Exploring Current Patterns of Care in the Community: Optimizing the Use of Oral Selective Estrogen Receptor Degraders for HR-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, October 29, 2025

5:00 PM – 6:00 PM ET

Faculty

Rinath M Jeselsohn, MD

Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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Faculty

Rinath M Jeselsohn, MD
Physician
Associate Professor of Medicine
Harvard Medical School
Director for ER+ Translational Discovery Research
Director of Lobular Breast Cancer
Dana-Farber Cancer Institute
Boston, Massachusetts

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Chair, Breast Disease Committee
Sarah Cannon Research Institute
Dallas, Texas

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Commercial Support

This activity is supported by an educational grant from Lilly.

Dr Love — Disclosures

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Dr Jeselsohn — Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Lilly, Pfizer Inc
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Dr O'Shaughnessy — Disclosures

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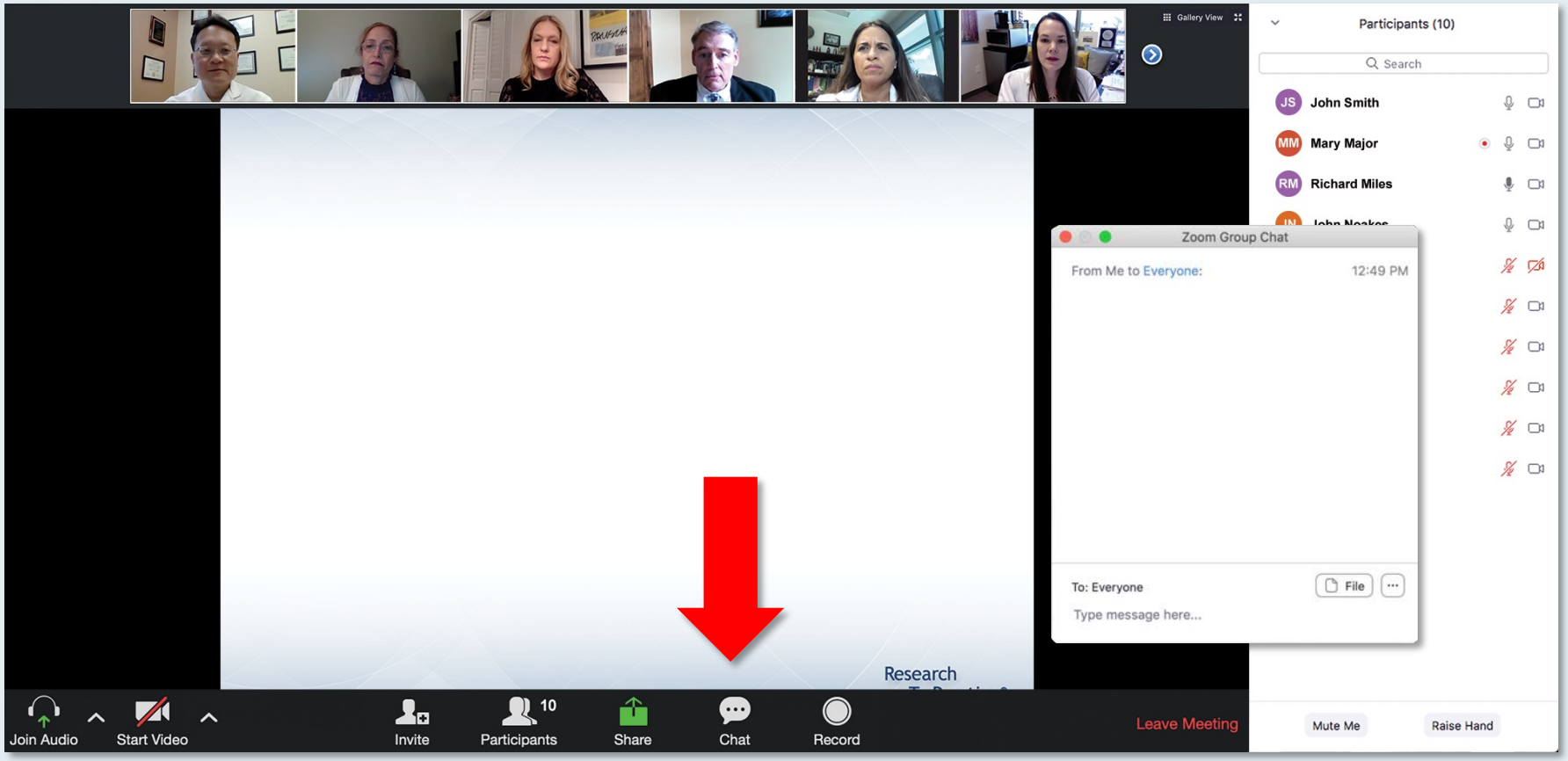

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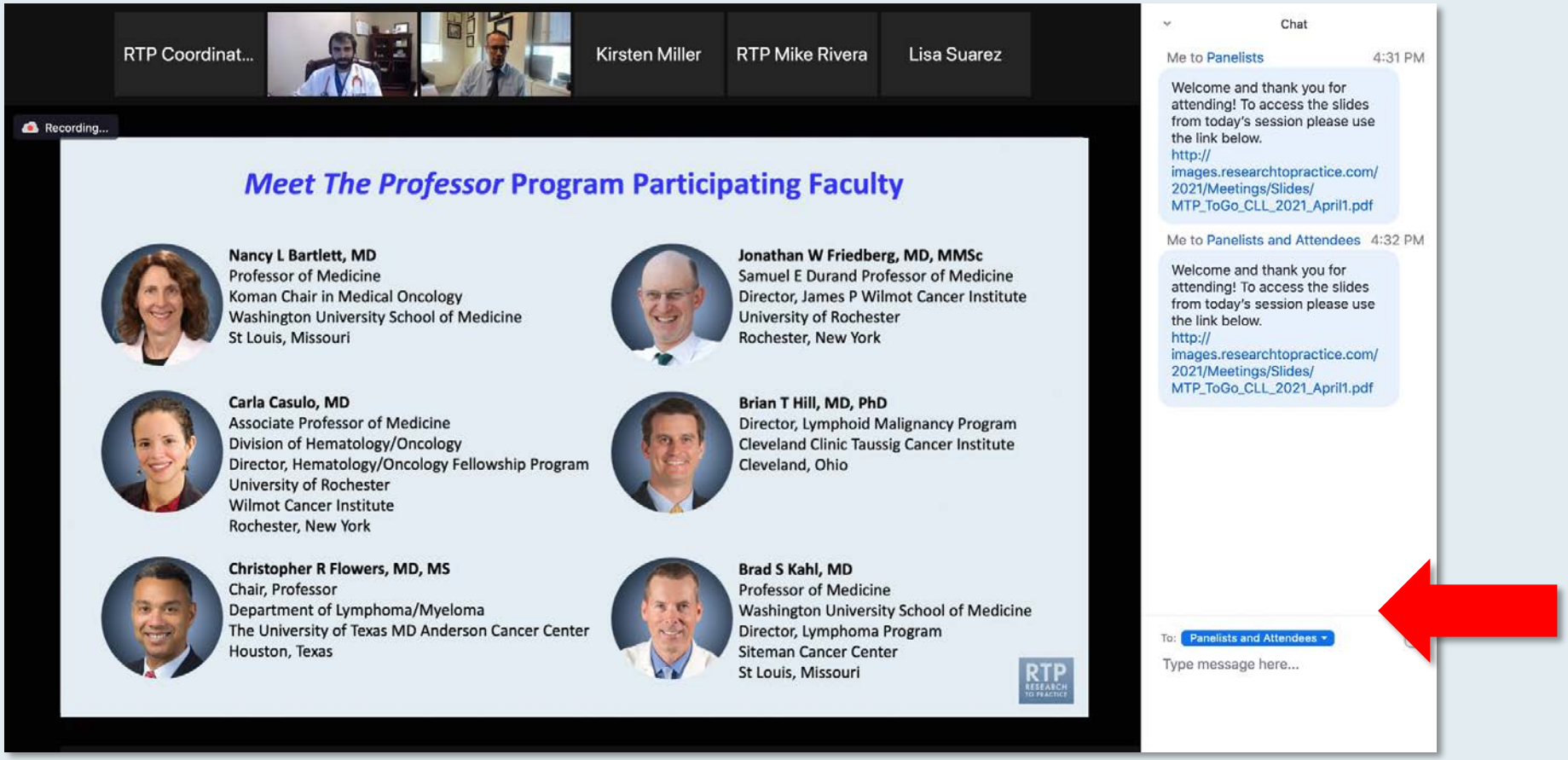

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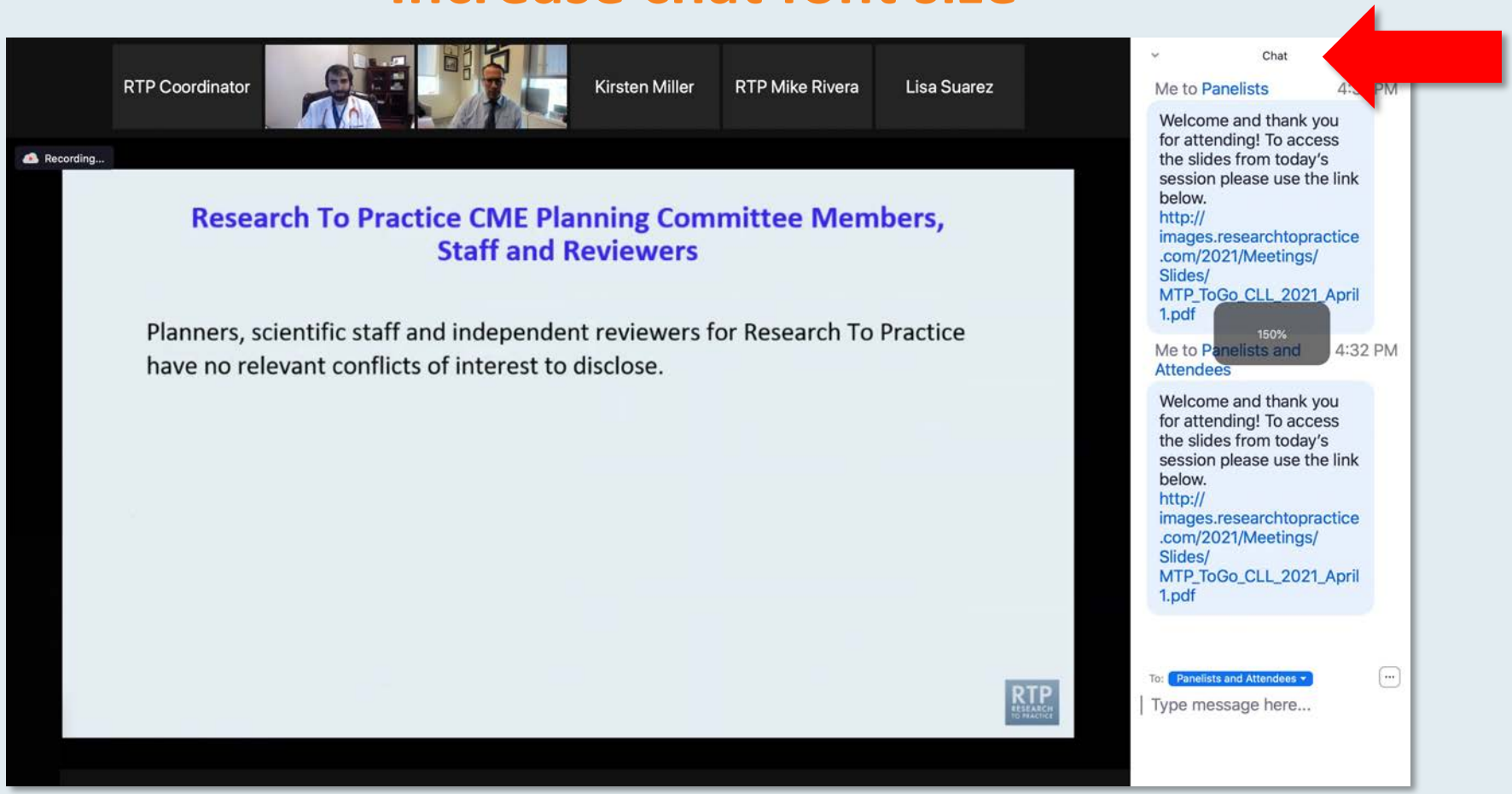

