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SERENA-6 interpretation and clinical implications: intercepting endocrine resistance in metastatic breast cancer

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In patients treated with first-line AI plus CDK4/6 inhibitor, SERENA-6 showed the benefit of switching from an aromatase inhibitor to the oral SERD camizestrant upon detection of an emerging *ESR1* mutation, before disease progression. While this adaptive oncology approach has shown key benefits for patients, the integration of emerging ctDNA targets into treatment decisions has been questioned. Here, we provide further clarification on several aspects of this clinically relevant discussion.

Advancing new strategies to monitor and treat metastatic cancers is a major goal in medical oncology that continues to evolve with emerging scientific insights. Advances in radiologic imaging have improved our ability to detect and measure tumor progression, from conventional X-ray studies to functional imaging with PET/CT. In parallel, molecular techniques now enable longitudinal monitoring of circulating tumor DNA (ctDNA), allowing assessment of tumor genomic evolution. Among recently identified targets, *ESR1* mutations (*ESR1m*) are a specific marker of resistance to aromatase inhibitors (AI) in hormone receptor–positive (HR+) metastatic breast cancer (mBC), typically emerging under AI pressure. Following the proof-of-concept PADA-1 trial[1], SERENA-6 was designed as the first global, randomized, double-blind registration study to evaluate switching from an AI to the oral SERD camizestrant upon detection of *ESR1m* in patients with HR+ mBC receiving first-line AI plus CDK4/6 inhibitor therapy[2]. This strategy aims to prolong first-line control through targeted intervention before clinical progression, which may be relevant in the recent context of another trial using an oral SERD in an untargeted first-line setting for all patients failing to meet its endpoint[3]. In tumors that escaped cell-cycle arrest, intervening at molecular resistance -before clonal dominance and diversification- may increase the likelihood of durable disease control, making early *ESR1m* targeting a proactive evolutionary strategy[4–7]. Unlike approaches based on genomic alterations present since the early oncogenesis (such as *TP53* or *PIK3CA* mutations), SERENA-6 tracks a resistance alteration that both drives endocrine failure and remains targetable with oral SERDs. Switching from an AI to a SERD aims to restore endocrine efficacy in the presence of *ESR1m* while maintaining CDK4/6 inhibition, particularly since some *ESR1m* may also contribute to resistance to CDK4/6i[8].

The adoption of new technologies is known to follow a bell-shaped curve[9]. While initial results from SERENA-6[10] have been described by some as the future of precision oncology[11], the integration of dynamic ctDNA changes into cancer treatment has been questioned[12]. In this context, some aspects of this far-ranging and clinically relevant discussion warrant further clarification:

Does the SERENA-6 trial demonstrate the benefit of camizestrant in the clinical context of the study?

The design of the randomized, double-blind, placebo-controlled SERENA-6 trial has been previously published (Fig. 1[2]). Patients with HR+ mBC receiving first-line AI and CDK4/6i therapy who developed *ESR1m* without synchronous clinical disease progression were randomized to continue the standard of care (AI and CDK4/6i, unchanged, with a placebo for camizestrant) versus, in the experimental arm, to switch from the AI to camizestrant with continuation of the same CDK4/6i (with an AI placebo). Notably, camizestrant has shown notable activity against *ESR1m* in a phase 1 study[13] and superiority to fulvestrant in a phase 2 trial[14]. Results from the second analysis of SERENA-6[15], summarized in Table 1, are, in our view, compelling in demonstrating the clinical benefit of switching to an oral SERD, camizestrant, at the time of *ESR1m* emergence.

The primary endpoint was progression-free survival (PFS), measured from the time of randomization (at *ESR1m* emergence during first-line treatment) until the first progression or death. Extending first-line PFS by introducing a new treatment during ongoing therapy is not a new approach, with many registration trials having used the same PFS endpoint as in SERENA-6: recent examples include the PATINA and Her2CLIMB-05 trials, which introduced first-line maintenance therapy for patients with HER2+ mBC[16,17]. The two only distinctions between classical maintenance trials and SERENA-6 lie in (i) the event triggering the switch: a somewhat arbitrary predefined chronological point in the patient's treatment course (as in PATINA and Her2CLIMB-05) versus a personalized approach using ctDNA in SERENA-6, to optimize the timing of the switch to maintenance therapy; By relying on molecular triggers rather than predefined time points, the design of SERENA-6 is arguably more rigorous than the calendar-based approaches used in maintenance trials. (ii) the size of the target population. In this adaptive strategy, not all patients receive maintenance or treatment intensification, but rather, only the molecularly-selected subgroup of patients who harbor a highly specific predictive biomarker (i.e., *ESR1m*) undergoes modification of the endocrine therapy backbone. This biologic enrichment approach limits exposure to an additional therapy to those most likely to benefit, thereby reducing unnecessary toxicity and minimizing

