results are unreliable due to infrequent events, poor data quality, uncertain clinical meaningfulness, and minimal changes observed relative to an arbitrary baseline. In addition, the lack of multiplicity control does not allow the use of these PRO data to support a claim of clinical benefit for camizestrant. Refer to Section 4.

c. **Other Exploratory Endpoints:** Chemotherapy/ADC-free survival also has significant limitations as it does not provide a direct assessment of disease status or patient benefit, but represents a clinical decision that may be impacted by drug availability, clinician and patient preference, and clinical setting. These analyses are unable to overcome the uncertainties in the PFS result to support clinical benefit for camizestrant. Refer to Section 2.3.3 and Section 4.

3. **Safety**

a. **Cardiac Safety Signal:** Camizestrant has heart rate lowering and QT prolonging effects, both of which synergistically increase proarrhythmic risk. The Application proposes combining camizestrant with ribociclib which also has a QT prolonging effect, further increasing the risk of developing a life-threatening arrhythmia. One patient enrolled in the phase 1 trial SERENA-1 received camizestrant and ribociclib at the doses used in SERENA-6 and experienced bradycardia, QT prolongation and life-threatening arrhythmia (TdP). Refer to Section 3.

The FDA agrees that patients with HR+HER2- ABC have unmet medical need for therapies that can improve long-term outcomes, including OS. However, it is unclear that switching ET at *ESR1*m detection prior to radiographic progression will fulfill this unmet medical need. There is no internal evidence from SERENA-6 or external evidence to support this early switch strategy. A trial that is adequately designed to establish evidence of benefit for the early treatment-switching strategy would demonstrate that switching treatment early at *ESR1*m detection is beneficial compared to switching at radiographic progression. For example, such a trial may randomize patients to a prespecified treatment sequence of continued 1L therapy followed by a pre-defined 2L regimen initiated upon radiographic progression.

FDA remains committed to innovative strategies and precision approaches to improve treatment for patients with breast cancer. To support approval of a new drug for an intended patient population, clinical benefit must be established, and the benefits must outweigh the risks of treatment. FDA continues to be uncertain whether SERENA-6 demonstrates an overall positive benefit-risk for camizestrant in patients with ER+HER2- ABC upon detection of an *ESR1*m.

6. Draft Topics for Discussion by the Advisory Committee

The FDA's Position: FDA asks that the advisory committee consider the following voting question:

Based on the results of SERENA-6, is the benefit-risk assessment favorable for camizestrant in combination with a CDK4/6 inhibitor in patients with HR+HER2- advanced breast cancer upon detection of an *ESR1* mutation while receiving a CDK4/6 inhibitor plus aromatase inhibitor?

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8. Appendix

Appendix 1 Protocol Amendments Related to Changes in Study Conduct

Substantial Changes made after the start of patient recruitment:

Amendment number and date	Key details of amendment	Main reason(s) of amendment
Protocol Amendment 4.0 dated 06 November 2024	Target number of PFS2 events updated.	Since multiple current treatment options are available post treatment with CDK4/6 inhibitors, the accrual of PFS2 events takes much longer than initially anticipated when the protocol was developed. In order to get a timely assessment of PFS2 prior to OS, sponsor reduced the target number of PFS2 events while still retaining sufficient power to observe the hypothesized difference.
Protocol Amendment 2.0 dated 23 March 2023	• Text was updated in all occurrences of CDK4/6 inhibitor to include ribociclib. • Background information on current approvals for ribociclib in the US and the EU was added. Also, on dose reductions of ribociclib which do not impact the PFS, when combined with AI or SERD. • Ribociclib treatment schedule was added. • Known and expected risks of ribociclib were added. • Inclusion and exclusion criteria updated to include ribociclib as part of the study treatment. • Exclusion criterion was updated to suit the ribociclib ADR of QT interval prolongation. • Details of ribociclib dose formulation, unit dose strength, dosage level, use, packaging and labelling, and dosing schedule were added. • Specified that for patients treated with the ribociclib regimen, hematology assessment was to be done every 4 months prior to the beginning of a cycle. • Information on management of toxicities due to ribociclib was added.	Ongoing Phase I data allowed the use of ribociclib in combination with camizestrant, after IDMC review of the safety data, as all CDK4/6 inhibitors used in combination with ET had similar PFS. Therefore, eligibility criteria were updated to allow patients treated with ribociclib as the CDK4/6 inhibitor, to remove barriers to enrolment of patients previously treated with ribociclib. The ribociclib combination cohort was not to be opened until agreed by the IDMC based on appropriate safety data.
Protocol Amendment 2.0 dated 23 March 2023	An inclusion criterion was updated to state that patients must be willing to provide archival radiological images “whenever feasible or available”.	To clarify that provision of archival scans was not required for eligibility.

