FDA is committed to ensuring digital accessibility for people with disabilities. We are continually improving the user experience for everyone and applying the relevant accessibility standards. At the time of initial posting on **April 30, 2026**, the attached **Event Materials** may not be fully accessible to users using assistive technology. A fully accessible version of the **Event Materials** is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

Please let us know if you encounter accessibility barriers by contacting **Division of Advisory Committee and Consultant Management (DACCM)** at:

- **ODAC@fda.hhs.gov**

U.S. FOOD & DRUG ADMINISTRATION

NDA 220359
Camizestrant

FDA Presentation
Oncology Drugs Advisory Committee

April 30, 2026

Mirat Shah, MD
Division of Oncology 1
Office of Oncologic Diseases

Outline

- Disease Background
  - Hormone Receptor (HR)-Positive, Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Metastatic Breast Cancer
  - Estrogen Receptor 1 Gene *(ESR1)* Mutation
- SERENA-6 Design and Challenges
- SERENA-6 Results and Issues
  - Progression-Free Survival (PFS), Progression-Free Survival 2 (PFS2), Overall Survival (OS)
- Considerations for Committee
- Voting Question

HR+, HER2- Metastatic Breast Cancer

- All treatment is palliative with the aims of prolonging survival while reducing disease symptoms and preserving ability to function

- Patients will typically need treatment for the rest of life
  - Receive one treatment regimen until progression, then start new treatment

- **Goal is to maximize benefit from each line of treatment**

- First-line (1L) therapy typically aromatase inhibitor with CDK4/6 inhibitor
  - After 1L, options include other endocrine therapy-based regimens, antibody-drug conjugates, chemotherapies

CDK4/6 = cyclin-dependent kinases 4 and 6

ESR1 Mutation in Metastatic Breast Cancer

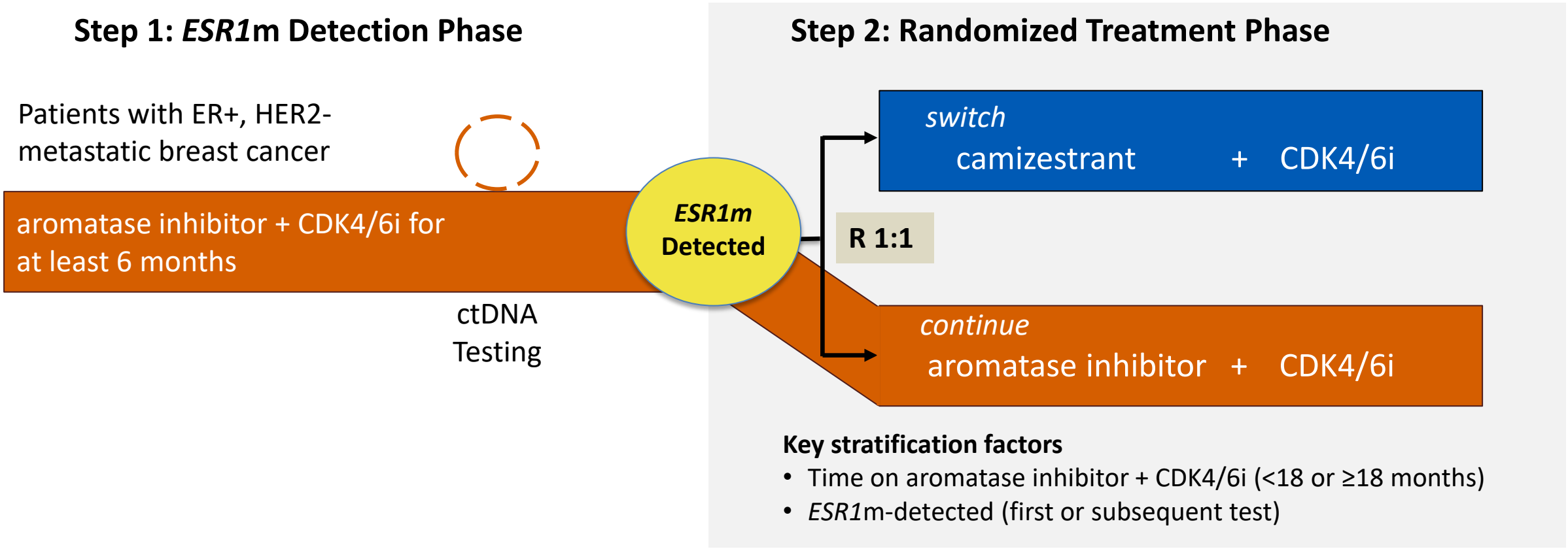
- *ESR1* mutation is an acquired resistance mutation to aromatase inhibitor
  - At metastatic diagnosis: < 5% of patients
  - After disease progression on aromatase inhibitor: 40–50% of patients

- Several oral estrogen receptor antagonists are FDA approved for patients with tumor *ESR1*m after disease progression on an aromatase inhibitor and CDK4/6 inhibitor

- Unknown if starting a new therapy earlier, at detection of *ESR1*m and prior to disease progression, provides long-term benefit to patients

- Applicant seeks indication for camizestrant, an oral estrogen receptor antagonist, in patients with tumor *ESR1*m detected “during 1L endocrine-based therapy”

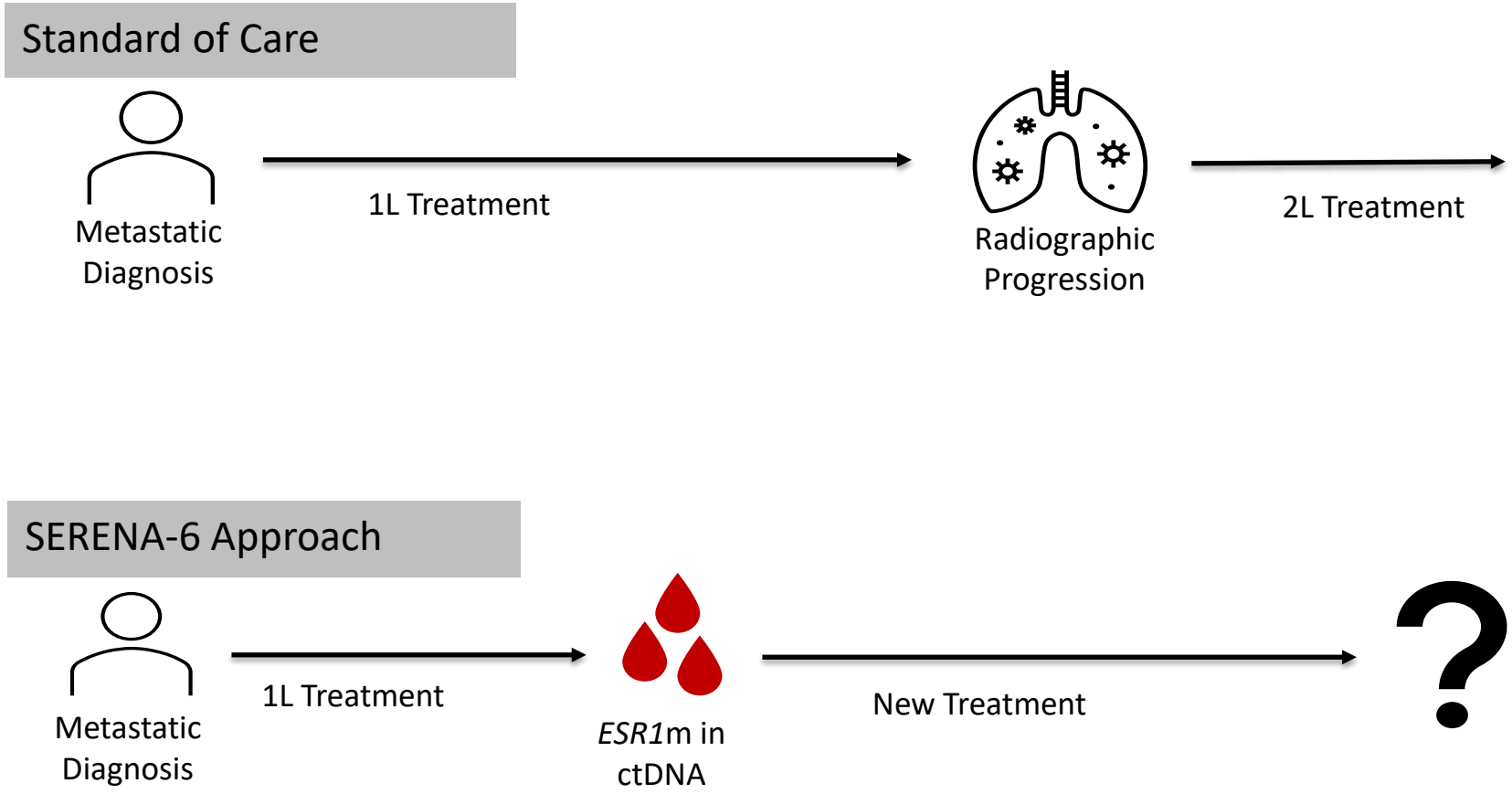
SERENA-6 Trial Design



Primary Endpoint	PFS per investigator
Secondary Endpoints	PFS2 per investigator, OS