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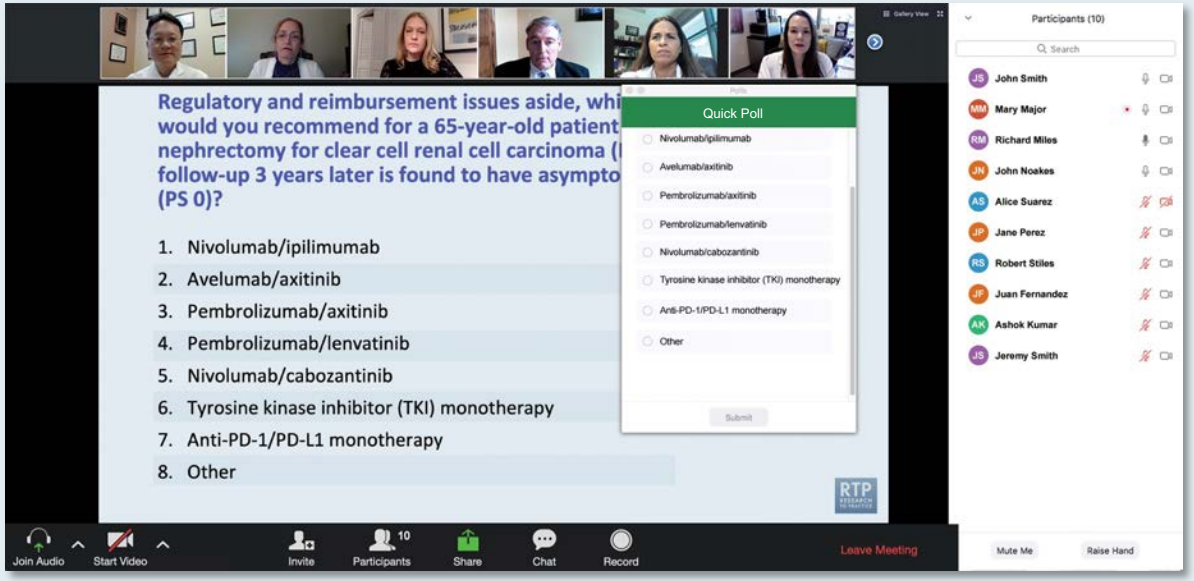

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DR LAURA HUPPERT
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

Saturday, November 8, 2025

Lung Cancer

Faculty

Justin F Gainor, MD

Corey J Langer, MD

Chronic Lymphocytic Leukemia

Faculty

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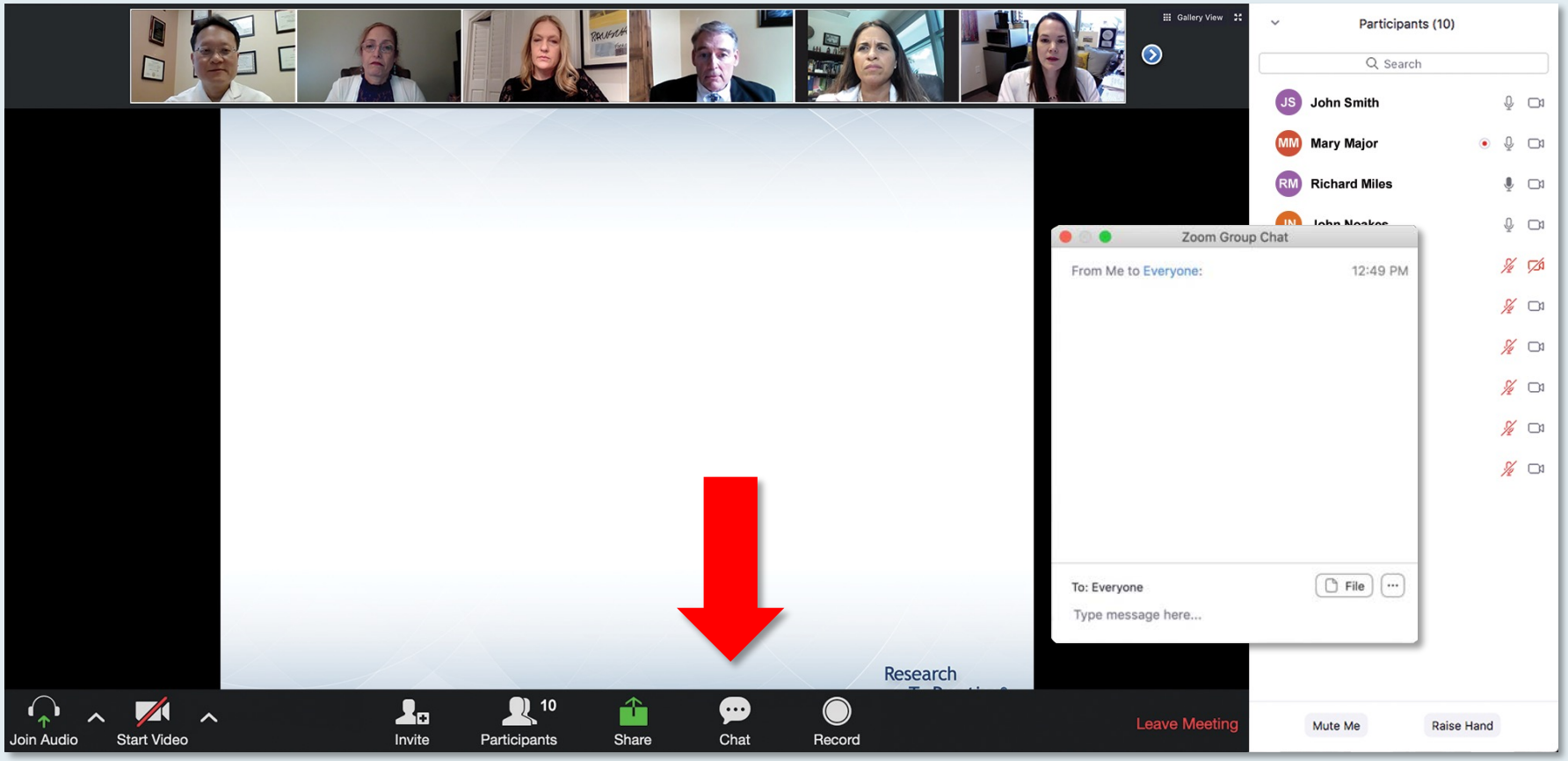

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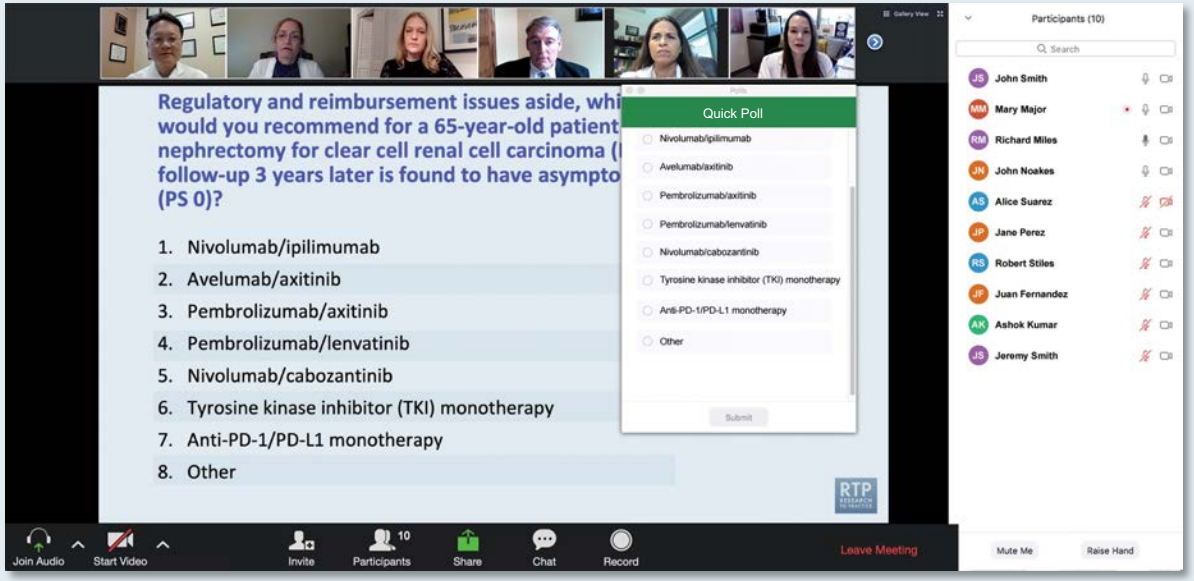