Amendment number and date	Key details of amendment	Main reason(s) of amendment
Protocol Amendment 2.0 dated 23 March 2023	An exclusion criterion was updated to allow patients with controlled stable hepatitis B virus (HBV) infection to be eligible. HBsAg and HBV DNA were added to the table of laboratory safety variables.	To remove barriers to patient enrolment without impacting safety, in line with Health Authority guidance (FDA).
Protocol Amendment 2.0 dated 23 March 2023	Text updated in all Sections applicable to clarify that archived tissue tumor sample (either "FFPE blocks [preferred] or unstained slides") was to be provided <u>if available</u>.	To clarify that provision of archived tissue tumor sample was not mandatory.
Protocol Amendment 2.0 dated 23 March 2023	Removal of the censoring rule for patients who receive another anticancer therapy prior to RECIST 1.1 progression from PFS analysis.	Censoring rule was updated to align with the intent-to-treat principle.
Protocol Amendment 2.0 dated 23 March 2023	Inclusion criterion was updated to change organ and marrow function thresholds.	To simplify the text to be in line with CDK4/6 inhibitor label on the management of aspartate transaminase and alanine transaminase elevation, without impacting safety.
Protocol Amendment 2.0 dated 23 March 2023	Exclusion criterion updated to state Torsade de Pointes (TdP) is as defined by CredibleMeds.	To provide clarity on the definition of drugs with a "known risk of TdP".
Protocol Amendment 2.0 dated 23 March 2023	Removal of text recommending an alternative to atropine eye drops.	The atropine restrictions were clarified due to emerging nonclinical data on atropine.
Protocol Amendment 1.0 dated 17 May 2022	• Objective revised as the investigator's assessment of the date of second progression according to local standard clinical practice was to be the primary measure of PFS2, with RECIST 1.1 as a supplementary measure. • Added that after first progression, tumor assessments were to be performed every 8-12 weeks until RECIST 1.1-defined second radiological PD and PFS2/survival follow-up window changed from ± 14 to + 28 days. • Updated text to specify the requirement of RECIST scan prior to start of subsequent anticancer therapy if >4 weeks had elapsed since the previous RECIST scan.	To increase robustness of PFS2 data, to align with the change to include RECIST 1.1 assessment of PFS2, to ensure there was a RECIST-compliant baseline scan for PFS2.
Protocol Amendment 1.0 dated 17 May 2022	Amended eGFR criteria to include additional method and assessment for patients receiving abemaciclib.	To reflect latest guidance for abemaciclib.

Amendment number and date	Key details of amendment	Main reason(s) of amendment
Protocol Amendment 1.0 dated 17 May 2022	Opening of the abemaciclib combination cohort in this study was agreed based on latest available data on abemaciclib.	The IDMC confirmed the acceptability of abemaciclib in this study.
Protocol Amendment 1.0 dated 17 May 2022	Reduced resting heart rate from < 60 bpm to < 55 bpm.	Following internal review of safety data and external expert consultation.
Protocol Amendment 1.0 dated 17 May 2022	Added patients who were screen failures for STEP 1 could be rescreened; screen failures from STEP 2 could be rescreened after consultation with the Global Study Team.	To provide flexibility for STEP 1 rescreening; and for STEP 2 screening in exceptional circumstances (eg, delays in STEP 2 screening due to COVID-19).
Protocol Amendment 1.0 dated 17 May 2022	Addition of option for one dose level reduction of 2 weeks on and 2 weeks off for palbociclib treatment.	To provide additional guidance regarding permitted palbociclib dose regimens.
Protocol Amendment 1.0 dated 17 May 2022	Included visual effects as an AESI and added guidance on Case Report Form (CRF) completion.	To reflect latest information on camizestrant and for clarity.
Protocol Amendment 1.0 dated 17 May 2022	Correction of a previous error as the study would not be stopped if superiority in PFS was met at the interim analysis.	Correction.
Protocol Amendment 1.0 dated 17 May 2022	• Ciprofloxacin and erythromycin were removed from the list of moderate CYP3A4/5 inhibitors permitted with caution as they have a known risk of TdP. • Concomitant medication Section for drugs that are sensitive to P-gp inhibition and inhibitors or inducers of CYP3A4 was revised based on additional data. • Text updated to confirm that drugs with a known risk of TdP were not to be co-administered with camizestrant during study and for a period of 2 weeks after discontinuing study.	To correct guidance on concomitant medication use.

Source: SERENA-6 CSR Table 6.

Appendix 2 Multiple Testing Procedure and Summary of Statistical Methodology

PFS was analyzed using a stratified log-rank test adjusting for the stratification factors. The PFS2 and OS were analyzed using identical methods as for PFS and adjusting for the same set of stratification factors subject to the pooling strategy described in the primary analysis of the primary endpoint. To preserve the overall type I error (family-wise error rate) at 5% in the strong sense, an MTP including the primary and key secondary endpoints is implemented at DCO1, DCO2, DCO3 and DCO4 (OS only). An overview of the MTP is provided in Figure 17.

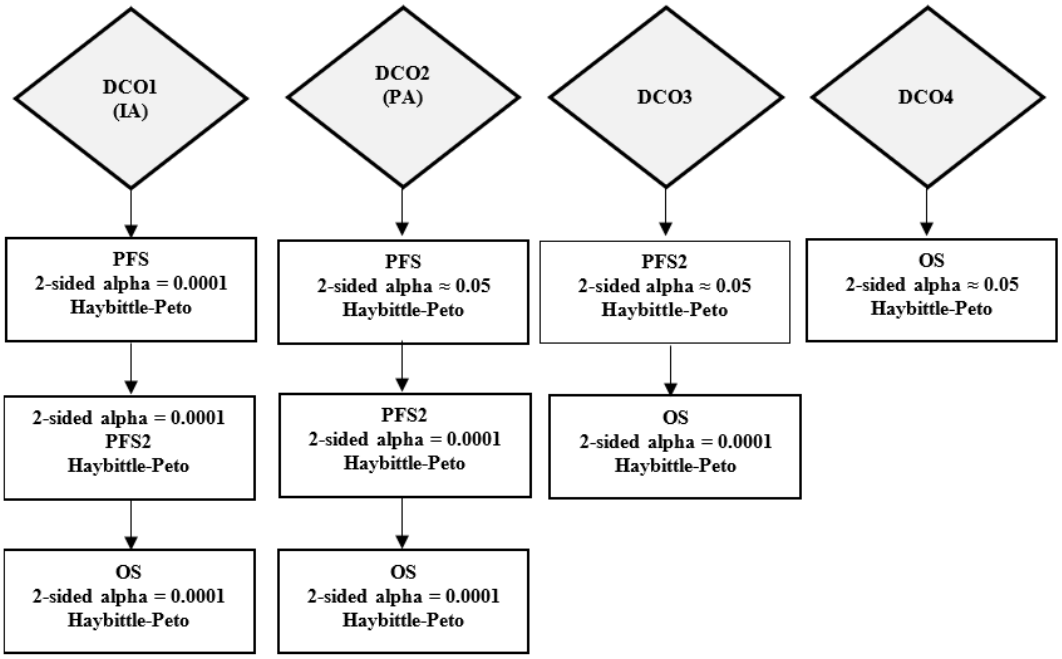
At DCO1 and DCO2, PFS was tested first and depending on whether statistical significance was achieved further endpoint testing would follow for each endpoint in the hierarchy in turn. That is, PFS2 would be tested only if PFS meets statistical significance, and OS would be tested only if PFS and PFS2 met statistical significance.