ctDNA = circulating tumor DNA; ESR1m = ESR1 mutation; ER = estrogen receptor

Benefit of Switching Treatment At *ESR1*m Detection Is Not Established

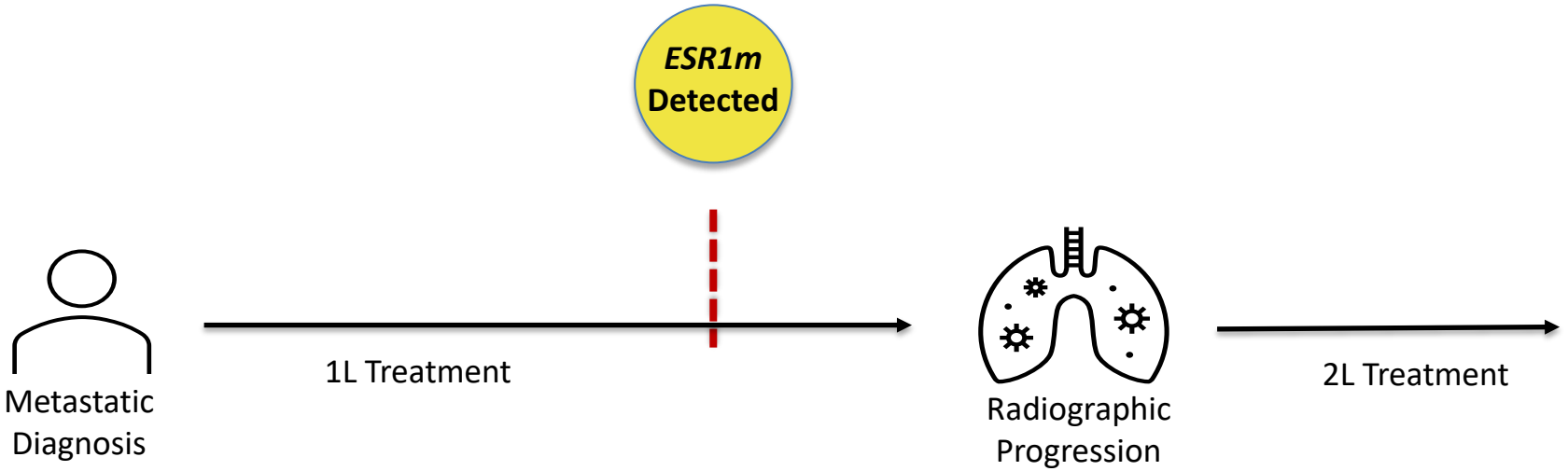


SERENA-6 did not evaluate whether changing treatment at *ESR1*m detection improves long-term outcomes compared to changing treatment at radiographic progression

Summary of SERENA-6 Results

- Primary PFS endpoint met
  - PFS HR 0.44 (95% CI: 0.31, 0.60; p<0.00001), estimated median 16 months for camizestrant with CDK4/6i and 9.2 months for aromatase inhibitor with CDK4/6i
- PFS2 statistically significant
- Current OS data immature

Clinical Meaningfulness of PFS Improvement Measured from *ESR1*m Detection is Uncertain



- Trials usually enroll patients and start measuring PFS at metastatic diagnosis (1L) or after radiographic progression (2L), when new treatment is clearly indicated

- **At *ESR1*m detection, not clear that a treatment switch is needed**
  - Patients on SERENA-6 control arm had estimated median PFS of 9.2 months

PFS2 Inadequate to Show Evidence of Clinical Benefit

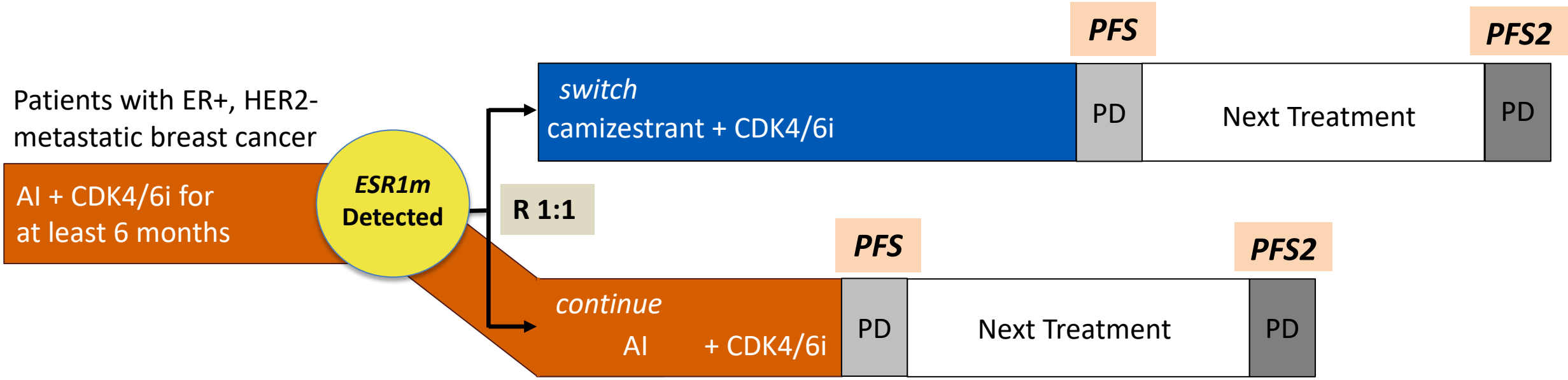
- Defined as time from randomization to second disease progression (RECIST, non-RECIST, or clinical), or death

- Not typically used in regulatory decision-making because it does not isolate the effect of the experimental drug

- In SERENA-6, additional challenges with PFS2 included
  - Heterogeneity in choice and timing of subsequent therapies
  - Selection of therapy affected by regional availability and local standards
  - Variability in assessments to determine second disease progression

RECIST = Response Evaluation Criteria in Solid Tumors

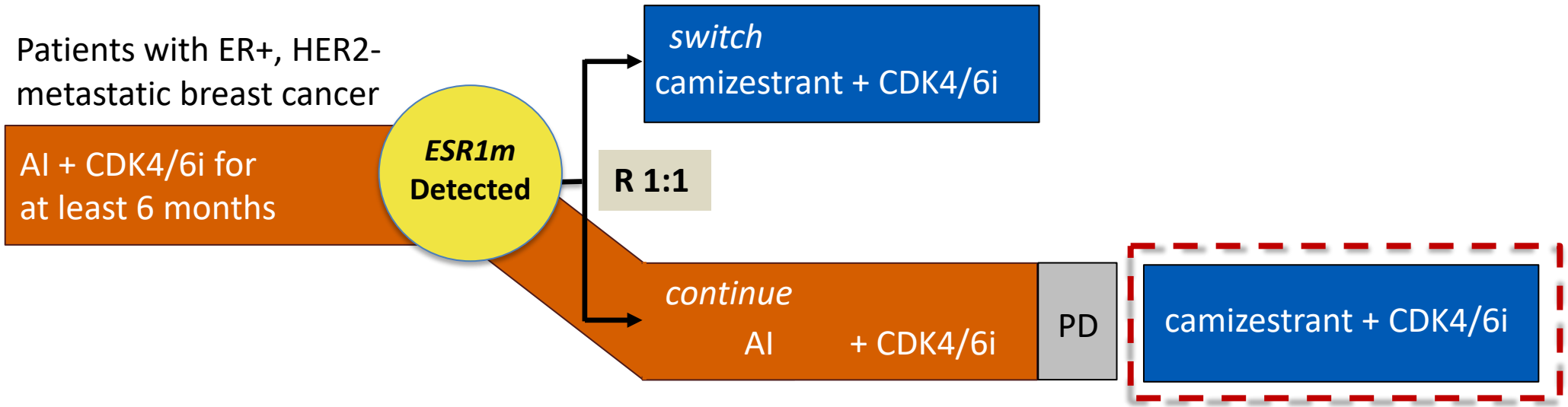
Neither PFS nor PFS2 Evaluate Benefit of Switching Treatment at *ESR1*m Detection



PFS per investigator: randomization to progression (RECIST) or death
PFS2 per investigator: randomization to second progression (RECIST, non-RECIST, clinical) or death

AI = aromatase inhibitor; PD = progression of disease

No Crossover Permitted in SERENA-6



AI = aromatase inhibitor

Current OS Data Cannot Overcome Uncertainties with Trial Design and PFS Results

- OS data are currently immature (58% information fraction)
  - Final OS not expected until 2028
- Trial underpowered for OS
  - Target power is 63% for final analysis
- SERENA-6 may not reach statistical significance for OS

Cardiac Safety

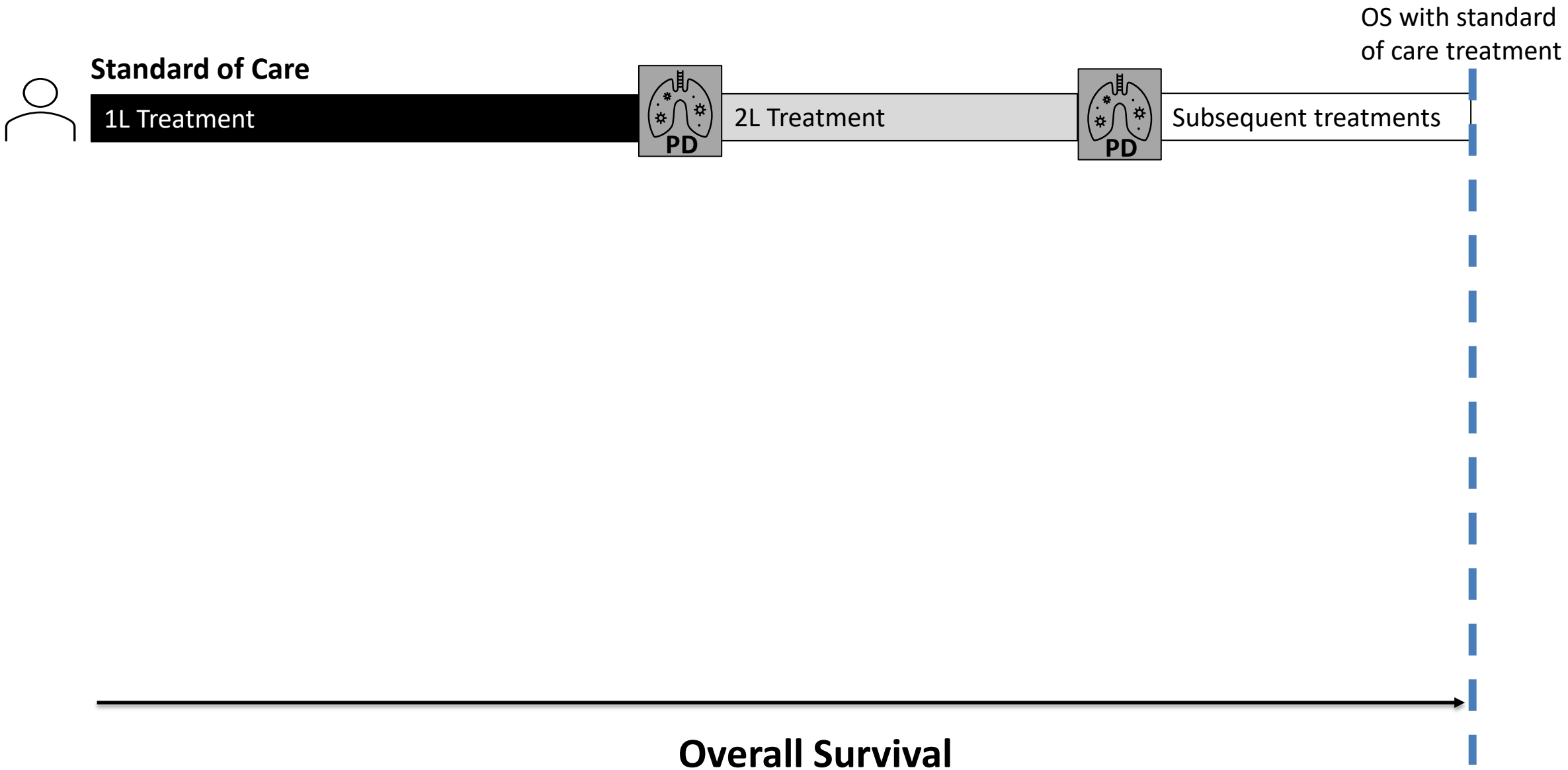
- Camizestrant associated with bradycardia and QT interval prolongation, which both have proarrhythmic risk