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Dr Jeselsohn — Disclosures

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Module 1: SERD Monotherapy

Module 2: SERD + CDK Inhibitor Combination — EMBER-3

Module 3: SERD for “Molecular Progression” — SERENA-6

Module 4: Other SERD Issues

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Faculty

Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI

Moderator

Neil Love, MD

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ONCOLOGY TODAY: Current and Future Management of HER2-Altered Non-Small Cell Lung Cancer – John V Heymach, MD, PhD

October 27, 2025

Data + Perspectives: Clinical Investigators Discuss the Emerging Role of AKT Inhibitors in the Care of Patients with Prostate Cancer

A CME Satellite Symposium Held in Conjunction with the American Urological Association Annual Meeting 2025 (AUA2025)

Saturday, April 26, 2025

8:00 AM – 9:30 AM PT (11:00 AM – 12:30 PM ET)

Faculty

Leonard G Gomella, MD

Evan Y Yu, MD

Moderator

Daniel George, MD

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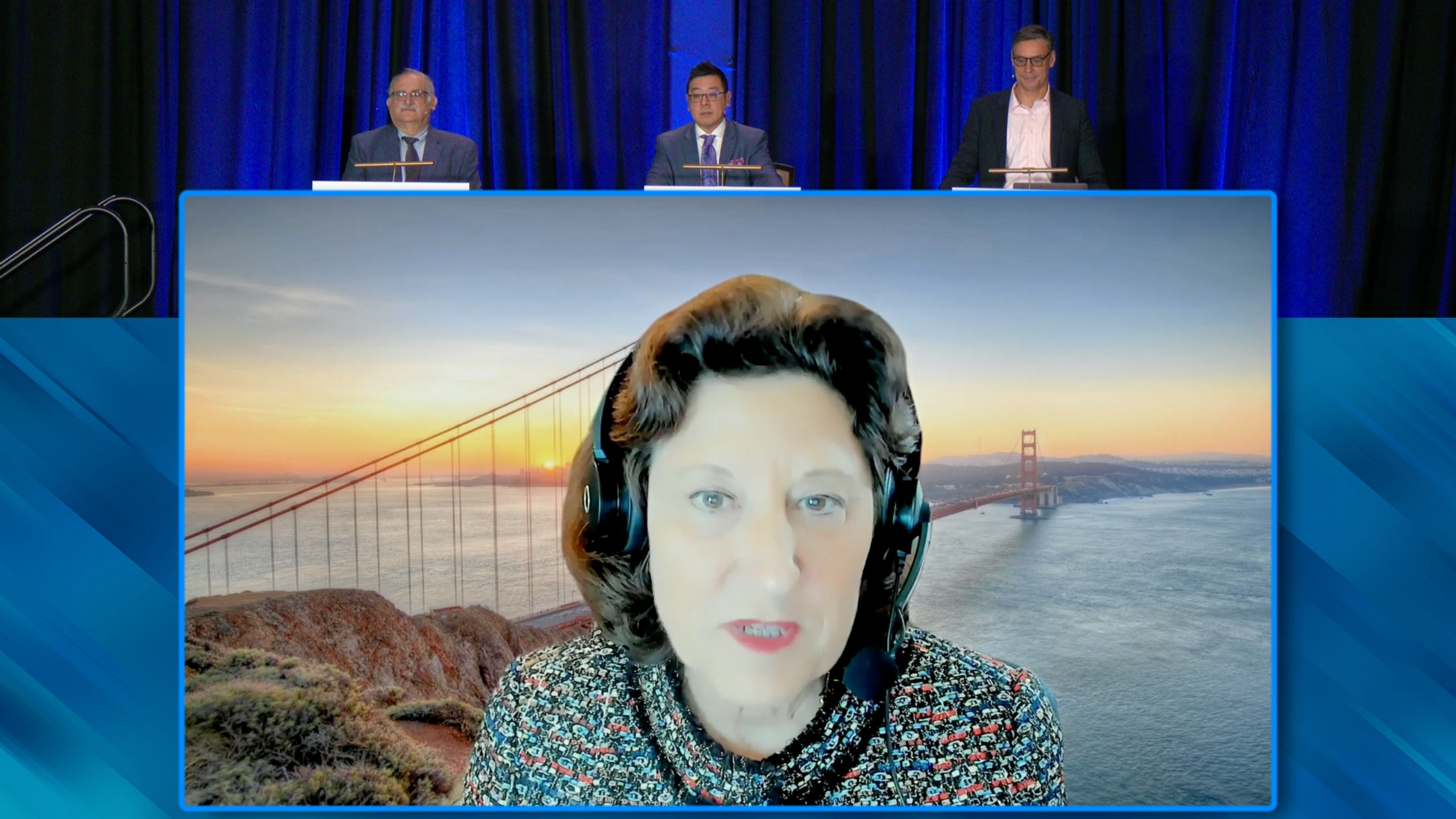


BERLIN 2025 ESMO congress

A Phase 3 study of capivasertib plus abiraterone versus placebo plus abiraterone in patients with PTEN deficient *de novo* metastatic hormone-sensitive prostate cancer: CAPItello-281

Karim Fizazi, Noel W. Clarke, Maria De Santis, Hirotsugu Uemura, Andre Poisl Fay, Nuri Karadurmus, Mariusz Kwiatkowski, Carlos Alvarez-Fernandez, Shusuan Jiang, Miguel Sotelo, Dominique Parslow, Niara Oliveira, Tae Gyun Kwon, Dingwei Ye, Steve Boudewijns, Pongwut Danchaivijitr, Mahmuda Khatun, Marc Yeste-Velasco, Jill Logan, Daniel J. George

Karim Fizazi MD, PhD

Department of Cancer Medicine, Institut Gustave Roussy, Centre Oscar Lambret, University of Paris Saclay, Villejuif, France

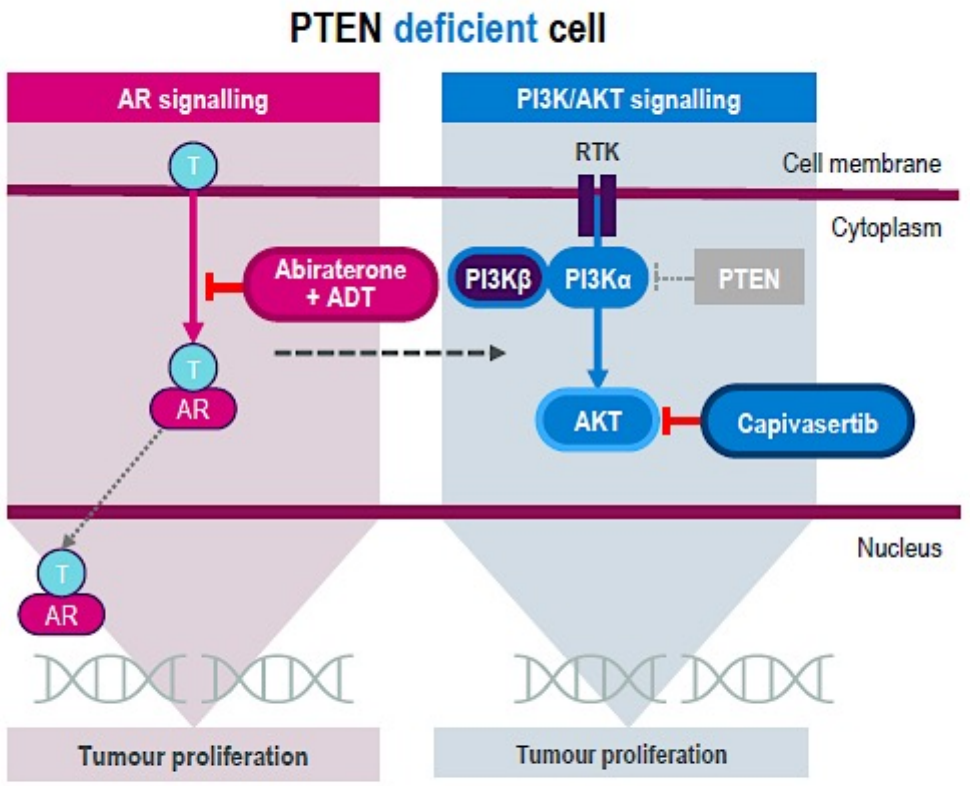
Berlin, Germany
17–21 October

Abstract 2383O

RTP RESEARCH TO PRACTICE

PTEN deficiency in prostate cancer

- In **PTEN-proficient** hormone-sensitive tumour cells, **AR signalling** is the key driver of proliferation[1]
- In PTEN-deficient tumour cells, there is an **additional proliferative drive** from upregulation of the PI3K/AKT pathway, that **complements** and provides an alternative survival mechanism to AR signalling[2]
- **PTEN deficiency** is associated with poor prognosis[2–4]
- **Capivasertib** is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- **Phase 2/3 evidence** showed benefits with ipatasertib (AKTi) plus abiraterone in **PTEN deficient mCRPC**[2,3]



AR, androgen receptor; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; T, testosterone

1. Quistini A, *et al. Res Rep Urol.* 2025;17:211-223; 2. De Bono JS, *et al. Clin Cancer Res* 2019;25:928–936; 3. Sweeney C, *et al. Lancet* 2021;398:131–42; 4. Rathkopf D, *et al. J Clin Oncol* 2025;43:abst 5096. .

Karim Fizazi MD, PhD

Fizazi K et al. ESMO 2025;Abstract 2383O.

CAPItello-281 Study Design

A global, multicentre, randomized, double-blind, Phase 3 study

Patients with PTEN deficient *de novo* mHSPC

- PTEN deficiency: (diagnostic cut-off of **≥90%** of viable malignant cells with **no specific cytoplasmic staining** by IHC)*
  - i.e. ≤10% of cells expressing PTEN by IHC

Of ~6,200 patients submitting tumour tissue **97%** had a valid IHC result and **25%** were **PTEN deficient**

1,012 patients (R 1:1)

Capivasertib	400 mg BID 4 days on, 3 days off
Abiraterone/pred + ADT	1000 mg/5 mg QD + ADT
Placebo	400 mg BID 4 days on, 3 days off
Abiraterone/pred + ADT	1000 mg/5 mg QD + ADT

Primary endpoint

- **Investigator assessed rPFS**

Secondary endpoints

- Overall survival
- Time to first subsequent therapy
- Symptomatic skeletal-event free survival
- Time to pain progression
- Time to castration resistance
- Time to PSA progression

Exploratory *post-hoc* PTEN deficiency subgroups

Stratification factors:†

- M1 volume (CHAARTED criteria) and visceral mets
- Geography

Study timeline

Current analysis

Enrolment period	Primary rPFS DCO	Final OS DCO
13 July 2020–5 Feb 2024	7 Oct 2024 Median rPFS follow-up:‡ ~18 mo	Planned for 522 deaths (52.2% maturity)

NCT04493853. Full eligibility criteria available in the online article. *Determined using investigational antibody for PTEN (SP218) (Roche Diagnostics).
†High-vol. disease with visceral mets, high-vol disease without visceral mets, low-vol. disease; North America; Western Europe and Australia; Latin America and Eastern Europe; Asia. ‡In censored patients.
ADT, androgen deprivation therapy; BID, twice daily; IHC, immunohistochemistry; mHSPC, metastatic hormone-sensitive prostate cancer; pred, prednisone/prednisolone; QD, once daily; rPFS, radiographic progression-free survival

Karim Fizazi MD, PhD

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Fizazi K et al. ESMO 2025;Abstract 2383O.