If PFS and PFS2 met statistical significance by DCO2, then OS would be tested at:

- DCO3 if it did not meet statistical significance at DCO2
- DCO4 if it did not meet statistical significance at DCO3

For all planned analyses of PFS, PFS2, and OS the Haybittle-Peto boundary is used to ensure maintenance of an overall 2-sided type I error. No multiplicity adjustment will be applied for other endpoints as other endpoints will be considered supportive endpoints.

Figure 17 Multiple Testing Procedure



Appendix 3 Changes to Planned Analyses

Changes made after unblinding of study data:

Key details of change	Reason for change	SAP amendment?
After data unblinding, it was determined that a patient randomized to the AI + CDK4/6 inhibitor arm received treatment with camizestrant instead of with camizestrant-matching placebo for 1 cycle due to a study treatment kit dispensing error. According to the SAP, this patient should have been included in the camizestrant + CDK4/6 inhibitor arm for safety analysis, but was analyzed in the AI + CDK4/6 inhibitor arm based on the ITT principle.	Based on the ITT principle, the patient was analyzed in the AI + CDK4/6 inhibitor arm for safety analysis, instead of in the camizestrant + CDK4/6 inhibitor arm.	N/A

Changes made before unblinding of study data:

Key details of change	Reason for change	SAP amendment?
Reduction of PFS2 events to 158 to provide 77% power to detect a treatment effect with an average HR of 0.65 in the FAS.	Since multiple current treatment options are available post treatment with CDK4/6 inhibitors, the accrual of PFS2 events takes much longer than initially anticipated when the protocol was developed. In order to get a timely assessment of PFS2 prior to OS, sponsor reduced the target number of PFS2 events while still retaining sufficient power to observe the hypothesized difference.	Yes
Key additional analyses added: OS subgroup analysis, ORR and duration of response based on BICR evaluation.	These analyses were planned in line with FDA advice.	No
Per protocol analysis set Section was removed and Supplementary Analysis 7 - Deviation Bias was updated with details of patients who were to be excluded from that analysis.	This has been updated in line with new planned methodology.	No

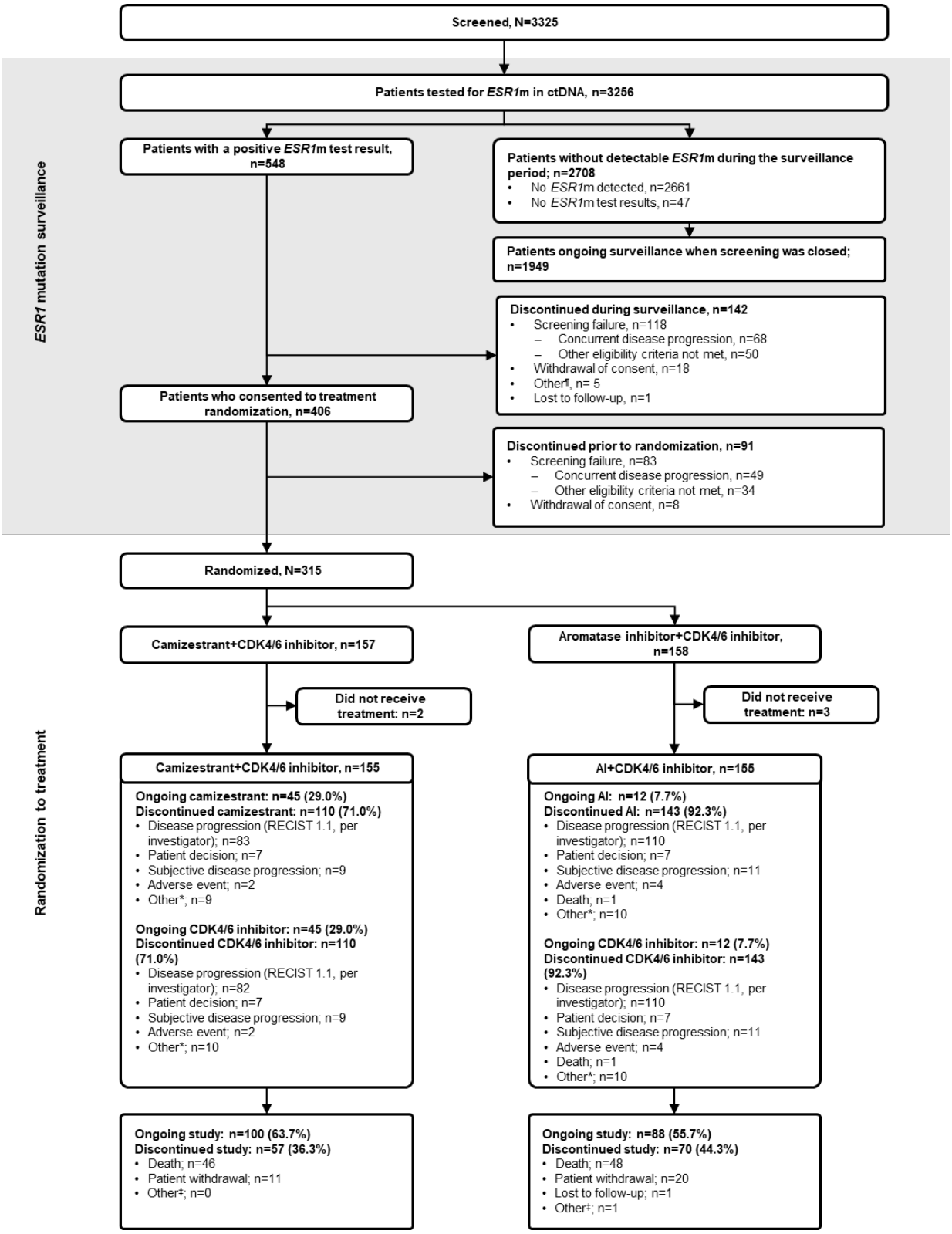
Key details of change	Reason for change	SAP amendment?
Summary statistics for only presence/absence of the *ESR1* biomarker at baseline was to be reported. Text on analysis of ER and PgR biomarker data was removed as it was included in another Section in the SAP, edition 3.0 dated 18 September 2024.	This was updated as per availability of data.	No
Analyses of CBR Section was updated to state that CBR24 will be analyzed using the same primary and sensitivity analyses as for ORR.	This was updated for consistency with protocol and SAP.	Yes
Sensitivity analyses of ORR was updated to include sensitivity analyses of ORR using logistic regression.	This was updated for consistency with protocol and SAP.	Yes
Primary Analysis of ORR was updated to remove relative risk.	Updated in line with planned methodology.	N/A
Supplementary Analysis of Time from Randomization to Second Progression or Death Supplementary analysis 3 (excluding time between first PD and start of subsequent therapy) was removed.	This was updated in line with new planned methodology.	N/A
Subgroup analyses of PFS The following subgroups were added: age, race, ethnicity, menopausal status, number of organs involved, number of lesions, disease history. Subgroup analyses of PFS2 The following subgroups were added: disease site, *ESR1*m status, time from initiation of CDK4/6 inhibitor, previous response to AI + CDK4/6, region, *ESR1*m clones and compare the 3 most frequent ESR1m variants. Further additional subgroups were added. Confirmed that stratification factors were to be based on the data recorded in the eCRF. Unstratified Cox proportional hazards models will be estimated for subgroup analyses.	The additional subgroups were added due to FDA requirements. The texts regarding the use of eCRF stratification factors and the use of unstratified models for the subgroup analyses were added for clarification.	N/A