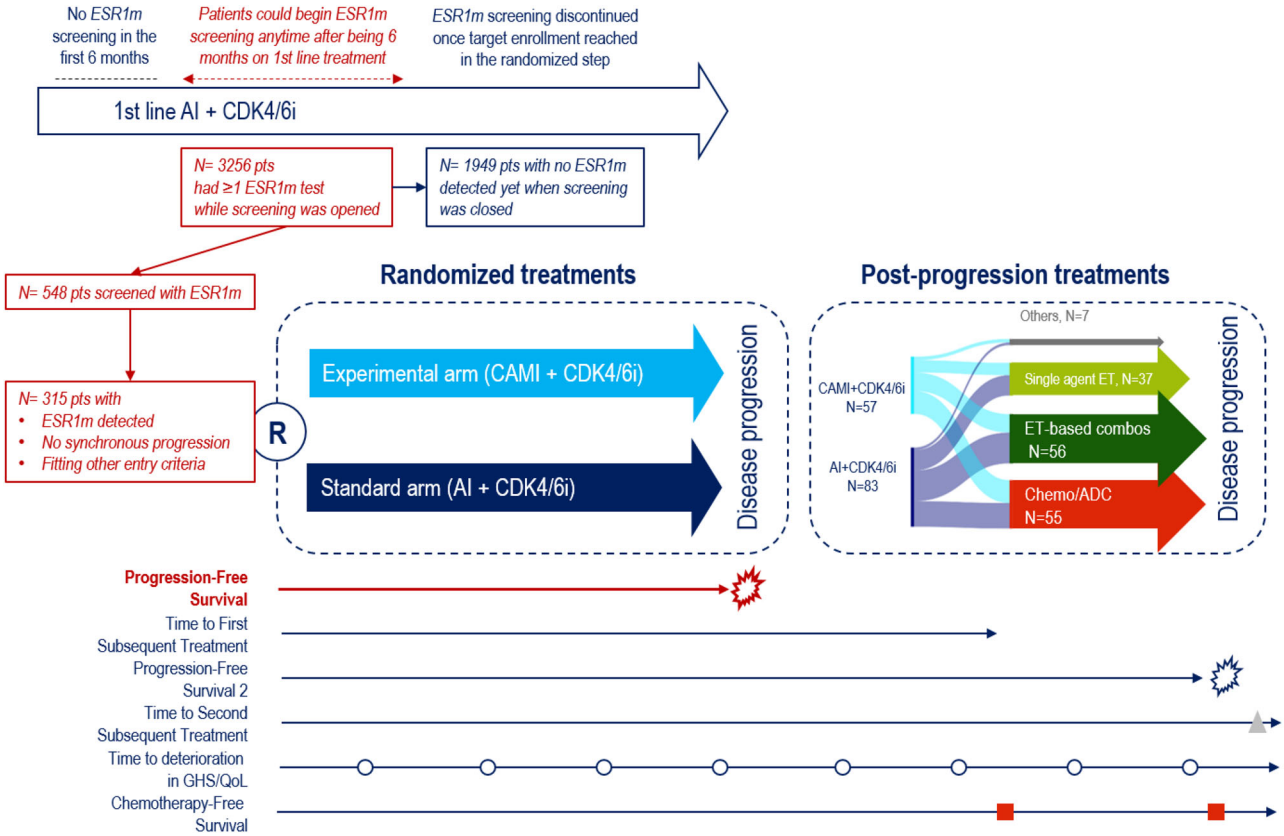

Fig. 1 | SERENA-6 design, objectives and patient flow. The crude estimate of the proportion of patients with emergent *ESR1*m in SERENA-6 is 42% (calculated as 548 patients with a positive test/(number of patients tested for *ESR1*m [$n = 3256$]—number of patients still ongoing in surveillance when screening closed [$n = 1949$]). Post-progression treatment allocation, pooled across arms, was obtained from the 2025 interim [10] analysis and will be updated in future communications.

overtreatment associated with universal maintenance strategies. In this context, ctDNA-guided adaptation represents not only a biologically rational model but also a clinically more sustainable precision-based framework for treatment optimization.