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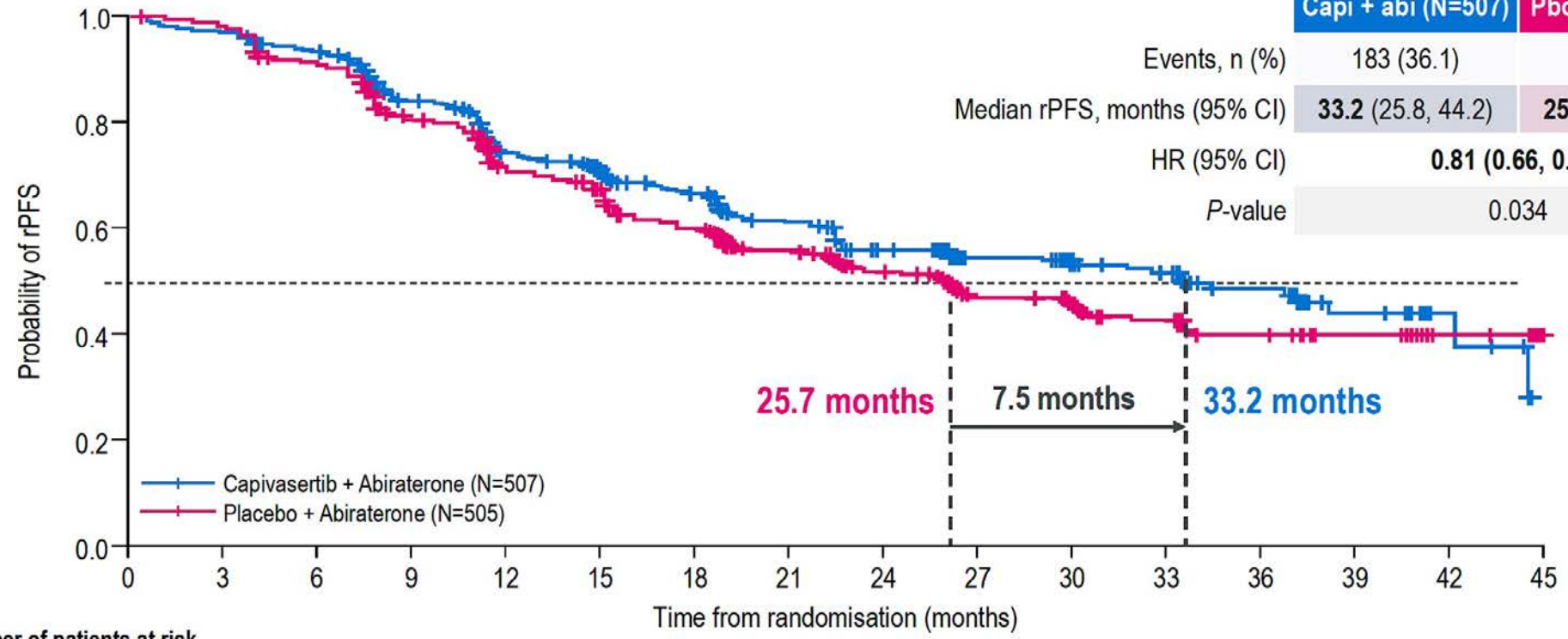
CAPItello-281 Primary endpoint: investigator-assessed rPFS



	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	183 (36.1)	215 (42.6)
Median rPFS, months (95% CI)	**33.2** (25.8, 44.2)	**25.7** (22.0, 29.9)
HR (95% CI)	**0.81 (0.66, 0.98)**	
P-value	0.034	

Number of patients at risk

Capi + abi	507	460	435	353	282	233	217	165	123	93	69	62	41	21	6	0
Pbo + abi	505	479	440	359	276	215	198	154	113	83	59	51	37	23	8	0

A stratified log-rank test was used to calculate two-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model. Median follow-up: 18.4 months (capi + abi), 18.5 months (pbo + abi)
abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; pbo, placebo; rPFS, radiographic progression-free survival

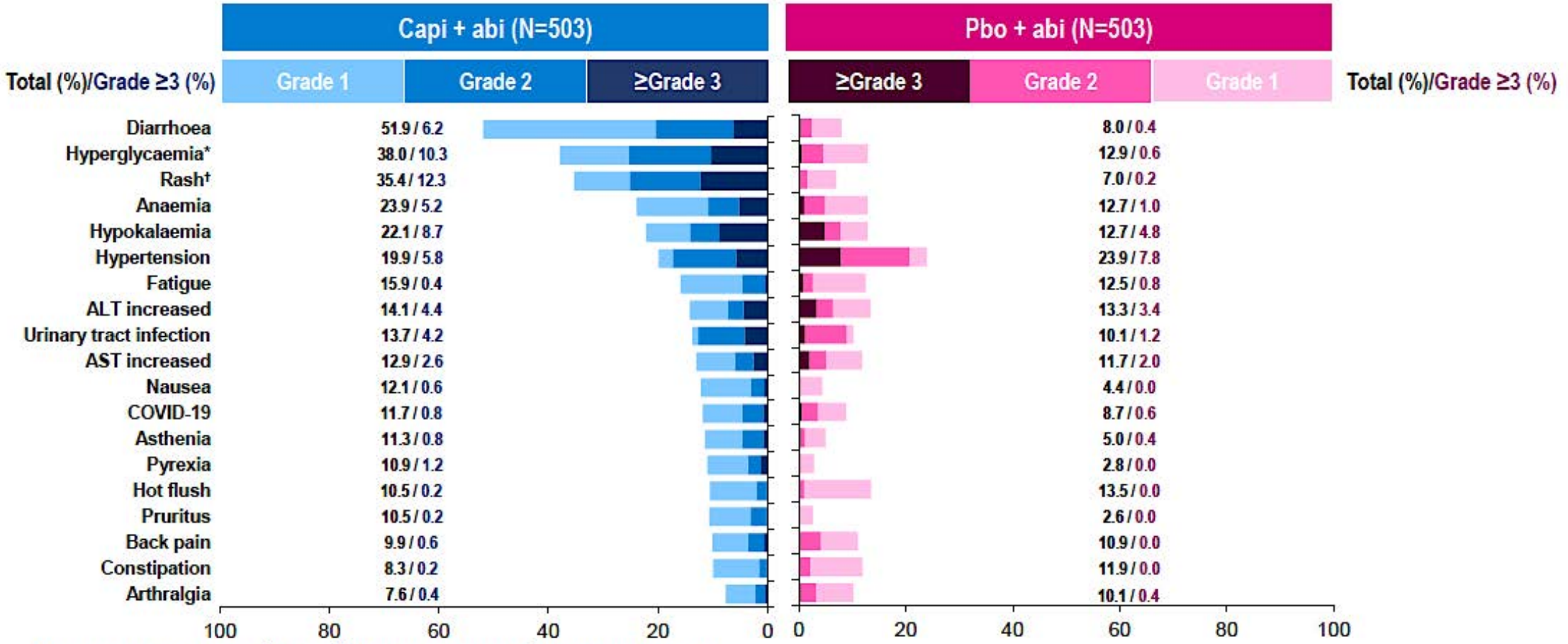
Karim Fizazi MD, PhD

BERLIN 2025 ESMO congress

Fizazi K et al. ESMO 2025;Abstract 2383O.

RTP RESEARCH TO PRACTICE

CAPItello-281: Adverse events (≥10% of patients)



Diabetic ketoacidosis was reported in 6 patients (1.2%) in the capi + abi arm, and 0 patients in the pbo + abi arm.
*Grouped term (includes the preferred terms of blood glucose increased, hyperglycaemia). †Grouped term (includes the preferred terms of erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic).
abi, abiraterone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; capi, capivasertib; pbo, placebo

Karim Fizazi MD, PhD

BERLIN 2025 ESMO congress

Fizazi K et al. ESMO 2025;Abstract 2383O.

RTP RESEARCH TO PRACTICE

CAPItello-281: Conclusions

- Patients with **PTEN deficient mHSPC** have **poor prognosis** and reduced benefit from current SoC
- CAPItello-281 met its primary objective showing a **statistically significant rPFS benefit with capi + abi** vs pbo + abi
  - Median rPFS: capi + abi arm **33.2** months vs pbo + abi **25.7** months (HR 0.81, 95% CI 0.66, 0.98; *P* = 0.034)
- Consistent benefits were also observed in **secondary endpoints** and **clinically relevant pre-defined subgroups**
  - OS was immature and further follow-up is planned
- Post-hoc analyses at **increased PTEN cutoffs** showed **greater treatment effect** with **capi + abi**
- The most common Grade ≥3 AEs of rash and hyperglycaemia are **expected with AKT inhibition**

Capivasertib in combination with abiraterone represents a potential first-in-class targeted treatment for patients with PTEN deficient mHSPC

abi, abiraterone; ADT, androgen deprivation therapy; capi, capivasertib; mHSPC, metastatic hormone-sensitive prostate cancer; pbo, placebo; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival; SoC, standard of care

Karim Fizazi MD, PhD

BERLIN 2025 ESMO congress

Fizazi K et al. ESMO 2025;Abstract 2383O.