Key details of change	Reason for change	SAP amendment?
Primary analysis of PFS Section was updated to include a listing for individual efficacy tumor response data. Sensitivity analysis of PFS Section was updated to add additional factors into the confounding bias analysis.	To provide additional presentation of efficacy tumor response data.	N/A
The Per Protocol analysis set was removed and details of the Important Protocol Deviations (IPDs) that could affect the efficacy of the Investigational Product (IP) were added to this Section to identify patients who were to be excluded from this analysis.	This was updated in line with new planned methodology.	No
Ribociclib was added, and palbociclib or abemaciclib replaced with CDK4/6 inhibitor where applicable.	Based on review of ongoing Phase I data.	Yes
CBR24 analysis methods updated to use Cochran–Mantel–Haenszel (CMH) analysis rather than logistic regression.	Updated in line with therapeutic area SAP updates.	No
Objective Response Rate (ORR) analysis methods updated to use CMH analysis rather than logistic regression. Analysis of unconfirmed ORR and confirmed and unconfirmed using patients with measurable disease at baseline added as supplementary analyses.	Updated in line with therapeutic area SAP updates.	No
The supplementary analyses Section for PFS2 was updated to include additional analysis using RECIST assessments.	To increase robustness of PFS2 data.	Yes
The sensitivity and supplementary analyses Sections were updated to include additional analyses and additional details of interval censoring and details of summaries of agreements between investigator and central review assessments.	Updated in line with therapeutic area SAP updates.	N/A
A table was added to clarify the censoring rules, and censoring for receiving subsequent therapy was removed.	Updated in protocol to align with intent-to-treat principle.	Yes

Key details of change	Reason for change	SAP amendment?
Definitions of ORR updated to include confirmed and unconfirmed and definition of best overall response updated and table of response categories added.	Updated in line with therapeutic area SAP updates.	N/A
The definition of the PFS for the primary analysis was changed. Patients who received another anticancer therapy prior to RECIST 1.1. progression were not censored. The censoring approach was included as a supplementary analysis instead.	Updated in protocol to align with intent-to-treat principle.	Yes

Source: SERENA-6 CSR Table 7.

Appendix 4 Patient Disposition



¶'Other' includes detection of other mutations and sponsor closure.

*'Other' includes treatment discontinuation due to severe non-compliance to protocol, a development in study-specific discontinuation criteria, investigator decision, consent withdrawal and other (reason not stated).

‡Reason for study discontinuation not stated.

A crude estimate of the proportion of patients with emergent *ESR1* mutation during the study period is 42%, calculated as 548 patients with a positive test/(the number of patients tested for *ESR1* mutation [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).

The *ESR1*m surveillance period (pre-randomization) is highlighted in gray.

DCO: 02 January 2026 (DCO3)

Source: Figure S2, Bidard et al 2025; DCO3 Table 14.1.1, IEMT 000343 Table 1.

Appendix 5 PFS Based on Investigator Assessment, Subgroup Analysis (FAS)