- Risk of life-threatening arrhythmia when combined with other QT prolonging drugs
  - Ribociclib, one CDK4/6 inhibitor on SERENA-6, has known QT prolonging effects
  - Emerging as preferred CDK4/6 inhibitor option

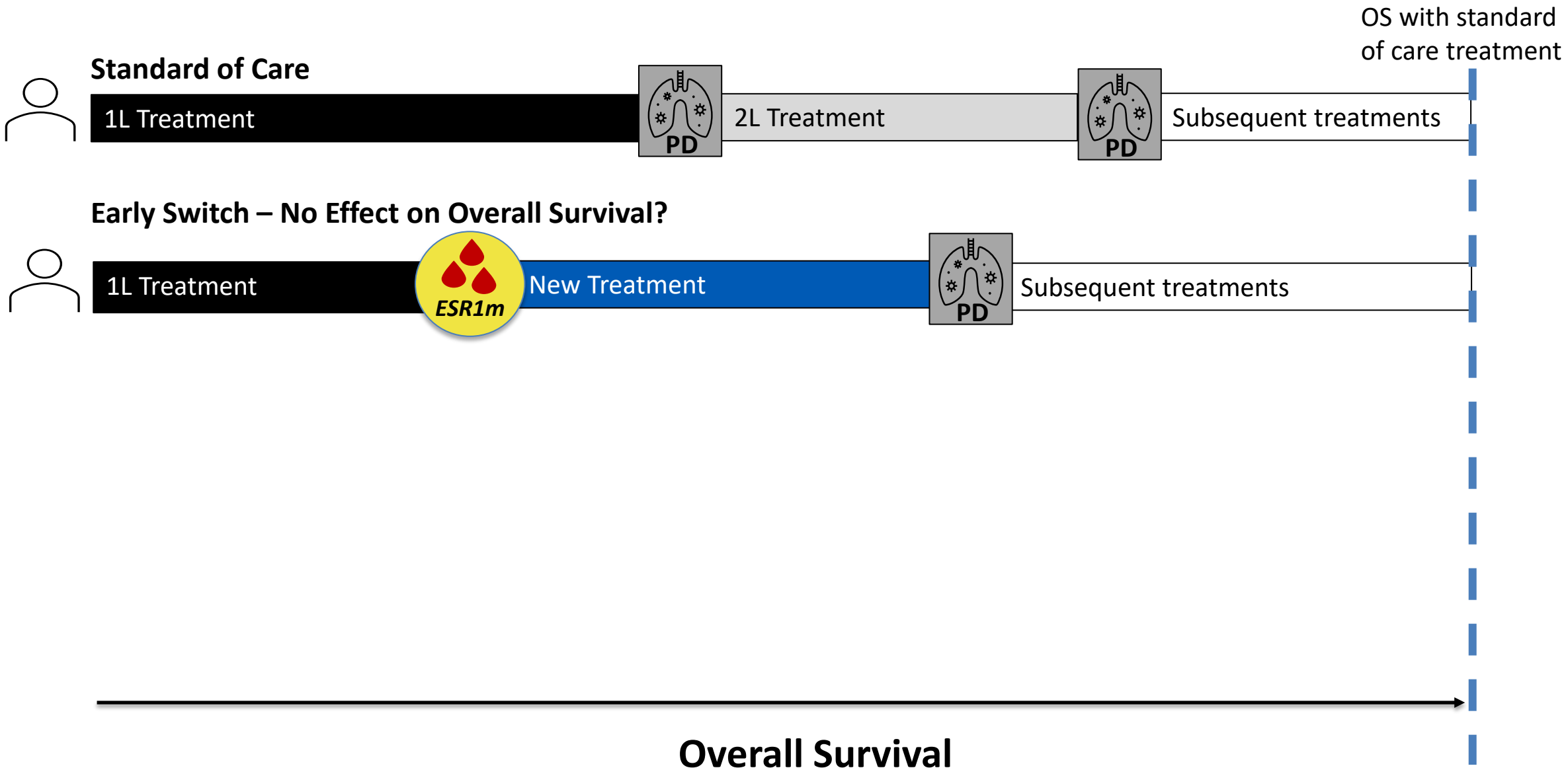
- One patient in SERENA-1 received camizestrant and ribociclib and experienced Torsades de Pointes requiring defibrillation
  - Limited safety database for camizestrant and ribociclib combination

- Patients may be accepting a serious risk to receive a treatment with uncertain clinical benefit

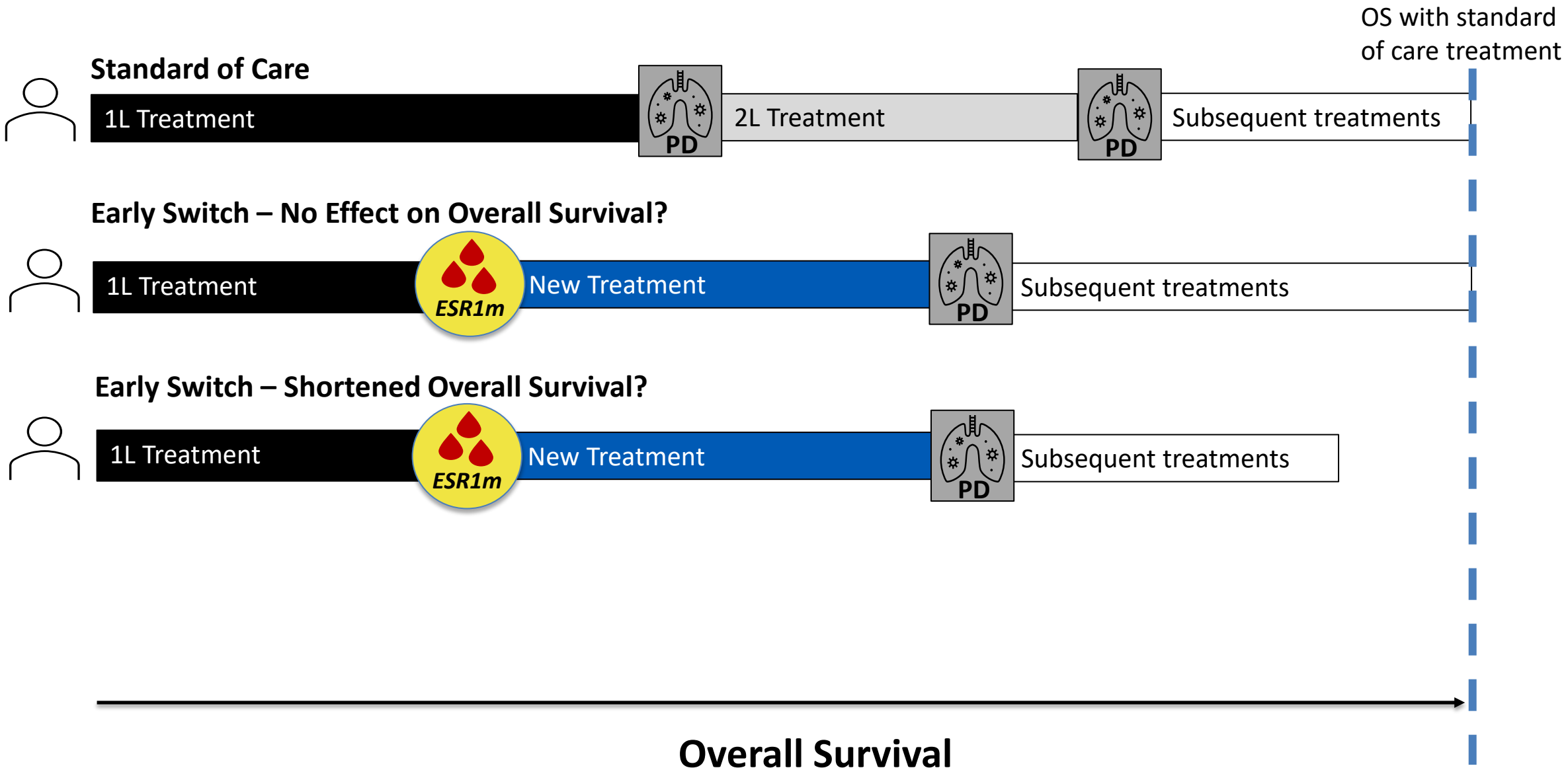
Long-Term Effect of Early Switch Approach is Unknown



