The management of hormone receptor-positive, HER2-negative (HR+/HER2−) metastatic breast cancer (mBC) is undergoing a profound transformation due to advances in precision medicine and genomic profiling. Despite major progress with endocrine therapies and CDK4/6 inhibitors, acquired resistance—often driven by genomic alterations such as *ESR1* mutations—frequently challenges durable disease control. Integrating genomic biomarkers into clinical decision-making now offers new opportunities to personalize therapy and improve patient outcomes.

Selective estrogen receptor degraders (SERDs) have emerged as a promising therapeutic class for overcoming endocrine resistance. Camizestrant, an oral next-generation SERD, is at the forefront of this evolution, offering potent estrogen receptor antagonism and degradation in the context of both wild-type and mutant ESR1, and promising improved efficacy over existing agents such as fulvestrant.

The phase III SERENA-6 study critically examines the role of camizestrant in a contemporary precision medicine strategy for HR+/HER2− mBC. The trial investigates a “switch maintenance” approach: patients with advanced HR+/HER2− disease receiving first-line aromatase

inhibitor plus CDK4/6 inhibitor are monitored for emerging circulating ESR1 mutations via genomic testing. Upon detection of ESR1 mutation, patients are randomized to switch their endocrine backbone from an aromatase inhibitor to camizestrant, while continuing CDK4/6 inhibition. By directly targeting the mechanistic driver of resistance—the mutated estrogen receptor—this strategy seeks to prolong responsiveness and combat disease progression.

SERENA-6 is the first large randomized study to prospectively integrate real-time liquid biopsy monitoring of genomic biomarkers into therapeutic selection for breast cancer. The outcome of this study will have far-reaching implications: demonstrating the feasibility and clinical importance of adaptive treatment modification in response to evolving tumor biology. The anticipated benefits include improved progression-free survival, delayed onset of endocrine resistance, and enhanced quality of life. The trial also highlights the increasing role of non-invasive genomic surveillance in the personalized management of metastatic breast cancer.

The integration of camizestrant and genomic biomarkers in SERENA-6 exemplifies the shift toward precision

medicine in breast oncology, redefining the treatment paradigm for HR+/HER2− mBC. Ongoing results will help clarify patient selection, sequencing, and the broader impact of biomarker-driven therapy, paving the way for future strategies that can further individualize care.