RTP RESEARCH TO PRACTICE

Select Clinical Trials in HR-Positive Metastatic Breast Cancer

- **EMERALD: A Phase III trial evaluating elacestrant versus standard endocrine therapy (ET) for ER-positive, HER2-negative advanced breast cancer previously treated with ET, a CDK4/6 inhibitor and chemotherapy**
- **SERENA-6: A Phase III switching trial of camizestrant for ESR1-mutant breast cancer during first-line treatment**
- **EMBER-3: A Phase III trial of imlunestrant with or without abemaciclib for patients with ER-positive, HER2-negative advanced breast cancer who experienced disease progression on or after an aromatase inhibitor (AI) with or without a CDK4/6 inhibitor**
- **SOLAR-1: A Phase III trial of alpelisib with fulvestrant for patients with HR-positive, HER2-negative advanced breast cancer who experienced disease progression on or after AI treatment**
- **CAPItello-291: A Phase III trial of capivasertib with fulvestrant for patients with ER-positive, HER2-negative advanced breast cancer who experienced disease progression on or after an AI with or without a CDK4/6 inhibitor**

RTP RESEARCH TO PRACTICE

- **INAVO120: A Phase III trial of first-line inavolisib with palbociclib and fulvestrant for PIK3CA-mutated ER-positive, HER2-negative endocrine-resistant advanced breast cancer**
- **DESTINY-Breast04: A Phase III trial of trastuzumab deruxtecan for previously treated HER2-low advanced breast cancer**
- **DESTINY-Breast06: A Phase III trial evaluating trastuzumab deruxtecan versus chemotherapy for ER-positive, HER2-low or ultralow advanced breast cancer previously treated with ET**
- **TROPION-Breast01: A Phase III trial evaluating datopotamab deruxtecan versus chemotherapy for previously treated inoperable or metastatic ER-positive, HER2-negative breast cancer**
- **TROPiCS-02: A Phase III trial evaluating sacituzumab govitecan versus treatment of physician's choice for previously treated ER-positive, HER2-negative advanced breast cancer**
- **PATINA: A Phase III trial evaluating palbociclib with anti-HER2 therapy and ET versus anti-HER2 therapy and ET, after induction therapy for ER-positive, HER2-positive metastatic breast cancer**
- **VERITAC-2: A Phase III trial evaluating vepdegestrant versus fulvestrant for ER-positive, HER2-negative advanced breast cancer after treatment with a CDK4/6 inhibitor and ET**

Survey of 50 General Medical Oncologists: Breast Cancer

Survey Dates: 7/22/25 to 7/25/25

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Clinical Investigator Survey Participants

Francois-Clement Bidard, MD, PhD

Virginia F Borges, MD, MMSc

Harold J Burstein, MD, PhD

Lisa A Carey, MD, ScM, FASCO

Professor Giuseppe Curigliano, MD, PhD

Angela DeMichele, MD, MSCE

Matthew P Goetz, MD

Stephanie L Graff, MD, FACP

Sara A Hurvitz, MD, FACP

Virginia Kaklamani, MD, DSc

Kevin Kalinsky, MD, MS, FASCO

Ian E Krop, MD, PhD

Kathy D Miller, MD

Shanu Modi, MD

Ruth O'Regan, MD

Joyce O'Shaughnessy, MD

Hope S Rugo, MD

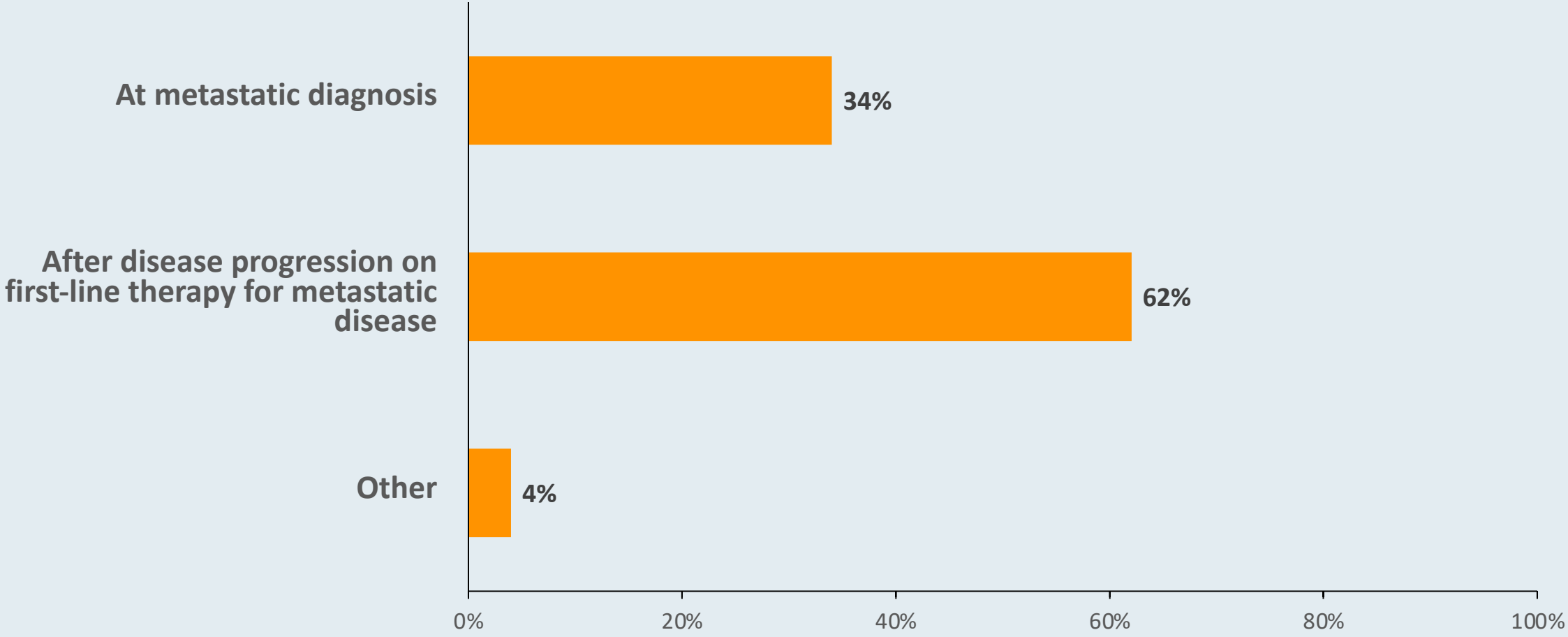
Priyanka Sharma, MD

Rebecca Shatsky, MD

Seth Wander, MD, PhD

RTP RESEARCH TO PRACTICE

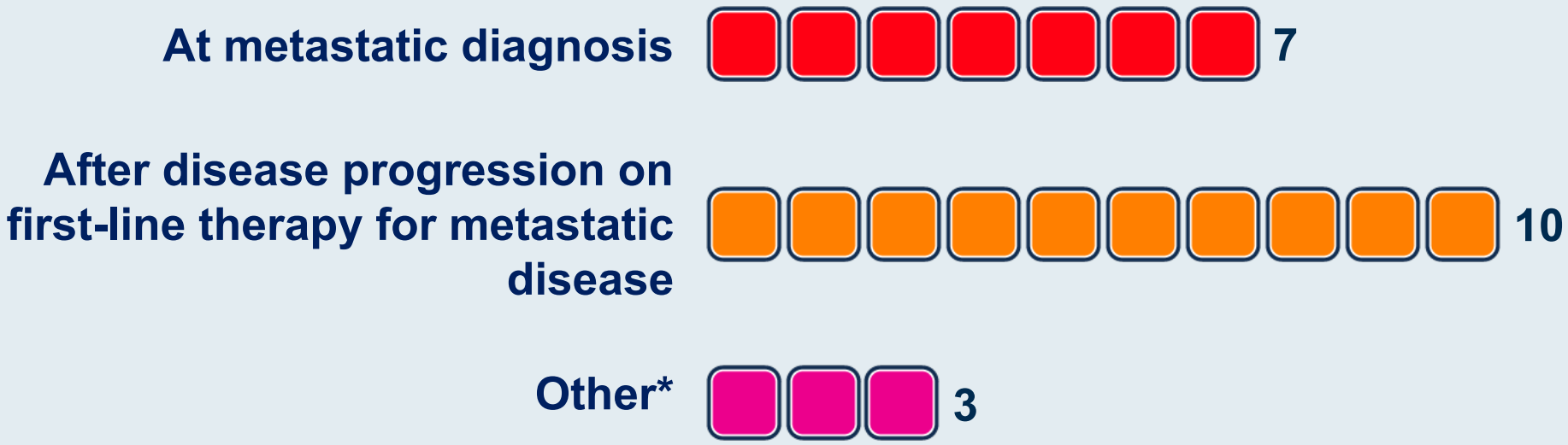
At what point do you typically first assess ESR1 mutation status in your patients with ER-positive, HER2-negative breast cancer?



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

At what point do you typically first assess ESR1 mutation status in your patients with ER-positive, HER2-negative breast cancer?



* Depends on whether they progress on AI (aromatase inhibitor) or not; At metastatic diagnosis if relapsing on or within a year of an AI, otherwise with PD on 1st line and then again on 2nd line therapy if still eligible for ET; After disease progression on second- or later-line therapy for metastatic disease

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

Agenda

Introduction: Oral SERDs for the General Medical Oncologist

Module 1: SERD Monotherapy

Module 2: SERD + CDK Inhibitor Combination — EMBER-3

Module 3: SERD for “Molecular Progression” — SERENA-6

Module 4: Other SERD Issues

Appropriate Identification of Candidates for and Practical Implementation of Oral Selective Estrogen Receptor Degraders (SERDs) for Progressive ER-Positive, HER2-Negative Metastatic Breast Cancer (mBC)