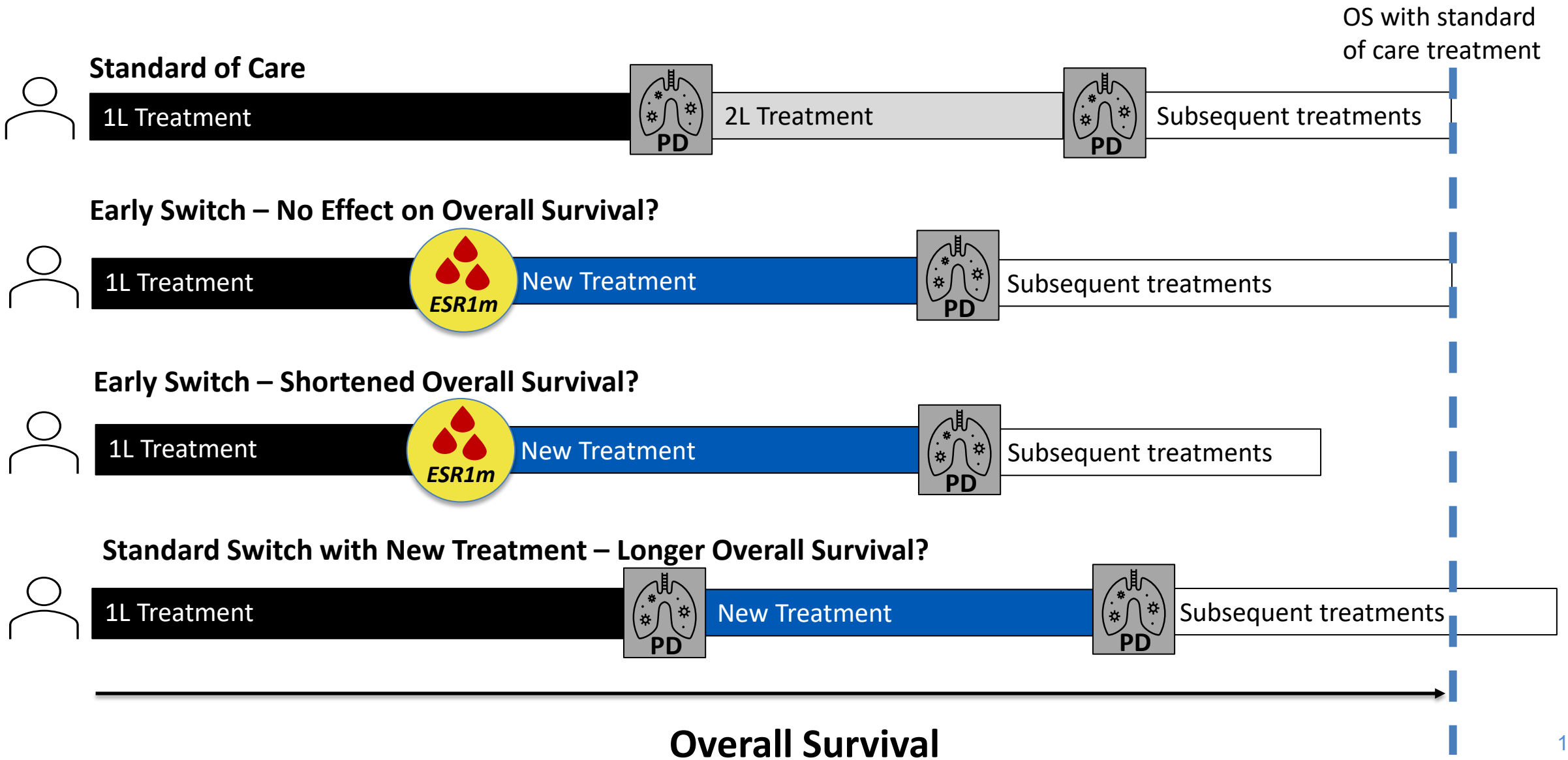
Long-Term Effect of Early Switch Approach is Unknown



Long-Term Effect of Early Switch Approach is Unknown

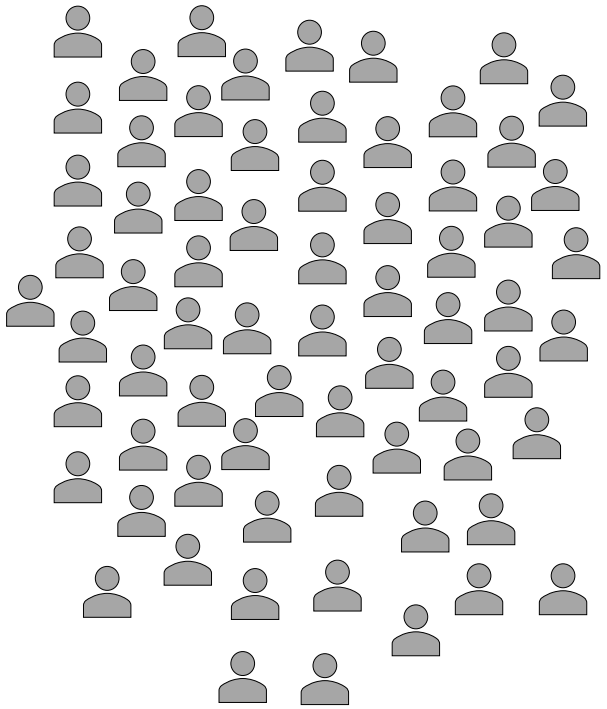


Long-Term Effect of Early Switch Approach is Unknown

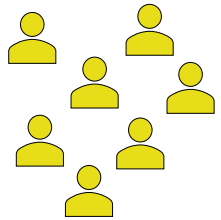


Many Patients Tested, Few Patients Treated, Uncertain Clinical Benefit

SERENA-6 Step 1
3325 Patients



SERENA-6 Step 2
315 Patients



Clinical Benefit

?

Future Implications

- Early switch approach (at *ESR1*m detection) adopted into breast cancer clinical practice and future trials without knowing if patients will have long-term benefit or live longer

- Future trials may introduce therapies with more toxicity earlier into metastatic breast cancer treatment

- Other cancer types may implement an early switch approach at detection of a resistance mutation without evidence of long-term benefit or longer life

Regulatory Considerations

- FDA supports innovative strategies to improve long-term outcomes for patients with metastatic breast cancer

- Ultimately, drug must meet criteria for approval[1,2]
  - Demonstrate benefit that is clinically meaningful
  - Benefit outweighs risks for indicated population

[1]Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products
[2]Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Summary of Issues

- Unknown if switching treatment at *ESR1*m detection prior to radiographic progression improves long-term outcomes for patients
- Clinical meaningfulness of a PFS improvement measured from *ESR1*m detection is uncertain
- PFS2 is inadequate to show evidence of clinical benefit
- Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

Voting Question

Based on the results of SERENA-6, has clinically meaningful benefit for camizestrant been demonstrated for the treatment of patients with HR+/HER2- metastatic breast cancer with a tumor *ESR1* mutation detected while on aromatase inhibitor and CDK4/6 inhibitor treatment, prior to radiographic progression?

U.S. FOOD & DRUG ADMINISTRATION

NDA 220359
Camizestrant

FDA Presentation
Oncology Drugs Advisory Committee

April 30, 2026

Joshua Donaldson, MD, PhD
Clinical Reviewer
Division of Oncology I
Office of Oncologic Diseases