A criticism of the study has been an "absence of crossover" to a SERD in the control arm. Treatment at progression was actually left to the investigators' discretion, in line with the latest guidelines, with the possibility of unblinding. Several clinical and methodological arguments argue against including a crossover in the standard arm. First, an optional cross-over after progression was offered in PADA-1 and resulted in a short PFS (mPFS 3.5 months), numerically shorter than with fulvestrant used before progression. Second, SERENA-6 was initiated before phase 3 results of second-line oral SERD trials (EMERALD, EMBER-3[18]) and their approvals, with neither elacestrant nor imlunestrant showing an overall survival (OS) benefit. Also, multiple treatment options are available in the second-line setting. These include endocrine therapy-based combinations for patients with somatic PI3K pathway alterations, PARP inhibitors for patients harboring *BRCA1/2* or *PALB2* mutations, and chemotherapy (and most recently, antibody-drug conjugates, ADCs) for patients with a high burden of visceral disease and/or symptomatic disease requiring a more rapid therapeutic response. It would have been highly questionable and of borderline ethical acceptability to design a trial with a mandatory crossover for all patients to an unproven therapy at progression (i.e., a trial in which 100% of patients allocated to the standard arm must receive camizestrant +/− continuation of the same CDK4/6i at disease progression). In addition, crossover to camizestrant would have also prevented the study from assessing the impact of camizestrant on OS, while an adverse effect of a new agent on OS remains an important regulatory assessment. Alternatively, if crossover to a SERD in the standard arm had been part of the trial design, but as a not mandatory option (like in PADA-1), such crossover would have been introduced selection bias, as only patients with the most favorable prognosis and with access to multiple alternative options would have crossed over to second line camizestrant +/− continuation of the same CDK4/6i, This would likely make any comparison between early and delayed treatment systematically biased and difficult to interpret.

Secondary efficacy endpoints in SERENA-6 included assessment of PFS2, defined as the time from randomization to the earliest of the progression or death event after the first subsequent therapy following the initial clinical/radiologic progression. In assessing the PFS2 metric in SERENA-6, it has been suggested that the experimental arm (switch to camizestrant plus CDK4/6i before clinical progression on AI plus CDK4/6i) should be considered as two lines of therapy. PFS2 is a potentially more robust surrogate of OS than PFS, as assessment of PFS2 captures the durability of disease control over two progressions (or death). PFS2 is not a metric that counts the number of therapies received, but rather assesses the ability of a treatment change to defer the second progression; ultimately, if the second progression can be deferred for longer, the more likely it is that this will impact OS. Differences in the number of treatments received per arm are very common; among many examples, trials comparing doublets versus triplets (such as the INAVO-120 trial) inherently illustrate asymmetry in treatment

Table 1 | SERENA-6 results

Endpoint	AI+CDK4/6i *N* = 158 patients	Camizestrant +CDK4/6i *N* = 157 patients	HR (95%CI) *p* value if available
Median progression-free survival, months (95% CI)	9.2 (7.2–9.7) [115 events]	16.6 (14.7–19.4) [90 events]	0.46 (0.34–0.62) $p < 0.00001$
Median time to deterioration in GHS/QoL, months (95% CI)	8.3 (2.8–26.7) [49/155 events]	23.0 (17.4–NC) [37/155 events]	0.49 (0.31–0.77)
Time to first subsequent therapy	ND	ND	0.47 (0.35–0.62)
Median progression-free survival 2, months (95% CI)	19.4 (17.8–21.4) [71 events]	25.7 (20.3–28.9) [62 events]	0.56 (0.39–0.80) $p = 0.00153$[a]
Time to second subsequent therapy	ND	ND	0.57 (0.40–0.81)
Median chemotherapy-free survival, months (95% CI)	18.7 (16.7–24.7) [76 events]	22.7 (20.3–31.5) [66 events]	0.69 (0.49–0.97)
Overall survival	N/A (immature) [35 events]	N/A (immature) [34 events]	0.92 (0.57–1.48)

Results displayed are those from the second data cut-off (DCO) June 30, 2025[15].