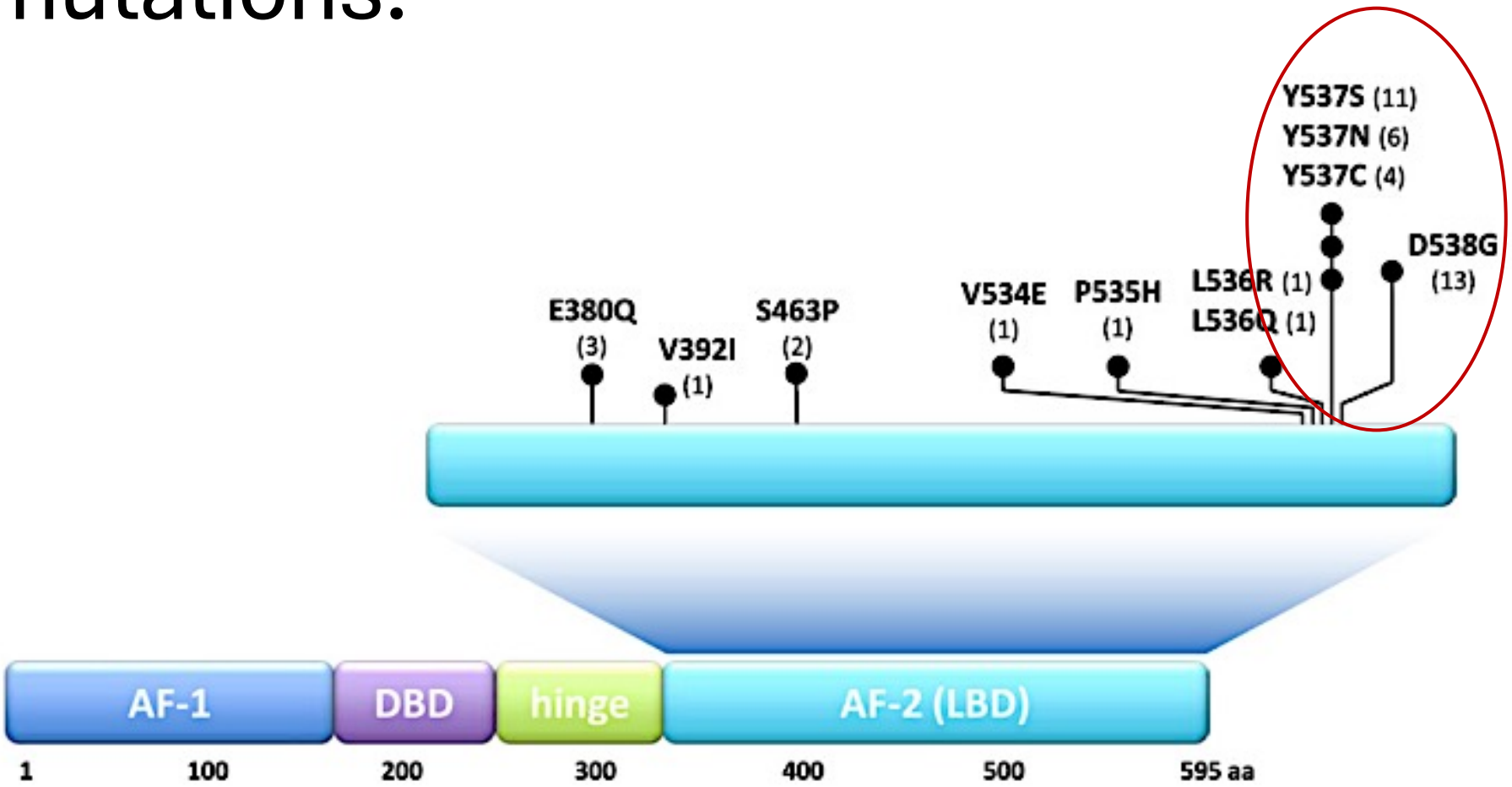
Rinath Jeselsohn MD
Associate Professor
Breast Oncology Center
Dana Farber Cancer Institute

67 yo woman who developed metastatic hormone receptor positive breast cancer 7 years after completion of 5 years of adjuvant endocrine therapy. At the time of relapse, she presented with a malignant pleural effusion. The effusion was drained, and she was started on treatment with ribociclib and an aromatase inhibitor.

After 3 years on treatment, she developed progressive disease with new bone metastases.

Should circulating tumor DNA (ctDNA) testing for an ESR1 mutation be performed?

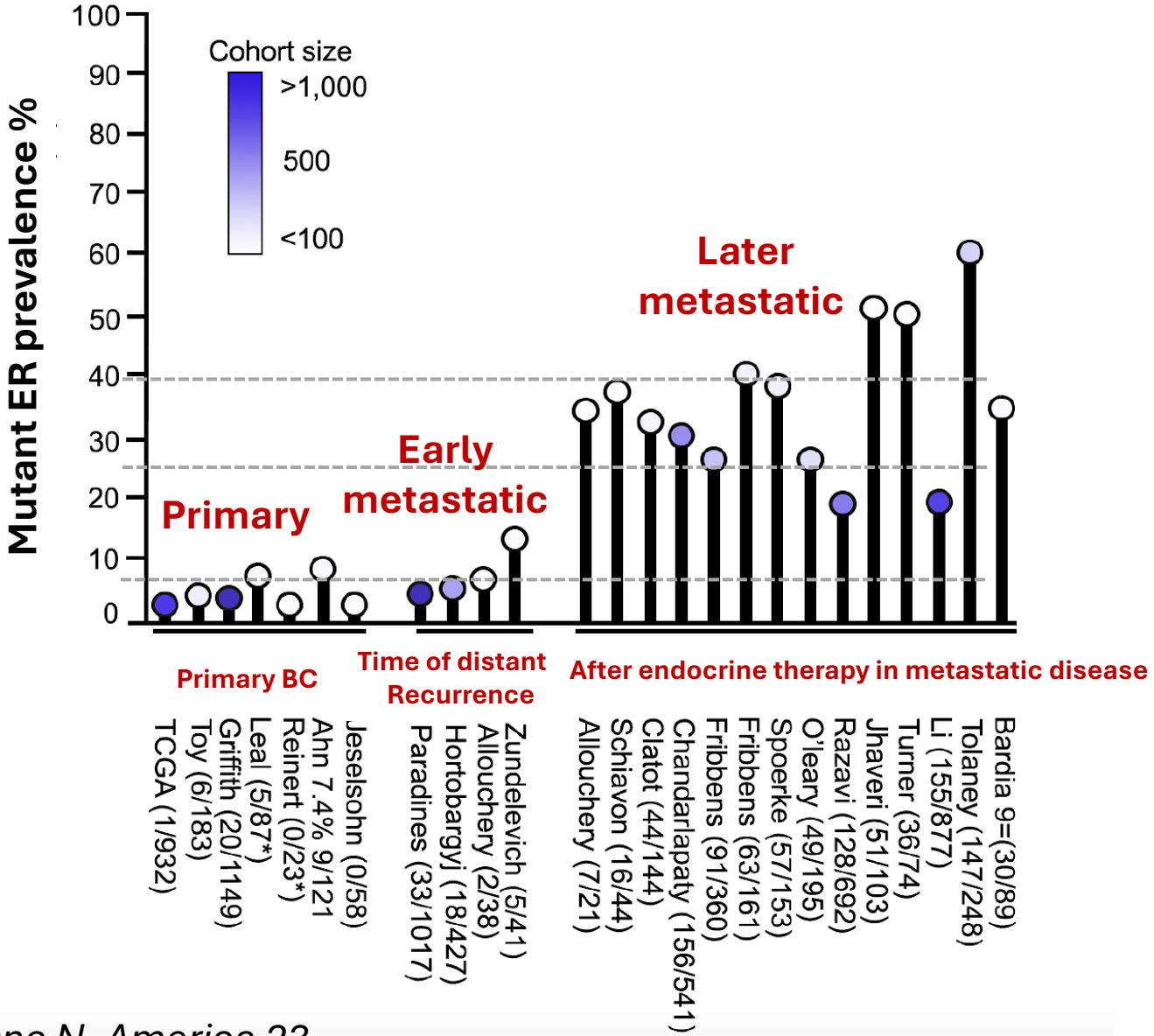
ESR1 mutations:



Biomarker of retained tumor dependency on ER signaling, albeit altered ER signaling

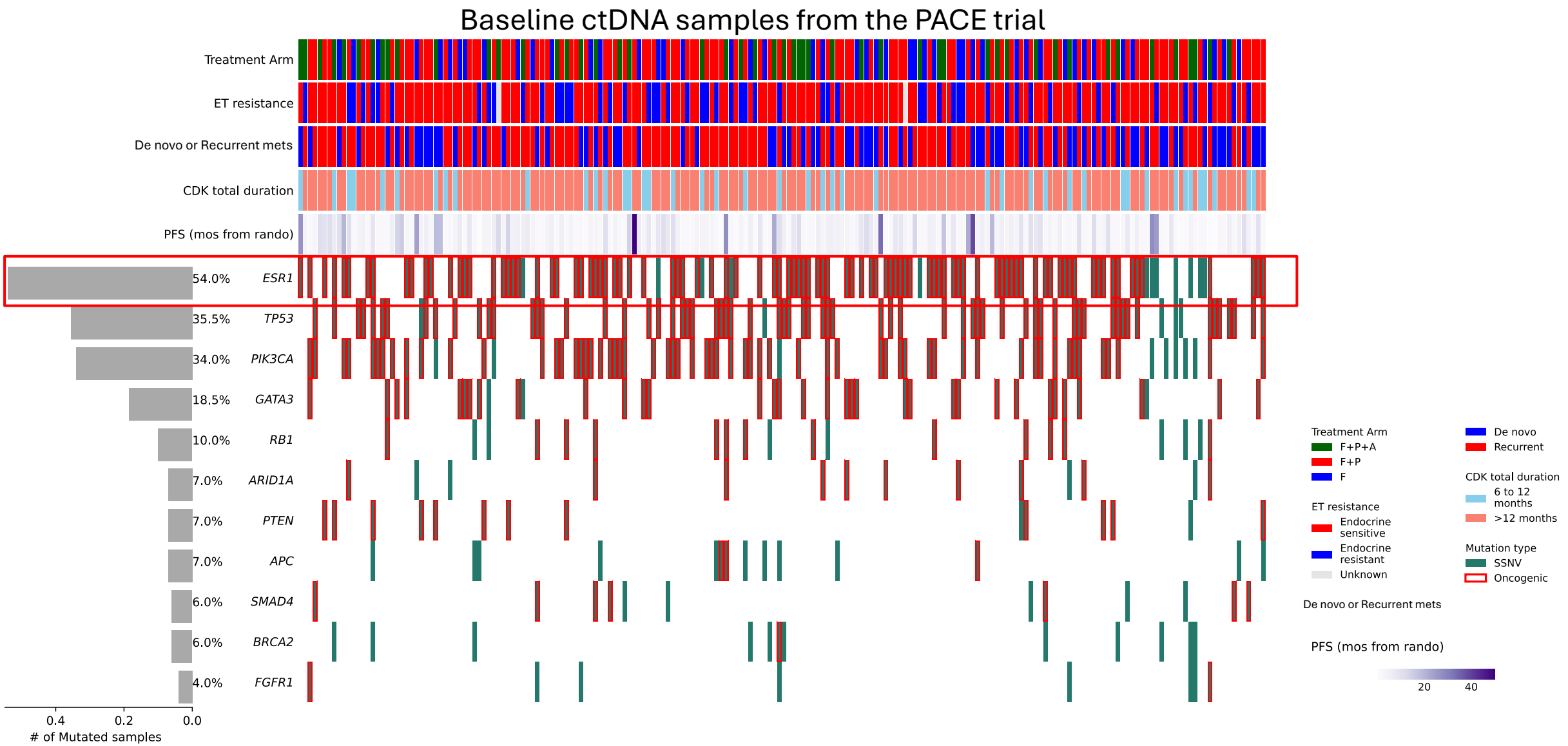
Jeselsohn et al, Nat Rev Clin Onc 2016

ESR1 Mutations are Enriched after ET in Metastatic Disease



Grinshpun, Jeselsohn, Heme Onc N. America 23

The Genomic Landscape after Progression on Palbociclib and an AI



Jeselsohn R et al, ESMO Open 2025

ctDNA testing was performed and patient was found to have an E538G ESR1 mutation and an H1047R PIK3CA mutation.