FDA Review Team

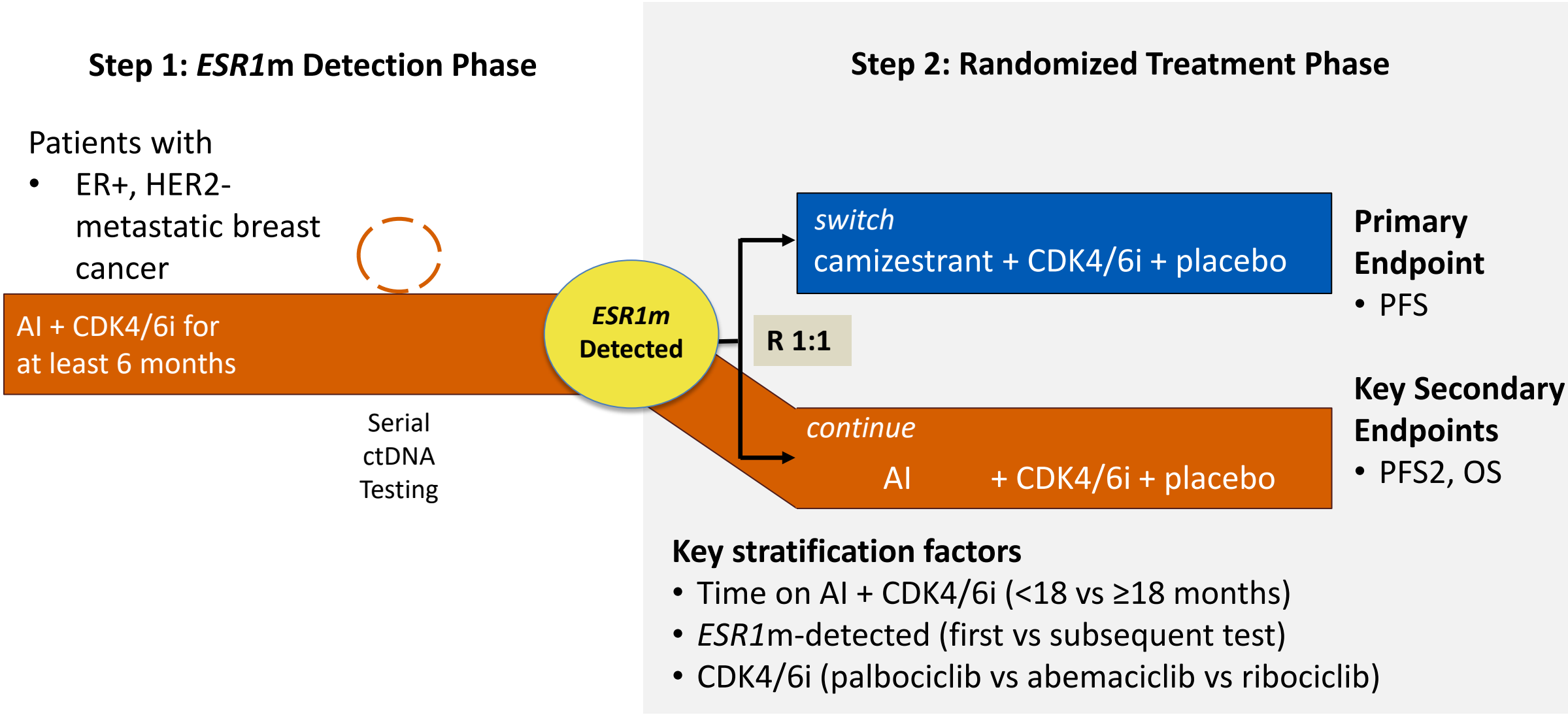
- Angelo DeClaro, Acting Director, Oncology Center of Excellence (OCE)
- Laleh Amiri-Kordestani, Director, Division of Oncology 1 (DO1)
- Mirat Shah, Cross Disciplinary Team Leader, DO1
- Joshua Donaldson, Clinical Reviewer, DO1
- Suparna Wedam, Clinical Reviewer, DO1
- Shenghui Tang, Division Director, Division of Biometrics V (DBV)
- Mallorie Fiero, Supervisory Mathematical Statistician, DBV
- Joyce Cheng, Statistical Team Lead, DBV
- Daeyoung Lim, Statistical Reviewer, DBV
- Saahithi Rao, Statistical Analyst, Division of Analytics and Informatics
- Nam Atiqur (Atik) Rahman, Division Director, Division of Cancer Pharmacology II (DCPII)
- Lauren Price, Clinical Pharmacology Team Lead, DCPII
- Lily Leu, Clinical Pharmacology Reviewer, DCPII
- Jingyu (Jerry) Yu, Pharmacometrics Team Lead, Division of Pharmacometrics (DPM)
- Frank Fang Li, Pharmacometrics Reviewer, DPM
- Tien Truong, Genomics Reviewer, Division of Translational and Precision Medicine (DTPM)
- Jeffrey Kraft, Genomics Team Lead, DTPM
- Ying-Hong Wang, PBPK Reviewer, DPM
- Yuching Yang, PBPK Team Lead, DPM
- Nikolett Biel, Nonclinical Team Lead, Division of Hematology Oncology Toxicology (DHOT)
- Durga Tripathi, Nonclinical reviewer, DHOT
- Haw-Jyh Chiu, Nonclinical reviewer DHOT
- Sso Hyeun Lee, Regulatory Project Manager, DO1
- Vishal Bhatnagar, Associate Director for Patient Outcomes, OCE
- Ilynn Bulatao, Safety Data Analyst, OCE
- Christine Garnett, Associate Director, Cardiac Safety IRT, Division of Cardiology and Nephrology (DCN)
- Jordan Pomeroy, Clinical Team Lead (Acting), DCN
- William M. Boyd, Division Director, Division of Ophthalmology (DO)
- Rhea Lloyd, Deputy Division Director, DO
- Jennifer Hammer, Ophthalmology Reviewer, DO
- Yu Han, Lead Biologist, Center for Devices and Radiological Health (CDRH)
- Liuya Tang, Biologist, CDRH
- Anand Pathak, Physician, CDRH

Applicant's Proposed Indication – *ESR1*m Emergent Population

Camizestrant is indicated in combination with a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer ***upon emergence of ESR1 mutation during first line*** *endocrine based therapy, based on an FDA approved test*

CDK4/6 = cyclin dependent kinases 4 and 6; *ESR1* = estrogen receptor 1 gene; HER2 = human epidermal growth factor receptor 2

SERENA-6 Trial Design



ER = estrogen receptor; AI = aromatase inhibitor; CDK4/6i = CDK4/6 inhibitor; ctDNA = circulating tumor DNA; PFS = progression-free survival; OS = overall survival

Key Regulatory History

- February 3, 2021
  - FDA requested a rationale for *ESR1*m surveillance and therapy switch strategy
- November 4, 2024
  - PFS2 not acceptable as a regulatory endpoint for efficacy for this trial design
- April 4, 2025
  - FDA agreed that an NDA based on SERENA-6 may be submitted
- May 13, 2025
  - Breakthrough therapy designation granted

Summary of SERENA-6 Results

- SERENA-6 met its primary PFS endpoint
- PFS2 was statistically significant
- Current OS data are immature

Uncertain Clinical Benefit for Camizestrant

- The Applicant hypothesizes that
  - Detecting *ESR1*m means no further clinical benefit from first-line AI therapy
  - Switching to another therapy before radiographic progression will benefit patients

- The FDA seeks substantial evidence that
  - Switching at *ESR1*m detection provides a clinical benefit
  - The risk-benefit is favorable for patients that are intended to be treated with camizestrant

Key Issues

Efficacy

1. Trial was not designed to assess the benefit of early switching to camizestrant at *ESR1* mutation detection rather than at radiographic progression
2. Clinical meaningfulness of a PFS improvement measured from *ESR1*m detection is uncertain
3. PFS2 is not adequate to demonstrate clinical benefit
4. Current OS data are immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

Safety

Cardiac Risk: bradycardia and QTc prolongation

Presentation Outline

- Key Efficacy Issues
  - Trial did not assess the benefit of switching at *ESR1*m detection
  - Clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection
- Key Safety Issue
  - Cardiac Risk: bradycardia and QTc prolongation
- Considerations for Committee and Voting Question

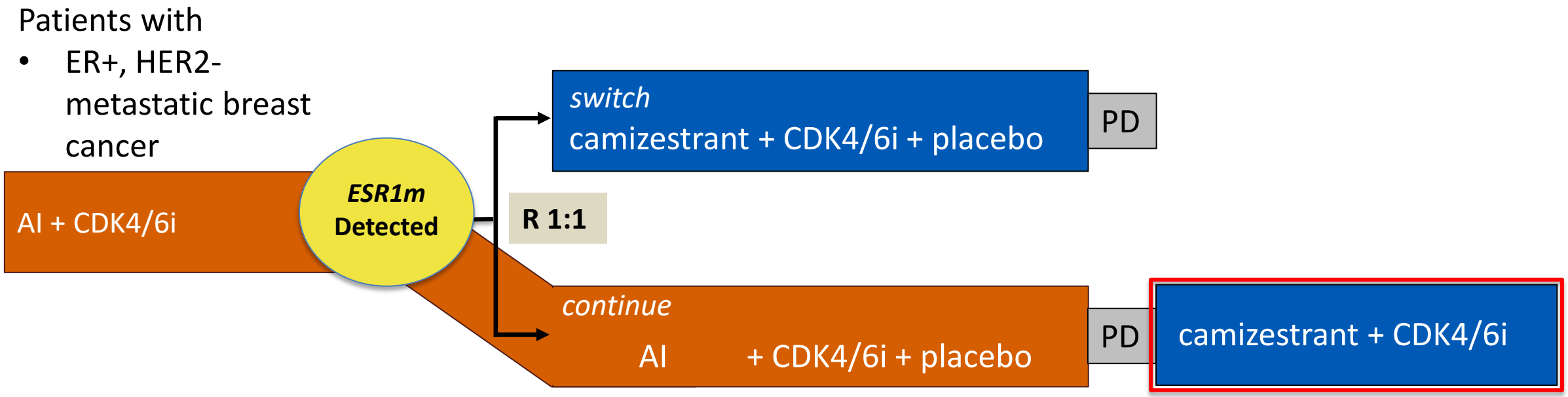
Key Issues

- Efficacy
  - Trial did not assess the benefit of switching at *ESR1*m detection
  - Clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

Switching Therapy Strategy at *ESR1*m Detection Was Not Evaluated

- SERENA-6 was not designed to demonstrate the benefit of the experimental strategy
  - It **did not evaluate** whether switching at *ESR1*m detection provides a clinical benefit compared to switching at radiographic progression
  - Although patients on both arms had detectable *ESR1*m, **the protocol did not specify that patients on the control arm receive therapy to target *ESR1*m** at radiographic progression