Subgroup	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO1	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO3
All patients		
Median PFS (months) (95% CI) [a]	15.97 (12.71, 18.23) vs 9.23 (7.23, 9.53)	16.76 (14.72, 19.35) vs 9.23 (7.23, 9.66)
HR (95% CI)	0.44 (0.31, 0.60)	0.45 (0.34, 0.59)
Disease site		
Visceral disease		
Total number of patients with events, n/N (%)	32/65 (49.2) vs 37/64 (57.8)	42/64 (65.6) vs 48/63 (76.2)
Median PFS (months) (95% CI) [a]	14.75 (11.07, 18.40) vs 9.46 (5.55, 14.92)	14.98 (11.07, 19.35) vs 9.23 (5.49, 12.68)
HR (95% CI)	0.57 (0.35, 0.92)	0.50 (0.33, 0.76)
Non-visceral disease		
Total number of patients with events, n/N (%)	39/92 (42.4) vs 63/92 (68.5)	57/93 (61.3) vs 76/94 (80.9)
Median PFS (months) (95% CI) [a]	15.97 (11.66, 19.35) vs 7.39 (6.74, 9.36)	16.99 (14.78, 20.47) vs 8.90 (6.74, 9.66)
HR (95% CI)	0.38 (0.25, 0.56)	0.42 (0.30, 0.60)
***ESR1*m detectable**		
First ctDNA test		
Total number of patients with events, n/N (%)	36/82 (43.9) vs 56/79 (70.9)	55/82 (67.1) vs 64/79 (81.0)
Median PFS (months) (95% CI) [a]	15.74 (11.30, NC) vs 7.26 (4.67, 9.23)	15.74 (12.81, 19.35) vs 7.26 (4.67, 9.23)
HR (95% CI)	0.32 (0.20, 0.49)	0.39 (0.27, 0.56)
Subsequent ctDNA test		
Total number of patients with events, n/N (%)	35/75 (46.7) vs 44/79 (55.7)	44/75 (58.7) vs 60/79 (75.9)
Median PFS (months) (95% CI) [a]	15.97 (11.24, 16.92) vs 10.12 (7.33, 14.78)	16.76 (11.83, 21.19) vs 10.02 (7.33, 14.59)
HR (95% CI)	0.64 (0.41, 0.99)	0.53 (0.36, 0.78)
Time from initiation of AI + CDK4/6 inhibitor to randomization		
<18 months		
Total number of patients with events, n/N (%)	28/50 (56.0) vs 29/46 (63.0)	36/49 (73.5) vs 36/46 (78.3)
Median PFS (months) (95% CI) [a]	11.24 (8.34, 16.62) vs 7.26 (3.91, 9.53)	15.74 (11.07, 18.43) vs 7.26 (4.21, 9.53)
HR (95% CI)	0.60 (0.35, 1.01)	0.58 (0.36, 0.92)
≥ 18 months		

Subgroup	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO1	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO3
Total number of patients with events, n/N (%)	43/105 (41.0) vs 69/110 (62.7)	63/108 (58.3) vs 88/112 (78.6)
Median PFS (months) (95% CI) [a]	16.76 (14.72, 21.88) vs 9.26 (7.16, 10.12)	16.92 (14.72, 24.87) vs 9.26 (7.23, 11.01)
HR (95% CI)	0.39 (0.26, 0.58)	0.41 (0.29, 0.57)
CDK4/6 inhibitor		
Palbociclib		
Total number of patients with events, n/N (%)	57/117 (48.7) vs 78/118 (66.1)	75/117 (64.1) vs 94/118 (79.8)
Median PFS (months) (95% CI) [a]	16.59 (13.01, 19.35) vs 9.30 (7.26, 11.04)	16.92 (14.75, 20.34) vs 9.36 (7.39, 11.07)
HR (95% CI)	0.45 (0.32, 0.64)	0.47 (0.34, 0.64)
Ribociclib		
Total number of patients with events, n/N (%)	4/23 (17.4) vs 13/23 (56.5)	11/23 (47.8) vs 18/23 (78.3)
Median PFS (months) (95% CI) [a]	NC (9.46, NC) vs 5.49 (3.84, 11.14)	16.99 (9.69, NC) vs 5.55 (4.01, 8.44)
HR (95% CI)	0.27 (0.08, 0.77)	0.28 (0.13, 0.59)
Abemaciclib		
Total number of patients with events, n/N (%)	10/15 (66.7) vs 9/15 (60.0)	13/15 (86.7) vs 12/15 (80.0)
Median PFS (months) (95% CI) [a]	7.36 (3.68, 16.43) vs 4.21 (3.52, NC)	7.39 (3.68, 16.43) vs 4.67 (3.52, 14.62)
HR (95% CI)	0.63 (0.25, 1.59)	0.72 (0.33, 1.62)
***ESR1*m first most frequent variant**		
D538G present		
Total number of patients with events, n/N (%)	29/70 (41.4) vs 52/82 (63.4)	47/70 (67.1) vs 65/82 (79.3)
Median PFS (months) (95% CI) [a]	16.76 (12.91, 24.87) vs 7.33 (6.74, 9.30)	16.76 (12.91, 20.34) vs 7.39 (6.74, 9.46)
HR (95% CI)	0.34 (0.21, 0.53)	0.40 (0.27, 0.59)
D538G absent		
Total number of patients with events, n/N (%)	42/87 (48.3) vs 48/76 (63.2)	52/87 (59.8) vs 59/76 (77.6)
Median PFS (months) (95% CI) [a]	15.01 (11.07, 16.76) vs 9.36 (5.55, 11.14)	16.62 (11.24, 20.99) vs 9.36 (5.55, 13.24)
HR (95% CI)	0.57 (0.37, 0.86)	0.51 (0.35, 0.75)
***ESR1*m second most frequent variant**		
Y537S present		
Total number of patients with events, n/N (%)	24/61 (39.3) vs 46/60 (76.7)	36/61 (59.0) vs 51/60 (85.0)
Median PFS (months) (95% CI) [a]	16.92 (11.30, NC) vs 7.26 (4.34, 9.53)	18.23 (15.01, 31.08) vs 7.26 (4.67, 9.36)

Subgroup	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO1	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO3
HR (95% CI)	0.29 (0.17, 0.47)	0.33 (0.21, 0.51)
Y537S absent		
Total number of patients with events, n/N (%)	47/96 (49.0) vs 54/98 (55.1)	63/96 (65.6) vs 73/98 (74.5)
Median PFS (months) (95% CI) [a]	15.11 (11.20, 16.76) vs 9.26 (7.26, 14.59)	15.11 (11.24, 19.35) vs 9.30 (7.23, 12.68)
HR (95% CI)	0.59 (0.40, 0.88)	0.56 (0.40, 0.79)
***ESR1*m third most frequent variant**		
Y537N present		
Total number of patients with events, n/N (%)	13/29 (44.8) vs 18/25 (72.0)	19/29 (65.5) vs 21/25 (84.0)
Median PFS (months) (95% CI) [a]	16.62 (5.42, NC) vs 9.36 (3.71, 14.59)	16.62 (8.21, 30.52) vs 9.40 (3.71, 16.59)
HR (95% CI)	0.44 (0.21, 0.90)	0.49 (0.26, 0.92)
Y537N absent		
Total number of patients with events, n/N (%)	58/128 (45.3) vs 82/133 (61.7)	80/128 (62.5) vs 103/133 (77.4)
Median PFS (months) (95% CI) [a]	15.97 (11.66, 18.40) vs 7.39 (7.03, 9.53)	16.76 (13.14, 19.35) vs 8.44 (7.03, 9.66)
HR (95% CI)	0.45 (0.32, 0.63)	0.45 (0.34, 0.61)

[a] Calculated using Kaplan-Meier method. For each subgroup level of a factor, the HR and 95% profile likelihood CIs are calculated from a Cox proportional hazards model with treatment, factor, and treatment-by-factor as the only covariates.