GHS/QoL global health status/quality of life, *ND* not disclosed in the DCO2 presentation, *HR* hazard ratio, *N/A* not available, *NC* not calculable.

[a]Threshold for significance at interim analysis for PFS2: $p = 0.0001$.

exposure. Furthermore, the above criticism regarding PFS2 does not actually challenge post-progression therapies (i.e., those administered after clinical progression), but rather the treatment given immediately after randomization (before the first clinical progression). This line of reasoning implies that the treatment given in the standard arm of SERENA-6 after randomization has no efficacy, despite a median PFS in the standard arm of 9.2 months, and the fact that staying on AI plus CDK4/6i until clinical disease progression remains, to this day, the standard of care for patients with an emerging *ESR1m*. Finally, it is unlikely that observed PFS2 in the control arm would have been longer if more patients in SERENA-6 had received an oral SERD post progression on AI plus CDK4/6i, given the modest PFS results that have been seen in the second-line setting with these agents[19].

Further follow-up to assess mature PFS2 and OS data will complement the already available results.

What clinical questions can registration drug trials answer?

If oral SERDs are approved for use both before and after clinical disease progression on AI plus CDK4/6i therapy, determining how to prioritize this interception approach compared with the currently conventional strategy, i.e., waiting for clinical disease progression and then determining whether oral SERDs are an acceptable treatment option, will be an important future consideration. SERENA-6 was a registrational study designed to assess the benefit of switching to camizestrant upon detection of emergent *ESR1m* during first-line therapy compared with continuing the standard of care. SERENA-6 was not designed to address the distinct clinical question of optimal timing of oral SERD therapy, and the hazard ratios reported in SERENA-6 cannot be compared with those from trials exploring novel oral SERD regimens in the second-line setting. Trials that assess optimal sequencing of therapies remain a highly important academic and clinical priority, but, to date, prior first-line registration trials have not addressed this issue. For example, the registrational trials of first-line CDK4/6i in HR+ mBC, first-line trastuzumab deruxtecan in HER2-low mBC, and first-line maintenance therapy with tucatinib in HER2-positive mBC did not have second-line cross-over to the investigational therapy in their designs, and thus did not assess optimal timing of therapy. We strongly endorse the need to design trials that assess the impact of treatment sequence and timing of therapy on OS. Such trials should ideally follow registrational trials; however, the SONIA trial illustrates the challenges of conducting these studies in a way that meaningfully impacts clinical practice[20]. Sequencing trials are operationally complex and time-consuming, and frequently read out after the therapeutic landscape has evolved. This is especially relevant in the second-line setting, after disease progression, where the rapid emergence of new targeted therapies may render single-agent oral SERDs (±continuation of the same CDK4/6 inhibitor) suboptimal, much like second line single-agent fulvestrant in the SONIA trial.

What can be learned from this new ctDNA monitoring strategy?

Overall, the advantages of the SERENA-6 approach for patients with HR+ HER2− mBC are supported by several observations.

First, the impact of switching to camizestrant on quality of life[21] is impressive, especially since the switch extends the durability of the best-tolerated treatment for mBC that any patient in this population is likely to receive. A significant delay in time to deterioration in global quality of life was actually reported in patients changing to oral SERD: in the standard arm, patients experienced an early deterioration in quality of life, likely reflecting the onset of clinical symptoms associated with impending subclinical tumor progression, such as pain or shortness of breath; in the investigational arm, this deterioration was substantially delayed by changing to the oral SERD. These quality of life data are particularly meaningful given that the QLQ-C30 scale is not a sensitive instrument, that the use of SERD after clinical progression has not demonstrated a clear quality-of-life benefit, and because of the randomized, double-blind design of the trial. Future research will help decipher who, among the first-line patients, are the ones most likely to experience symptoms before or at clinical progression and who could most benefit from an early treatment switch.