Switching Therapy Strategy at *ESR1*m Detection Was Not Evaluated



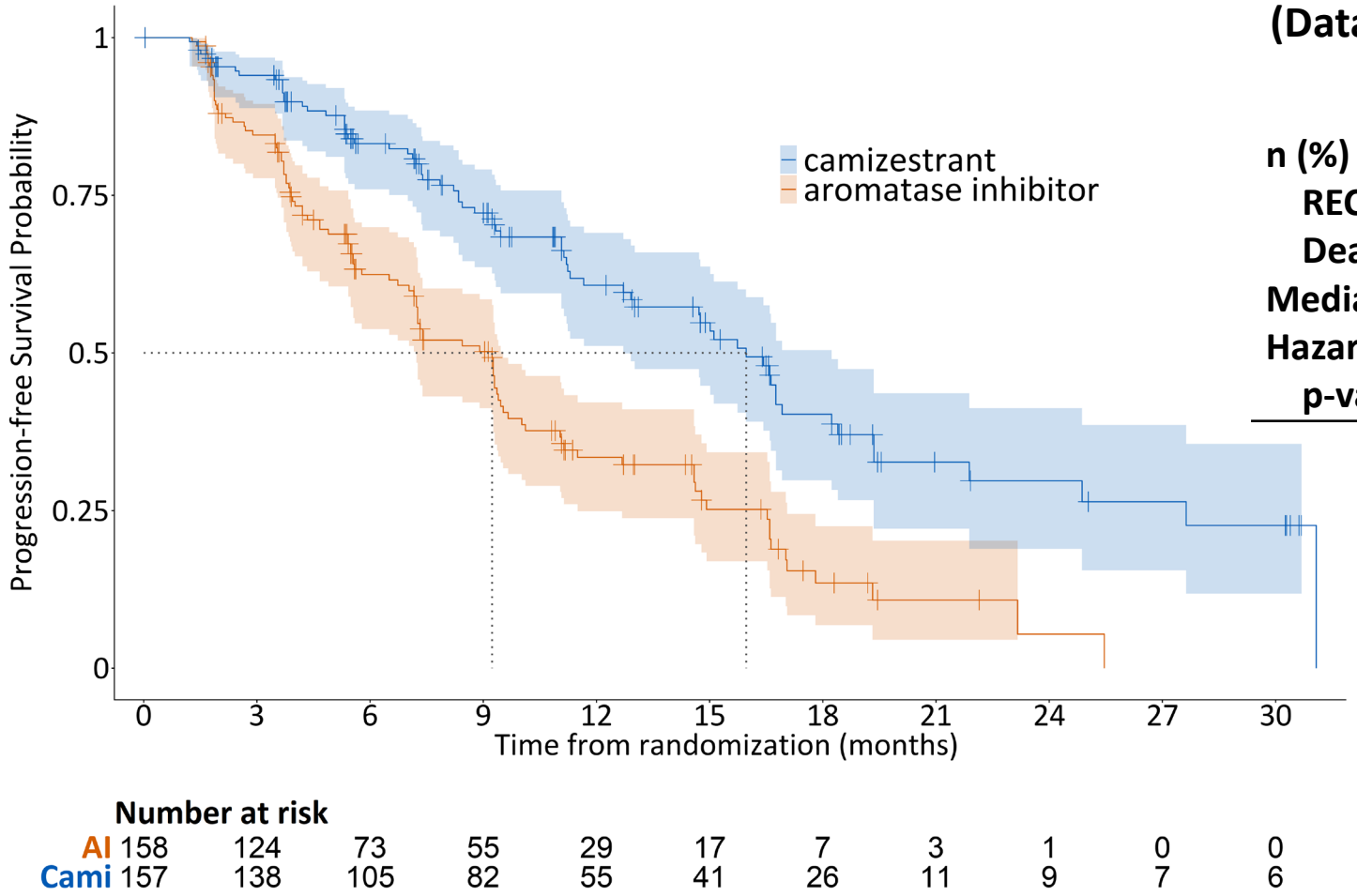
- Trial design does not evaluate whether switching therapy at *ESR1*m detection is better than at radiographic progression

PD = progression of disease

Key Issues

- Efficacy
  - Trial did not assess the benefit of switching at *ESR1*m detection
  - Clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

PFS per Investigator

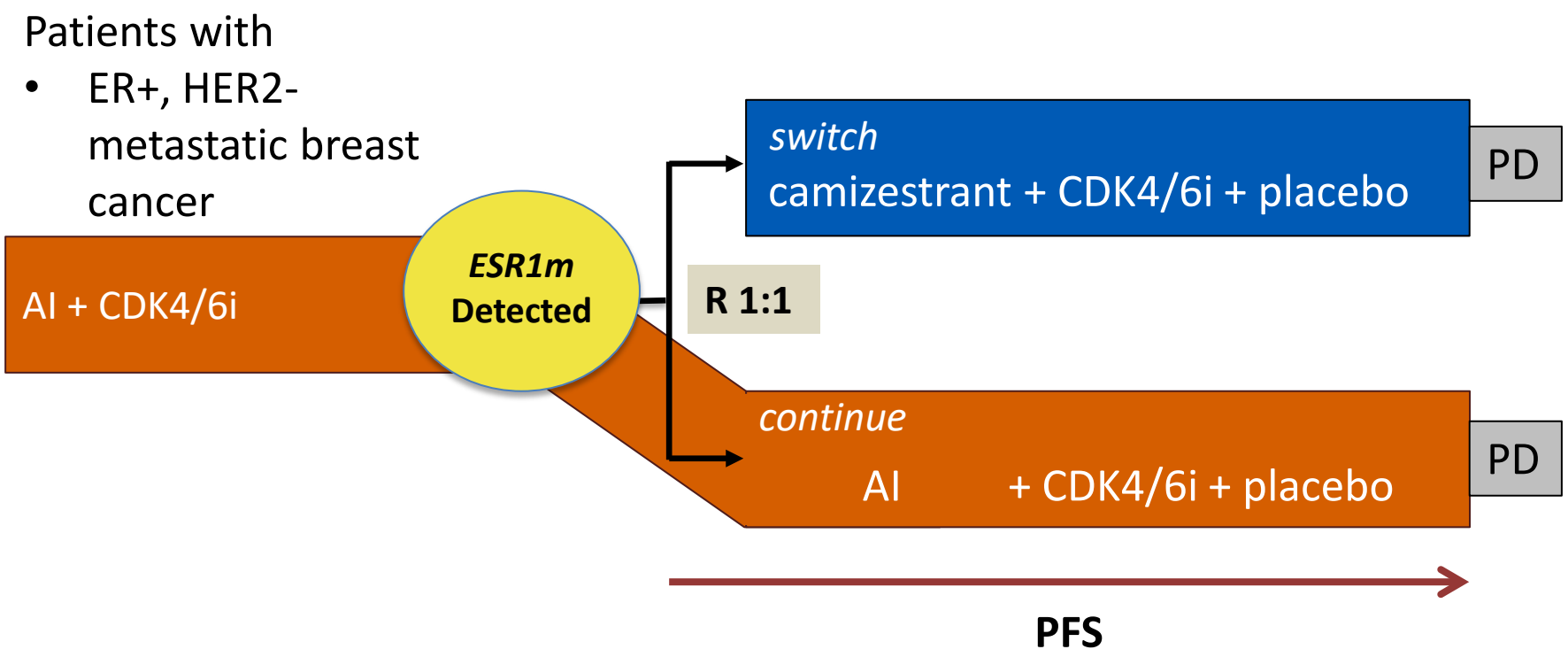


(Data Cutoff 1)	camizestrant+CDK 4/6i N = 157	AI+CDK4/6i N = 158
n (%)	71 (45.2)	100 (63.3)
RECIST Progression	66 (42.0)	99 (62.7)
Death	5 (3.2)	1 (0.6)
Median in months (95% CI)	16.0 (12.7, 18.2)	9.2 (7.2, 9.5)
Hazard Ratio (95% CI)	0.44 (0.31, 0.60)	
p-value	< 0.00001	

Traditional Start Time for Subsequent Therapies

- Starts at **radiographic progression**
  - May **maximize the benefit** of each therapeutic regimen
  - Provides clear evidence that a patient is **not benefiting** from their current therapy
  - Creates a more **uniform** patient population

Clinical Meaningfulness of PFS Improvement From *ESR1*m Detection is Uncertain



- Randomization is at *ESR1*m detection rather than after PD on previous line of therapy
- Clinical meaningfulness of the PFS improvement is uncertain

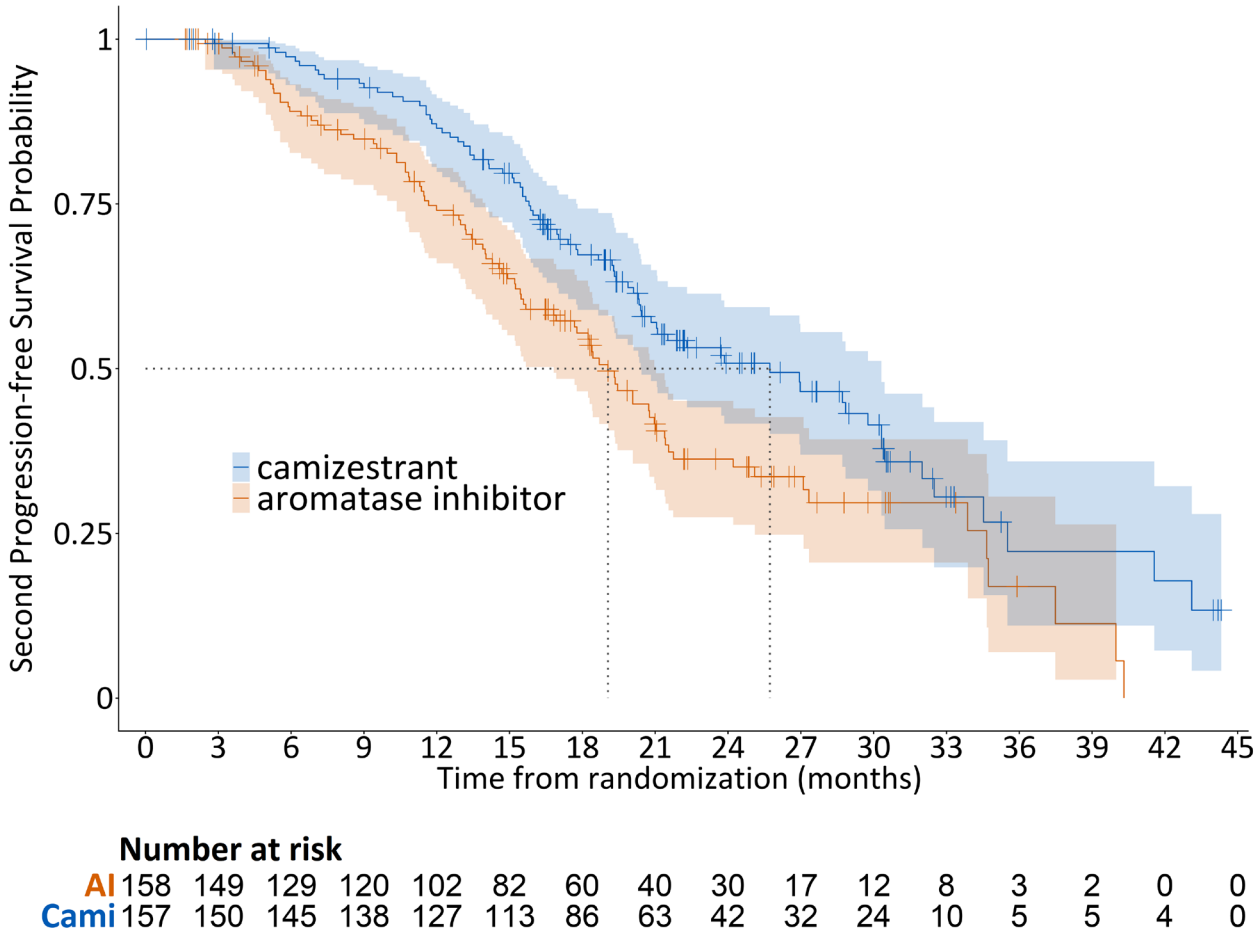
Concerns with PFS and Trial Design

- Seeking approval for a **new drug** and a **new treatment strategy**
  - Trial **not designed to assess the benefit of switching** to camizestrant at *ESR1*m detection rather than at radiographic disease progression (standard-of-care)
  - The PFS start time is new (starting at the time of *ESR1*m detection); therefore, the **clinical meaningfulness of the PFS improvement is uncertain**
  - **Approval could set new precedent** for trial design

Key Issues

- Efficacy
  - Trial did not assess the benefit of switching at *ESR1*m detection
  - Clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

PFS2



(Data Cutoff 3)	camizestrant+CDK4/6i N = 157	AI+CDK4/6i N = 158
n[1] (%)	80 (51.0)	90 (57.0)
Median in months	25.7	19.1
(95% CI)	(20.4, 30.3)	(16.8, 21.0)
Hazard Ratio (95% CI)	0.63 (0.46, 0.86)	
p-value	0.00373	

[1] **PFS2 event** included clinical progression, non-RECIST radiographic progression, RECIST progression and death without progression.