A HR < 1 favors camizestrant + CDK4/6 inhibitor. HRs and CIs are not produced for subgroups with < 20 events, except for CDK4/6 inhibitor subgroup. In such cases, only descriptive summaries are provided.

Patients without a progression event or who progress after 2 or more consecutive missed visits following the last assessment (or randomization) are censored at the date of last evaluable assessment.

DCO1: 28 November 2024; DCO3: 02 January 2026

Source: SERENA-6 CSR Table 14.2.1.11; DCO3 Table 14.2.1.11.

Appendix 6 Difference in First Subsequent Anticancer Regimens between Regions

Subsequent regimen	Asia Camizestrant + CDK4/6i N = 23, n (%)	Asia AI + CDK4/6i N = 33, n (%)	Europe Camizestrant + CDK4/6i N = 51, n (%)	Europe AI + CDK4/6i N = 64, n (%)	North America Camizestrant + CDK4/6i N = 13, n (%)	North America AI + CDK4/6i N = 20, n (%)
Cytotoxic therapy	**13 (56.5)**	**6 (18.2)**	**24 (47.1)**	**22 (34.4)**	**1 (7.7)**	**8 (40.0)**
ADC	**0**	**2 (6.1)**	**2 (3.9)**	**3 (4.7)**	**0**	**5 (25.0)**
Datopotamab deruxtecan	0	1 (3.0)	0	0	0	0
DB1303	0	0	1 (2.0)	0	0	0
Sacituzumab tirumotecan	0	0	1 (2.0)	1 (1.6)	0	1 (5.0)
Trastuzumab deruxtecan	0	1 (3.0)	0	2 (3.1)	0	4 (20.0)
Chemotherapy	**13 (56.5)**	**4 (12.1)**	**22 (43.1)**	**19 (29.7)**	**1 (7.7)**	**3 (15.0)**
Pyrimidine based regimen	6 (26.1)	2 (6.1)	15 (29.4)	10 (15.6)	0	2 (10.0)
Taxanes	5 (21.7)	1 (3.0)	6 (11.8)	5 (7.8)	1 (7.7)	1 (5.0)
Anthracycline	1 (4.3)	1 (3.0)	1 (2.0)	4 (6.3)	0	0
Other antineoplastic agent	1 (4.3)	0	0	0	0	0
Endocrine-based therapy	**10 (43.5)**	**26 (78.8)**	**26 (51.0)**	**40 (62.5)**	**12 (92.3)**	**12 (60.0)**
Endocrine + targeted therapy	**8 (34.8)**	**17 (51.5)**	**16 (31.4)**	**27 (42.2)**	**11 (84.6)**	**10 (50.0)**
ET + mTORi	5 (21.7)	7 (21.2)	7 (13.7)	10 (15.6)	2 (15.4)	1 (5.0)
AI + CDK4/6i	2 (8.7)	0	3 (5.9)	4 (6.3)	3 (23.1)	3 (15.0)
Fulvestrant + CDK4/6i	1 (4.3)	3 (9.1)	2 (3.9)	6 (9.4)	3 (23.1)	0
Fulvestrant + PI3Ki or AKTi	0	5 (15.2)	4 (7.8)	5 (7.8)	1 (7.7)	3 (15.0)
Fulvestrant + CDK4/6i + KRASi	0	0	0	0	1 (7.7)	0
Fulvestrant + PI3Ki or AKTi + CDK4/6i	0	0	0	0	0	2 (10.0)
Novel ET + CDK4/6i	0	2 (6.1)	0	1 (1.6)	0	1 (5.0)
Novel ET + PARPi	0	0	0	1 (1.6)	1 (7.7)	0
Endocrine monotherapy	**2 (8.7)**	**9 (27.3)**	**10 (19.6)**	**13 (20.3)**	**1 (7.7)**	**2 (10.0)**
Fulvestrant	1 (4.3)	6 (18.2)	7 (13.7)	7 (10.9)	0	1 (5.0)
AI	0	0	2 (3.9)	0	1 (7.7)	0
Tamoxifen	1 (4.3)	0	0	0	0	0
Novel ET	0	3 (9.1)	1 (2.0)	6 (9.4)	0	1 (5.0)
Others [a]	**0**	**1 (3.0)**	**1 (2.0)**	**2 (3.1)**	**0**	**0**

[a] Others include PAR inhibitors; (olaparib, talazoparib), antiangiogenic (bevacizumab) or androgen receptor modulator (enobosarm).
Patients that were treated with radiotherapy after discontinuing study treatment are not captured in this table. Only systemic therapy is reflected in this table.
Asia includes the countries Taiwan, Japan, Republic of Korea, and Israel.
Europe includes the countries Austria, Belgium, Bulgaria, France, Germany, Hungary, Italy, Norway, Poland, Portugal, Russia, Slovakia, Spain, Switzerland, Turkey, and United Kingdom.
North America includes the countries Canada and USA.
DCO: 02 January 2026 (DCO3)
Source: DCO3 IEMT 000291 Table 1