Second, data from clinical trials and real-world studies have identified that approximately 10–15% of patients never receive second-line therapy after first-line progression[22–24], and an additional proportion of patients require second-line chemotherapy or antibody-drug conjugate therapy due to aggressive and clinically concerning disease. Such patients may miss the potential benefit associated with targeting *ESR1m* with an oral SERD.

Third, and related to the above point, the populations studied in SERENA-6 and in second-/third-line trials are distinct. The latter trials were conducted in pretreated patients for whom fulvestrant or AI monotherapy in the control arm was considered acceptable at the time and enrolled a subpopulation for whom combination therapy or chemotherapy were not

medically necessary. In contrast, the first-line population eligible for ctDNA monitoring in SERENA-6 was much broader, suggesting that the benefits of this approach (including the reported improvement in chemotherapy-free survival) may apply to a larger proportion of the HR+ mBC population. Many patients are not considered to be suitable candidates for oral SERD monotherapy following progression on first-line CDK4/6i plus AI therapy due to a high disease burden and a high risk of early treatment failure, which is common, even among patients whose disease progresses after more than 12 months on first-line therapy. In contrast, by monitoring patients who do not have overt clinical progression, the SERENA-6 approach offers almost all patients who develop *ESR1m* the chance to benefit from an oral SERD.

While ctDNA testing is currently recommended in guidelines to detect *ESR1m* at the time of clinical progression, the SERENA-6 approach introduces more frequent testing, focused on *ESR1m*. The logistics and cost of *ESR1m* monitoring may be legitimate obstacles to implementation; however, another proposed concern, the risk of increased testing anxiety, is not likely to negatively impact patients, in our opinion. First, *ESR1m* testing can be performed at the time of routine imaging and laboratory assessments, reducing complexity, and disclosure of a newly detected *ESR1m* can occur when patients have stable disease, without clinical progression. Most importantly, the results are actionable as switching from an AI to camizestrant improves outcomes. In the experience of the PADA-1 and SERENA-6 investigators, there was minimal incremental patient stress related to *ESR1m* monitoring. Furthermore, our clinical observations suggest that many patients live a nearly normal life while on first-line therapy, and that the first clinical progression is often a psychologically challenging reminder that cancer control will not be indefinite -an observation in favor of implementing *ESR1m* monitoring. Of note, in both PADA-1 and SERENA-6 trials, the discontinuation of *ESR1m* screening when the target number of randomized patients was reached accounts for the seemingly lower observed incidence of *ESR1m*: a cumulative incidence of approximately 40% would likely have been observed if all enrolled patients had continued testing (see Fig. 1 caption for details). Future research may better clarify the optimal timing of initiation of *ESR1m* monitoring to maximize mutation detection, minimize unnecessary testing, and characterize any distress associated with it.

To conclude, by leveraging molecular monitoring to guide timely treatment adaptation, SERENA-6 introduces a pragmatic and individualized approach to prolong first-line disease control in HR+ mBC. We acknowledge the current lack of additional markers to identify which patients benefit more from this type of early intervention, and expect that future analyses of the rich SERENA-6 dataset will help elucidate this important question. The collective evidence suggests that this approach benefits patients, delays chemotherapy, and safeguards quality of life. There were a few downsides for patients, as camizestrant was very well tolerated, with a very low discontinuation rate due to adverse effects.

At a higher level, PADA-1 and SERENA-6 exemplify a shift from reactive to "anticipatory adaptive oncology", where molecular surveillance informs timely therapeutic adaptation before overt clinical failure. We are confident that evolution-informed strategies based on ctDNA monitoring will continue to expand and that the benefits to patients observed with molecularly guided treatment may extend beyond oral SERDs and *ESR1*-mutant breast cancer to other agents and tumor types.

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Author contributions

F.-C.B. conceived the manuscript, led the project, and wrote the manuscript. L.S. contributed to the technical preparation of the manuscript. F.-C.B., C.B., G.B., A.M.B., S.C., J.C., M.C., G.C., S.D., P.A.F., L.G., A.G., M.I., H.I., W.J., E.L., K.K., C.X.M., E.L.M., A.J.M., J.A.M., J.O., Y.H.P., J.P., P.R., S.S., J.L.S., L.S., P.T., S.A.W., G.W., and N.A.T. contributed to the interpretation of the data and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Competing interests

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