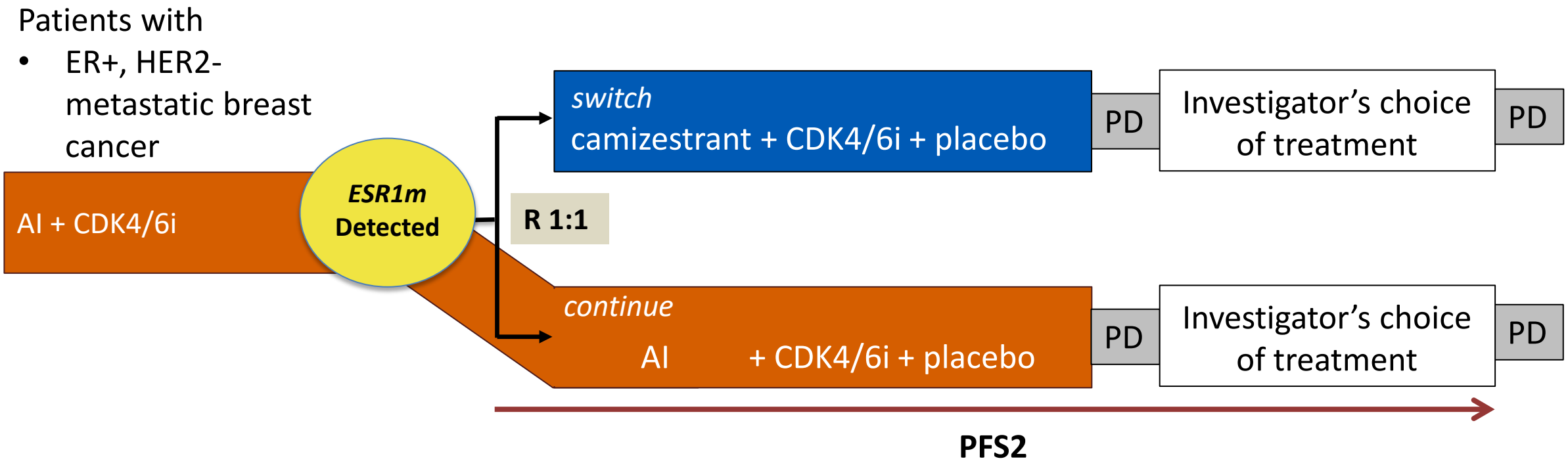
PFS2: Time from randomization (at *ESR1*m detection) to the progression event following the initial progression, or death.

PFS2 Limitations

- PFS2 does **not isolate the effect of the drug**
- Timing and choice of subsequent therapy were left to the investigator's discretion which **creates heterogeneity**
  - Selection of therapy is affected by regional availability and local standards
  - Relatively few patients received an oral estrogen receptor antagonist
- Investigators assessed PFS2 by clinical progression, non-RECIST radiographic progression, and RECIST **introducing variability**
- PFS2 is unable to demonstrate the **clinical benefit of the experimental strategy** of giving a new therapy at *ESR1*m detection

RECIST = Response Evaluation Criteria in Solid Tumors

PFS2 Does Not Evaluate the Switching Therapy Strategy at *ESR1*m Detection



- PFS2 does **not allow assessment of the experimental strategy** of receiving a new therapy at *ESR1*m detection

Subsequent Therapies

	camizestrant + CDK4/6i %	aromatase inhibitor + CDK4/6i %
Hormone Therapy	55	67
Oral ER antagonists	2.2	13
Chemotherapy/ADC	44	31
ADC	2.3	9

- Oral ER antagonists were rarely given as subsequent therapy despite all patients demonstrating a detectable *ESR1*m

Source: ODAC Briefing Document, Applicant Table 6

Chemotherapy/ADC-free Survival Limitations

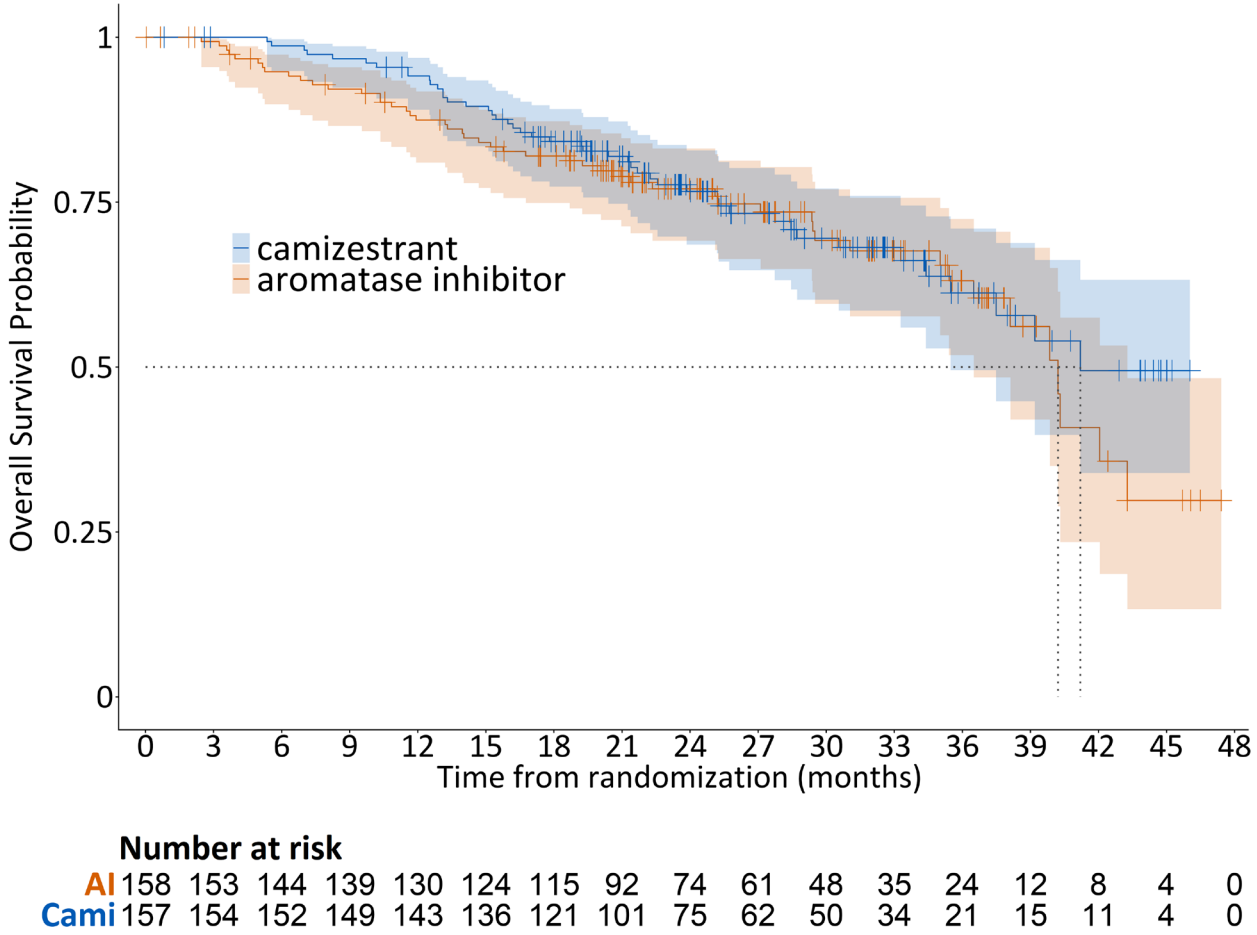
- Chemotherapy/ADC-free Survival
  - Initiating chemotherapy or ADC reflects clinical considerations rather than a direct assessment of disease status
  - Not reliable as a measure of clinical benefit because of lack of prespecification of subsequent therapy and heterogeneity of practice patterns
  - Does not isolate the effect of the drug
  - Compounds the uncertainties seen with PFS2 since it incorporates multiple subsequent therapies

ADC = antibody-drug conjugate

Key Issues

- Efficacy
  - Trial did not assess the benefit of switching at *ESR1*m detection
  - Clinical meaningfulness of the PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, underpowered, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection

Overall Survival (58% Information Fraction)



(Data Cutoff 3)	camizestrant+CDK4/6i N = 157	AI+CDK4/6i N = 158
n (%)	46 (29.3)	49 (31.0)
Median in months (95% CI)	41.2 (35.5, NC)	40.2 (36.5, 43.3)
Hazard Ratio (95% CI)	0.9 (0.6, 1.3)	
p-value	0.48777	