Appendix 7 Summary of First Subsequent Anticancer Regimen in the US

Subsequent regimen	Camizestrant + CDK4/6i N = 10 n (%)	AI + CDK4/6i N = 16 n (%)
ADC	**0**	**5 (31.3)**
Sacituzumab govitecan	0	1 (6.3)
Trastuzumab deruxtecan	0	4 (25.0)
Chemotherapy	**1 (10.0)**	**1 (6.3)**
Pyrimidine based regimen	0	1 (6.3)
Taxanes	1 (10.0)	0
Endocrine + targeted therapy	**8 (80.0)**	**8 (50.0)**
AI + CDK4/6i	2 (20.0)	2 (12.5)
ET + mTORi	1 (10.0)	1 (6.3)
Fulvestrant + CDK4/6i	3 (30.0)	0
Fulvestrant + CDK4/6i + KRASi	1 (10.0)	0
Fulvestrant + PIK3CAi or AKTi	0	3 (18.8)
Fulvestrant + PIK3CAi or AKTi + CDK4/6i	0	2 (12.5)
Novel ET [a] + PARPi	1 (10.0)	0
Endocrine monotherapy	**1 (10.0)**	**2 (12.5)**
AI	1 (10.0)	0
Fulvestrant	0	1 (6.3)
Novel ET [a]	0	1 (6.3)

[a] "Novel ET" subgroup includes the following terms - elacestrant, imlunestrant, camizestrant, vepdegestrant, lasofoxifene, and palazestrant.
DCO: 02 January 2026 (DCO3).
Source: DCO3 IEMT 000210 Table 1

Appendix 8 Overall Survival (FAS)

OS	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO1	Camizestrant + CDK4/6i vs AI + CDK4/6i - DCO3
Event, Death n/N (%)	20/157 (12.7) vs 19/158 (12.0)	46/157 (29.3) vs 49/158 (31.0)
Censored observations		
Any n/N (%)	137/157 (87.3) vs 139/158 (88.0)	111/157 (70.7) vs 109/158 (69.0)
Still in survival follow-up [a] n/N (%)	125/157 (79.6) vs 119/158 (75.3)	100/157 (63.7) vs 88/158 (55.7)
Terminated prior to death [b] n/N (%)	12/157 (7.6) vs 20/158 (12.7)	11/157 (7.0) vs 21/158 (13.3)
Lost to follow-up n/N (%)	0/157 (0) vs 0/158 (0)	0/157 (0) vs 0/158 (0)
Withdrawn consent n/N (%)	10/157 (6.4) vs 15/158 (9.5)	11/157 (7.0) vs 20/158 (12.7)
Other n/N (%)	2/157 (1.3) vs 4/158 (2.5)	0/157 (0) vs 1/158 (0.6)
Screen failure n/N (%)	0/157 (0) vs 1/158 (0.6)	
OS (months) [c, d]		
Median (95% CI)	37.49 (34.40, NC) vs NC (NC, NC)	41.20 (35.48. NC) vs 40.21 (36.50, 43.27)
Comparison of treatment groups [e]		
HR (95% CI); p-value	0.91 (0.48, 1.73) [f]	0.87 (0.57, 1.30); p = 0.48777
OS rate [c, d]		
At 12 months (%) (95% CI)	92.3 (85.7, 96.0) vs 89.0 (81.9, 93.4)	94.1 (89.0, 96.9) vs 87.4 (81.0, 91.8)
At 24 months (%) (95% CI)	78.0 (65.8, 86.3) vs 83.6 (74.5, 89.6)	76.6 (68.6, 82.9) vs 77.0 (69.1, 83.1)

[a] Included patients not known to have died on or before DCO date.

[b] Included patients with unknown survival status or patients who were lost to follow-up.

[c] The calculation was based on the Kaplan-Meier technique.

[d] The CI for OS was derived based on Brookmeyer-Crowley method.

[e] The HR and its CI were estimated using a Cox proportional hazards model, stratified by time from initiation of CDK4/6 inhibitor + AI to randomization. A HR < 1 favors camizestrant + CDK4/6 inhibitor.

[f] As per the MTP specified in the SAP, since the PFS2 analysis is not significant, the p-value is not presented.

DCO1: 28 November 2024; DCO3: 02 January 2026

Source: SERENA-6 CSR Table 14.2.3.1; DCO3 Table 14.2.3.1.

Appendix 9 Summary of All Deaths (Safety Analysis Set)

Event	Camizestrant + CDK4/6i N = 155 n (%)	AI + CDK4/6i N = 155 n (%)
Primary cause of death		
Any	20 (12.9)	18 (11.6)
Related to disease under investigation [a]	13 (8.4)	14 (9.0)
AE	2 (1.3)	1 (0.6)
On treatment [b]	2 (1.3)	0
Post treatment [c]	0	1 (0.6)
Other [d]	4 (2.6)	3 (1.9)
Missing	1 (0.6)	0
Secondary cause of death		
Any	2 (1.3)	4 (2.6)
Related to disease under investigation [a]	0	2 (1.3)
AE	0	1 (0.6)
On treatment [b]	0	1 (0.6)
Post treatment [c]	0	0
Other [d]	1 (0.6)	0
Missing	1 (0.6)	1 (0.6)

[a] Death related to disease under investigation as assessed by investigator.

[b] On treatment included AEs with an onset date or that worsened on or after the date of first dose of study treatment up to and including 28 days following the date of last dose of study treatment and prior to the start of any subsequent cancer therapy.

[c] Post treatment included AEs with an onset date more than 28 days after last dose of study treatment or once subsequent cancer therapy started, whichever came first.

[d] Patients who died and were not captured in the earlier categories.

This table includes all deaths throughout the study. Categories were mutually exclusive.
DCO: 28 November 2024 (DCO1).
Source: SERENA-6 CSR Table 14.3.3.1.1.