Treatment options:

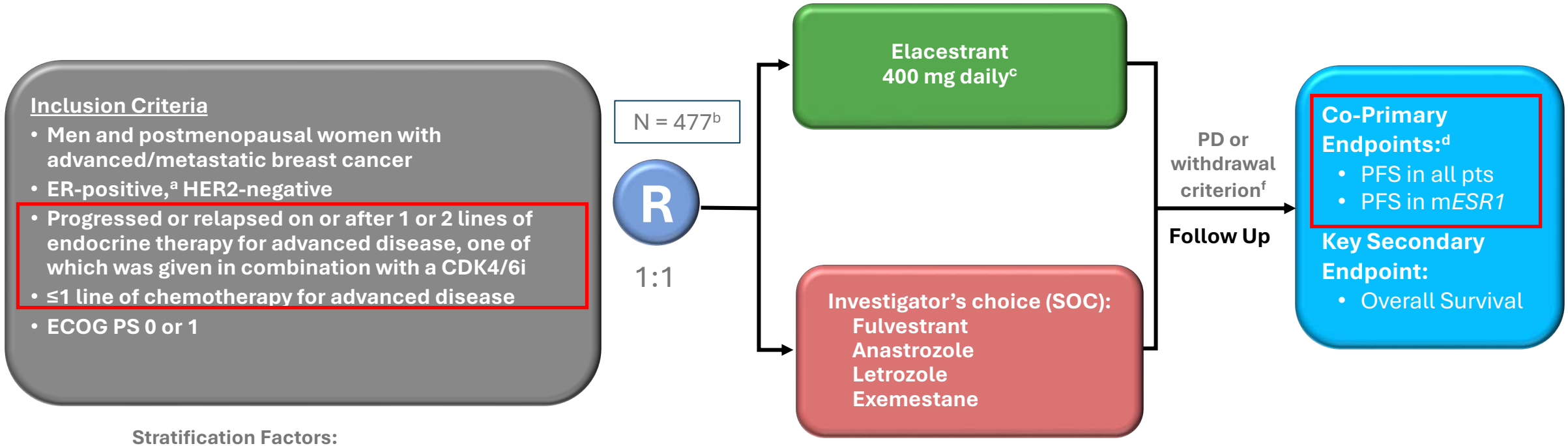
Elacestrant

Imlunestrant

Capivasertib plus fulvestrant

Alpelisib plus fulvestrant

EMERALD Phase 3



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant health, Redwood City, CA). [f]Restaging CT scans every 8 weeks.

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

Bardia A, SABCS 2021, Bidard FC JCO 2022

Baseline Demographic and Disease Characteristics

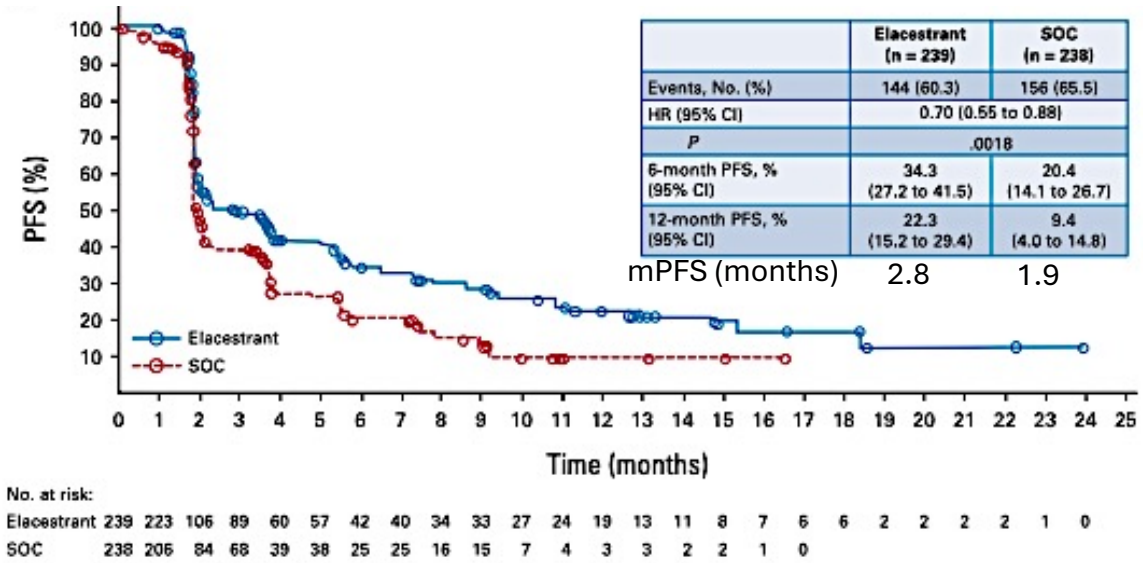
Parameter	Elacestrant		SOC	
	All (N=239)	*mESR1* (N=115)	All (N=238)	*mESR1* (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.5 (32-83)	63.0 (32-83)
Gender, n % Female Male	233 (97.5) 6 (2.5)	115 (100) 0	237 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.7) 102 (42.9) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	141 (59.2) 97 (40.8)	69 (61.1) 44 (38.9)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.6) 58 (24.4)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

Bardia A, SABCS 2021, Bidard FC JCO 2022

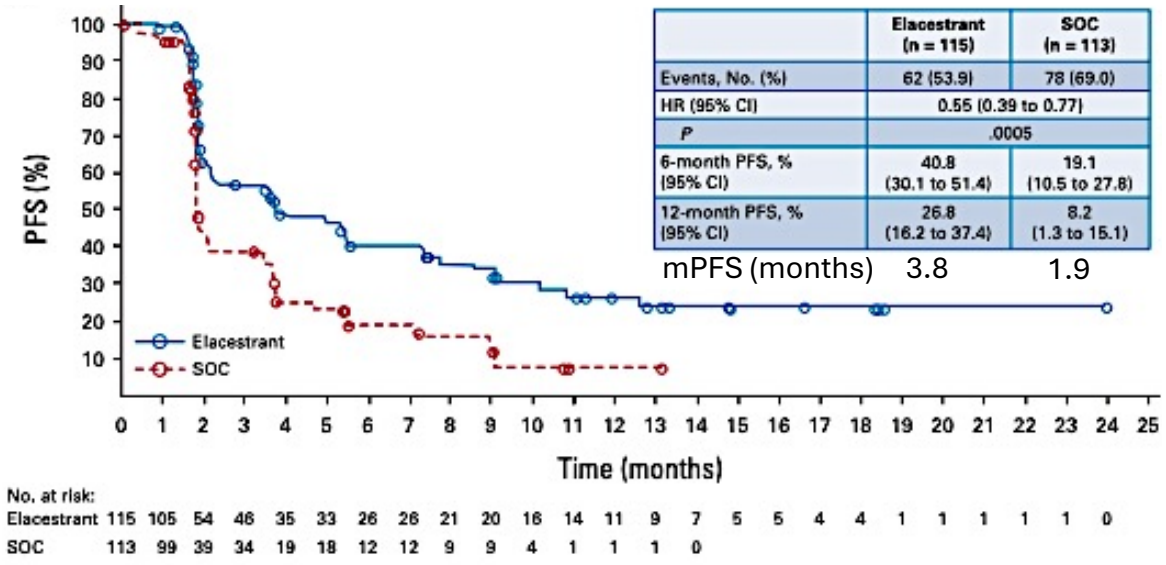
Primary end point: PFS in all and mESR1 Patients

All Patients (ITT)



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)
mPFS (months)	2.8	1.9

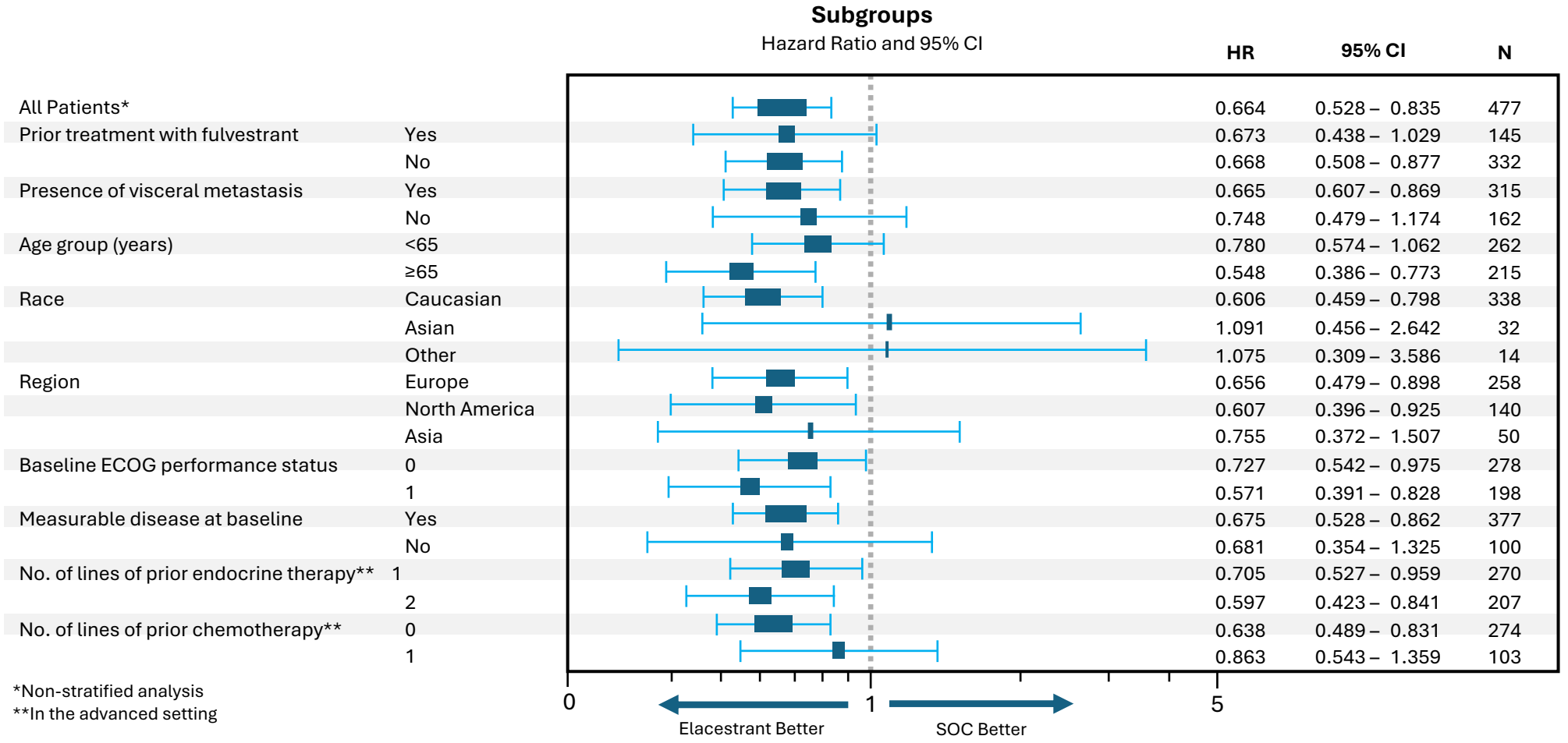
Patients With Tumors Harboring *mESR1*



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)
mPFS (months)	3.8	1.9

Bardia A, SABCS 2021, Bidard FC JCO 2022

Clinically Relevant Subgroups (All Patients)