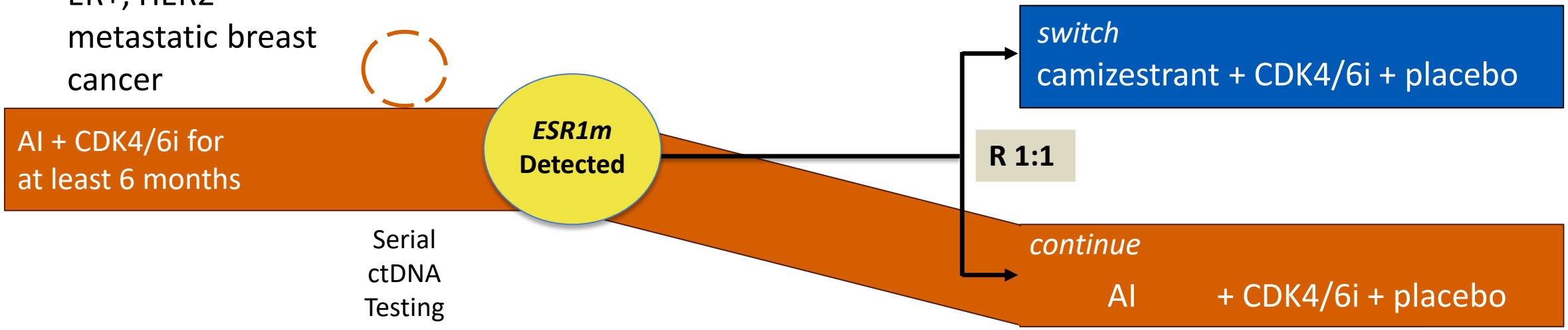
Overall Survival

- Cannot use OS to overcome uncertainties with PFS (and PFS2)
  - The data is currently **immature** (DCO3: 58% IF)
  - The trial **may not reach statistical significance** for OS (63% target power at final analysis – anticipated in 2028)
  - Multiple subsequent therapies and improved baseline survival make it **difficult to demonstrate an OS benefit** in ER+, HER2- MBC

IF = information fraction

Large Number of Patients Needed to be Tested for *ESR1*m

Patients with
- ER+, HER2- metastatic breast cancer



Initial Screening → *ESR1*m Detected → Second Screening → Enrolled to Trial

3325 patients → 521 patients → 406 patients → **315 patients**

Efficacy Summary

- SERENA-6 met its primary endpoint with a (HR 0.44, 95% CI: 0.31, 0.60, $p < 0.00001$) and estimated median PFS of 16.0 vs 9.2 months
- Uncertainty regarding clinical meaningfulness of this PFS result
- PFS2 is not suitable for regulatory decision making
- OS does not currently provide evidence to overcome the limitations of PFS
- Implementation of SERENA-6 would require serial testing of many patients to identify a relatively small number to receive camizestrant

Safety Issues

- Cardiac risk: bradycardia and QTc interval prolongation
- Visual disturbances occurred in 34% of patients
- Common toxicities (≥10%) for camizestrant and CDK4/6 inhibitor included musculoskeletal pain, hematologic toxicities, fatigue, and nausea

Cardiac Risk: Bradycardia and QTc Prolongation

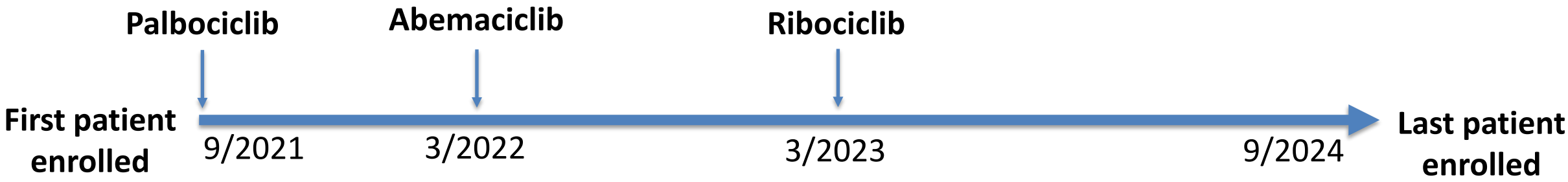
- Camizestrant is associated with dose-dependent bradycardia and QTc interval prolongating effects
  - Heart rate: median decrease of 14 beats/min from baseline in SERENA-6
  - QTc interval: cannot exclude clinically significant increase with data from SERENA-1/6
  - Together they **synergistically increase risk for life-threatening arrhythmias**
- Additive risk in combination with QTc interval prolonging drugs, including ribociclib (mean 20 msec increase per USPI)
- Ribociclib increases exposure of camizestrant ~2-fold, further potentiating the cardiac risk

USPI = U.S. Prescribing Information

Case of Torsades de Pointes

- Patient received camizestrant 75mg + ribociclib 600mg on SERENA-1 (phase 1 trial)
- Patient experienced QTcF > 500 msec (> 60 msec change from baseline) on Day 8
- One week later, patient had a syncopal event followed by ventricular fibrillation
- ECG waveforms reviewed by the FDA clinical cardiology staff confirmed significant QTc interval prolongation, bradycardia, and ultimately Torsades de Pointes (TdP)

Use of Ribociclib and Camizestrant



- Limited safety data for the ribociclib and camizestrant in SERENA-6
  - palbociclib with camizestrant: 118 patients
  - abemaciclib with camizestrant: 15 patients
  - **ribociclib** with camizestrant: **23 patients**
- In trials permitting a choice of CDK4/6 inhibitor, we observe a trend towards physicians preferring ribociclib

Eye Disorders (>2%)

	camizestrant + CDK 4/6i N = 155		AI + CDK 4/6i N = 155	
	All grades %	**Grades 3-4 %**	**All grades %**	**Grades 3-4 %**
Visual disturbances (GT)	34	0.6	16	0
Dry Eye	12	0	2.6	0
Vitreous Floaters	9	0	2.6	0

*Visual disturbances (GT): Diplopia, Photophobia, **Photopsia**, Vision blurred, Visual Field defect, Visual acuity decreased, Visual impairment and visual perseveration*

- Photopsia most common visual disturbance event (20% in camizestrant arm vs 8% in AI arm)
  - Photopsia reported as brief periods (<1 min/episode) of flashing lights
  - Not associated with structural findings on ophthalmic examination

GT = grouped term

Treatment Emergent AEs ≥10%

	camizestrant + CDK4/6i N = 155		AI + CDK4/6i N = 155	
	All grades %	Grades 3-4 %	All grades %	Grades 3-4 %
Patients with TEAEs	94	58	87	46
Musculoskeletal pain (GT)	35	0.6	32	1.3
Visual impairment (GT)	34	0.6	16	0
Neutropenia	29	23	25	17
Fatigue (GT)	23	0	19	0.6
Anemia	17	3.9	17	5
Dry eye	12	0	7	0
Nausea	10	0	14	0.6

Musculoskeletal pain (GT): Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, and Spinal pain; Visual impairment (GT): Diplopia, Photophobia, Photopsia, Vision blurred, Visual Field defect, Visual acuity decreased Visual impairment and visual perseveration; Fatigue (GT): Asthenia, and Fatigue; Headache (GT): Headache, Migraine, and Ophthalmic migraine.

AE = adverse event

Concerns Regarding PRO Time to Deterioration (TTD) Results

- **Sparse Assessment Schedule:** PROs were assessed only every 8 weeks after Week 12, making capture of deterioration events challenging

- **Key Issues with TTD Results:**
  - **Low Event Rates:** Deterioration events occurred in less than half of the patients in each trial arm for most PRO domains
  - **Poor Data Quality:** PRO compliance dropped substantially after Week 20

- **TTD PRO Analyses are Generally Unreliable:**
  - As described in the literature (Fiero et al., 2022), use of TTD analyses for PRO data are difficult to interpret due to intercurrent events, potential reversibility of the event, and potential data quality issues

PRO = patient-reported outcome

Further Concerns Regarding PRO Results

- **Questionable Relevance of Baseline Assessment:** PRO baseline at *ESR1m* detection instead of clinical/radiographic progression
- **Marginal Changes from Baseline:**
  - The magnitude of these differences is small and of uncertain clinical meaningfulness
  - E.g., the difference in mean change for physical functioning was less than 3 points on a 100-point scale
- **All PRO-Based Endpoints Were Not Controlled for Multiplicity**

PRO results from SERENA-6 do not demonstrate a benefit in symptoms and functioning for switching to camizestrant prior to radiographic disease progression.

Summary of SERENA-6 Results

- SERENA-6 met its primary PFS endpoint
- PFS2 is not an accepted regulatory efficacy endpoint for this trial design
- Current OS data are immature
- Cardiac Risk: QTc prolongation and bradycardia

FDA Supports Innovation

- HR+/HER2- metastatic breast cancer is an incurable disease and therapies that improve long-term outcomes are needed
- Innovative strategies may provide clinical benefit to patients
- FDA is deeply grateful to patients and caregivers who participate in clinical trials to answer these questions
- Flexibility does not negate the substantial evidence standard

Considerations for Trials Evaluating Treatment-Switch Strategy

- Inclusion of a randomized treatment arm with a prespecified treatment sequence of continued 1L therapy followed by the experimental drug (among other relevant pre-defined 2L regimens) initiated upon radiographic progression

- Evaluation of OS would be important

Consideration for the Committee and Voting Question

Considerations for the Committee

- Uncertainties regarding camizestrant from SERENA-6
  - Unknown if switching at *ESR1*m detection rather than radiographic progression improves long-term outcomes for patients
  - Clinical meaningfulness of a PFS improvement measured from *ESR1*m detection is uncertain
  - PFS2 is not adequate to demonstrate clinical benefit
  - Current OS is immature, may not reach statistical significance, and does not demonstrate long-term benefit of switching treatment at *ESR1*m detection
  - Chemotherapy/ADC-free survival and PROs do not provide evidence of clinical benefit
  - Observed cardiac toxicity in the setting of uncertain clinical benefit

Voting Question

FDA seeks input from the Committee on the following:

Voting Question:

Based on the results of SERENA-6, has clinically meaningful benefit for camizestrant been demonstrated for the treatment of patients with HR+/HER2- metastatic breast cancer with a tumor *ESR1* mutation detected while on aromatase inhibitor and CDK4/6 inhibitor treatment, prior to radiographic progression?