Appendix 10 Narrative for Subject [redacted] (DCO 16 September 2024)

The presented narrative concerns a 56-year-old female with past medical history of asthma, dyslipidemia, arthralgia and breast cancer diagnosed in 2019, treated with cyclophosphamide + doxorubicin (2019), paclitaxel (2020), and letrozole + palbociclib (2020-2023). No chest radiotherapy was noted. The subject had disease progression on letrozole + palbociclib and enrolled on SERENA-1 trial (75 mg camizestrant + 600 mg ribociclib on 17 October 2023. Baseline QTcF 429 msec, heart rate 83 bpm, left ventricular ejection fraction (LVEF) 60%, and all electrolytes in the normal range. The patient's concomitant medications included prophylactic acetylsalicylic acid and simvastatin.

A single dose of ribociclib 600 mg was given on 17 October 2023, and 75 mg camizestrant + 600 mg ribociclib started on 23 October 2023 (C1D1, Day 1), with QTcF 435 ms, heart rate 87 bpm. Vomiting, nausea, and diarrhea were reported between 25 October 2023 (Day 3) and 29 October 2023 (Day 5), requiring antiemetic treatment (metoclopramide +/- ondansetron).

On 31 October 2023 (Day 8): S-Potassium, and S-Magnesium were in the normal range. Heart rate 57 bpm, triplicate ECGs showed mean QTcF of 561ms by central read with new onset T-wave abnormality and heart rate of 55 bpm. QTcF locally reported at 455 msec. Treatment was continued with camizestrant and ribociclib, at the same dose levels. A new episode of diarrhea was reported on 04 November 2023 (Day 12).

On [redacted] an episode of syncope observed at around 03:00 to 04:00 am and was reported by the investigator. The subject received no treatment for the event, which was reported as recovered/resolved on the same day. Dosing with ribociclib and camizestrant was interrupted immediately (last dose on [redacted] The patient was transferred to a local hospital; upon arrival, ECG showed prolonged QT (result not reported), within a few minutes the patient had an episode of ventricular fibrillation, requiring defibrillation to sinus rhythm and the patient received IV amiodarone. A couple of asymptomatic non-sustained ventricular tachycardias (ns-VTs) were observed during the first 24 hours after arrival in the hospital. 69% LVEF reported. Hypokalemia (3.2 mmol/L) noted during the hospital stay. Follow-up ECGs recorded on [redacted] and [redacted] showed normal QTcF with heart rate of 78 bpm and the patient was discharged from the hospital. The QTcF value remained normal 435 msec to 438 msec at follow-up ECGs recorded on 30 November 2023 and 01 December 2023 and the heart rate range was 84 bpm to 87 bpm.

The Sponsor considers that the observed QTcF prolongation, with associated ventricular arrhythmia, is consistent with the known QT prolongation effect of ribociclib, noting that no action was taken with ribociclib on Day 8, with QTcF of >560ms, contrary to the ribociclib label.

The Sponsor also note that this is a heavily confounded case (with additional contributory factors including cardiovascular medical history, AEs of nausea, vomiting, diarrhea; concomitant medications with known QT prolonging effects). Upon detailed review, there is insufficient evidence to indicate a causal relationship of camizestrant.

Appendix 11 TTD in Patient-reported Functioning and Symptoms as Measured by EORTC QLQ C30 and BR23 (Sensitivity Analysis with Disease Progression and Death as Intercurrent Events)

Item	Analysis	Camizestrant + CDK4/6i Subjects with event, n (%)	AI + CDK4/6i Subjects with event, n (%)	Camizestrant + CDK4/6i Median TTD (months)	AI + CDK4/6i Median TTD (months)	Hazard ratio (HR)* (95% CI)
Functioning						
Physical	Primary analysis	33 (30.6)	29 (30.5)	23.03	15.67	0.74 (0.44-1.24)
	SA: Event definition incl. death	41 (38.0)	33 (34.7)	21.26	15.67	0.76 (0.47-1.25)
	SA: Event definition incl. progression, death	62 (57.4)	64 (67.4)	10.28	6.37	0.58 (0.40-0.84)
Role	Primary analysis	48 (44.4)	47 (50.0)	15.57	8.21	0.73 (0.48-1.10)
	SA: Event definition incl. death	56 (51.9)	51 (54.3)	10.18	8.21	0.78 (0.53-1.16)
	SA: Event definition incl. progression, death	71 (65.7)	74 (78.7)	8.34	4.60	0.68 (0.48-0.96)
Symptoms						
Pain	Primary analysis	42 (39.6)	49 (52.1)	16.56	6.47	0.57 (0.37–0.86)
	SA: Event definition incl. death	50 (47.2)	52 (55.3)	12.52	4.53	0.61 (0.41-0.91)
	SA: Event definition incl. progression, death	64 (60.4)	73 (77.7)	8.34	2.79	0.53 (0.37-0.75)
Fatigue	Primary analysis	34 (32.7)	33 (36.3)	NR	13.77	0.75 (0.46-1.24)
	SA: Event definition incl. death	43 (41.3)	36 (39.6)	20.01	10.35	0.82 (0.51-1.32)
	SA: Event definition incl. progression, death	62 (59.6)	64 (70.3)	10.12	5.55	0.62 (0.43-0.90)
Breast Symptoms	Primary analysis	13 (12.7)	16 (17.4)	NR	NR	0.59 (0.28-1.24)
	SA: Event definition incl. death	23 (22.5)	23 (25.0)	37.49	27.10	0.68 (0.37-1.25)
	SA: Event definition incl. progression, death	49 (48.0)	60 (65.2)	14.72	7.26	0.55 (0.37-0.81)
Arm Symptoms	Primary analysis	15 (15.0)	18 (20.0)	NR	NR	0.69 (0.34-1.39)
	SA: Event definition incl. death	26 (26.0)	27 (30.0)	37.49	27.10	0.69 (0.39-1.22)
	SA: Event definition incl. progression, death	46 (46.0)	60 (66.7)	15.11	7.03	0.52 (0.34-0.77)

* HR< 1 favors camizestrant + CDK4/6i.
DCO: 28 November 2024 (DCO1)
Source: SERENA-6 CSR Table 14.2.11.5, Table 14.2.12.5; IEMT 000179 Table 26, Table 27; IEMT 000298