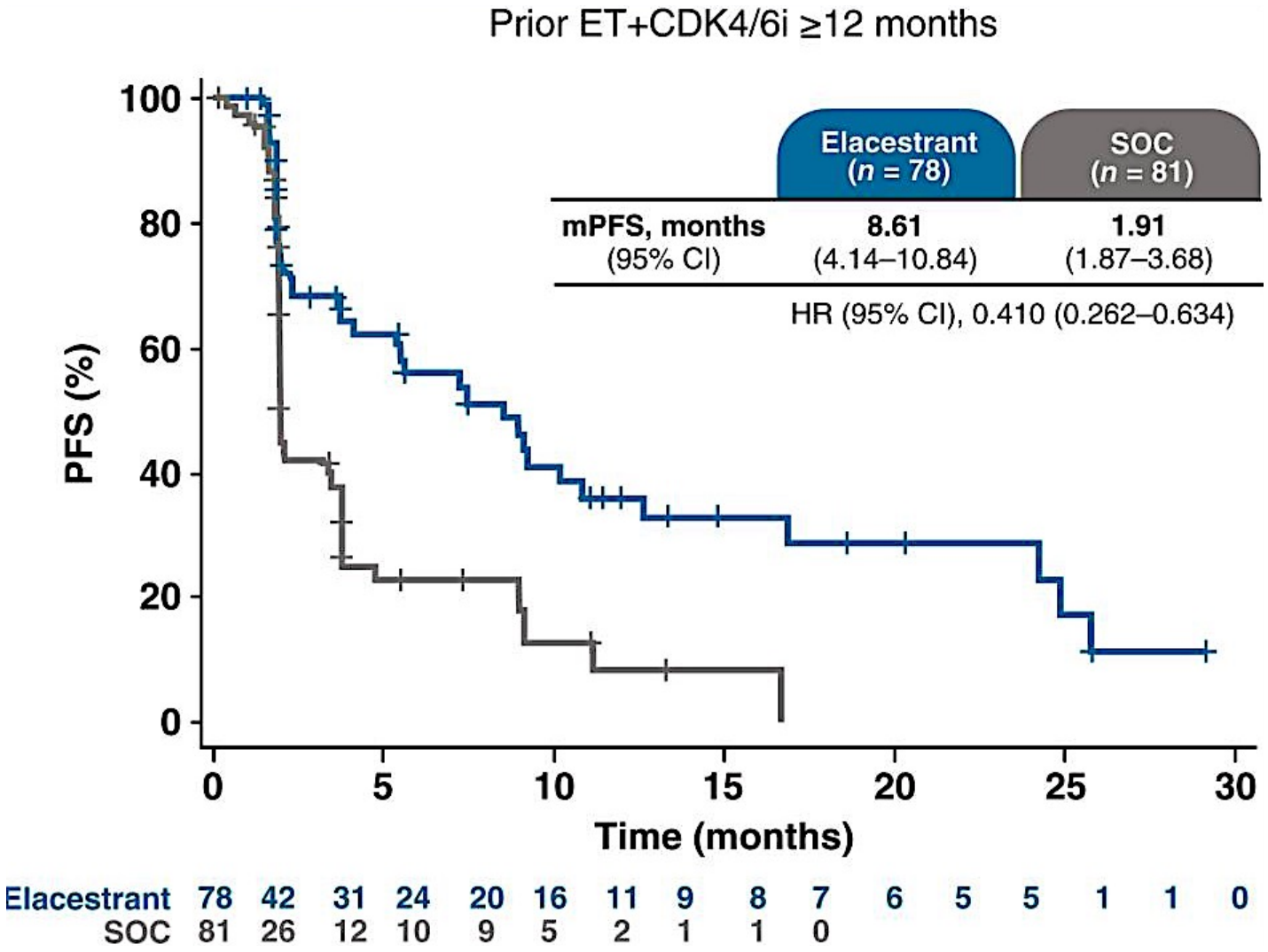


*Non-stratified analysis
**In the advanced setting

- Multiple pre-specified subpopulations showed a consistent trend for elacestrant versus SOC on PFS

Bardia A, SABCS 2021, Bidard FC JCO 2022

Subgroup analysis: patients with *ESR1*-mutated tumors and prior ET+CDK4/6i ≥12 months



Bardia A et al, CCR 2024

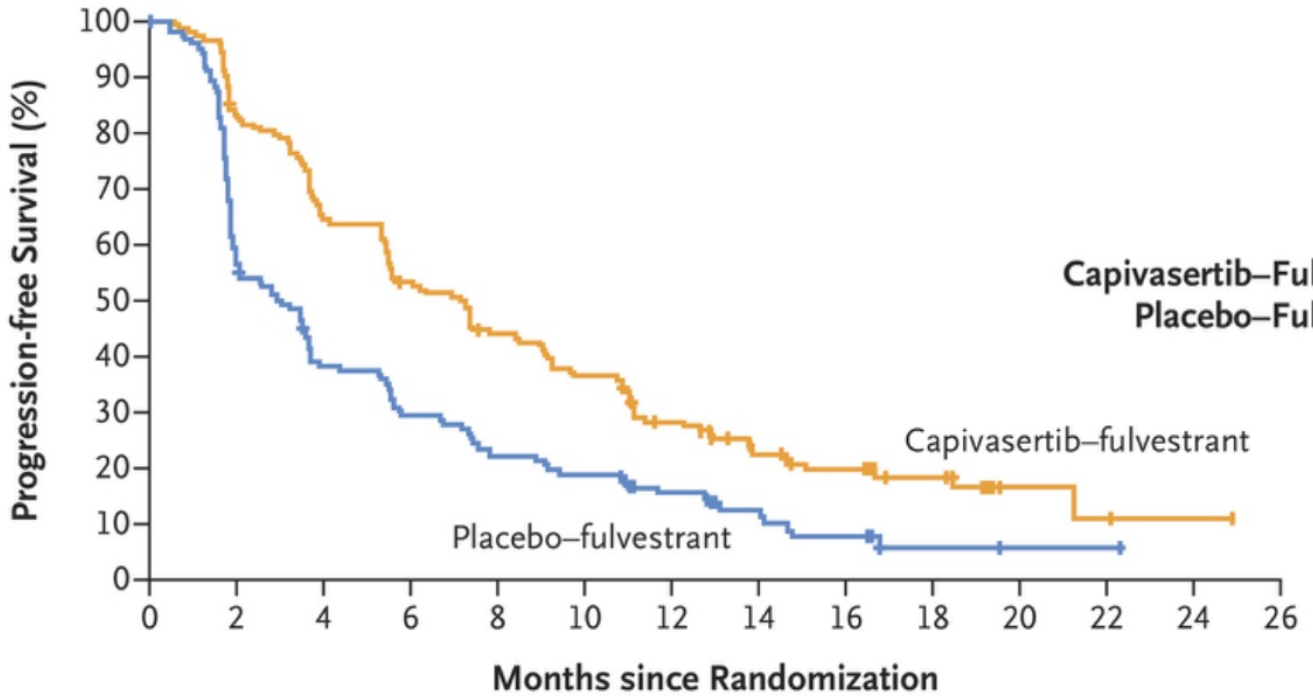
Subgroup analysis of patients with *ESR1*-mutated tumors and prior ET+CDK4/6i ≥12 months

Patient subgroup	*n* (%)	mPFS, months		HR (95% CI)
		Elacestrant	SOC	
All patients with *ESR1*-mutated tumors	159 (100)	8.6	1.9	0.41 (0.26–0.63)
ESR1-mutated tumors and bone metastases[a]	136 (86)	9.1	1.9	0.38 (0.23–0.62)
ESR1-mutated tumors and liver and/or lung[b] metastases	113 (71)	7.3	1.9	0.35 (0.21–0.59)
ESR1-mutated tumors and <3 metastatic sites[c]	82 (52)	9.0	1.9	0.41 (0.23–0.75)
ESR1-mutated tumors and ≥3 metastatic sites[c]	53 (33)	10.8	1.8	0.31 (0.12–0.79)
ESR1- and *PIK3CA*-mutated tumors[d]	62 (39)	5.5	1.9	0.42 (0.18–0.94)
ESR1- and *TP53*-mutated tumors	61 (38)	8.6	1.9	0.30 (0.13–0.64)
ESR1-mutated tumors and HER2-low expression[e]	77 (48)	9.0	1.9	0.30 (0.14–0.60)
ESR1 ^{D538G} -mutated tumors	97 (61)	9.0	1.9	0.38 (0.21–0.67)
ESR1 $^{Y537S/N}$ -mutated tumors	92 (58)	9.0	1.9	0.25 (0.13–0.47)

Bardia A et al, CCR 2024

CAPItello-291: Phase III randomized trial of Capivasertib plus Fulvestrant or Placebo plus Fulvestrant

B Patients with AKT Pathway–Altered Tumors



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Capivasertib–Fulvestrant	155	121	7.3 (5.5–9.0)
Placebo–Fulvestrant	134	115	3.1 (2.0–3.7)

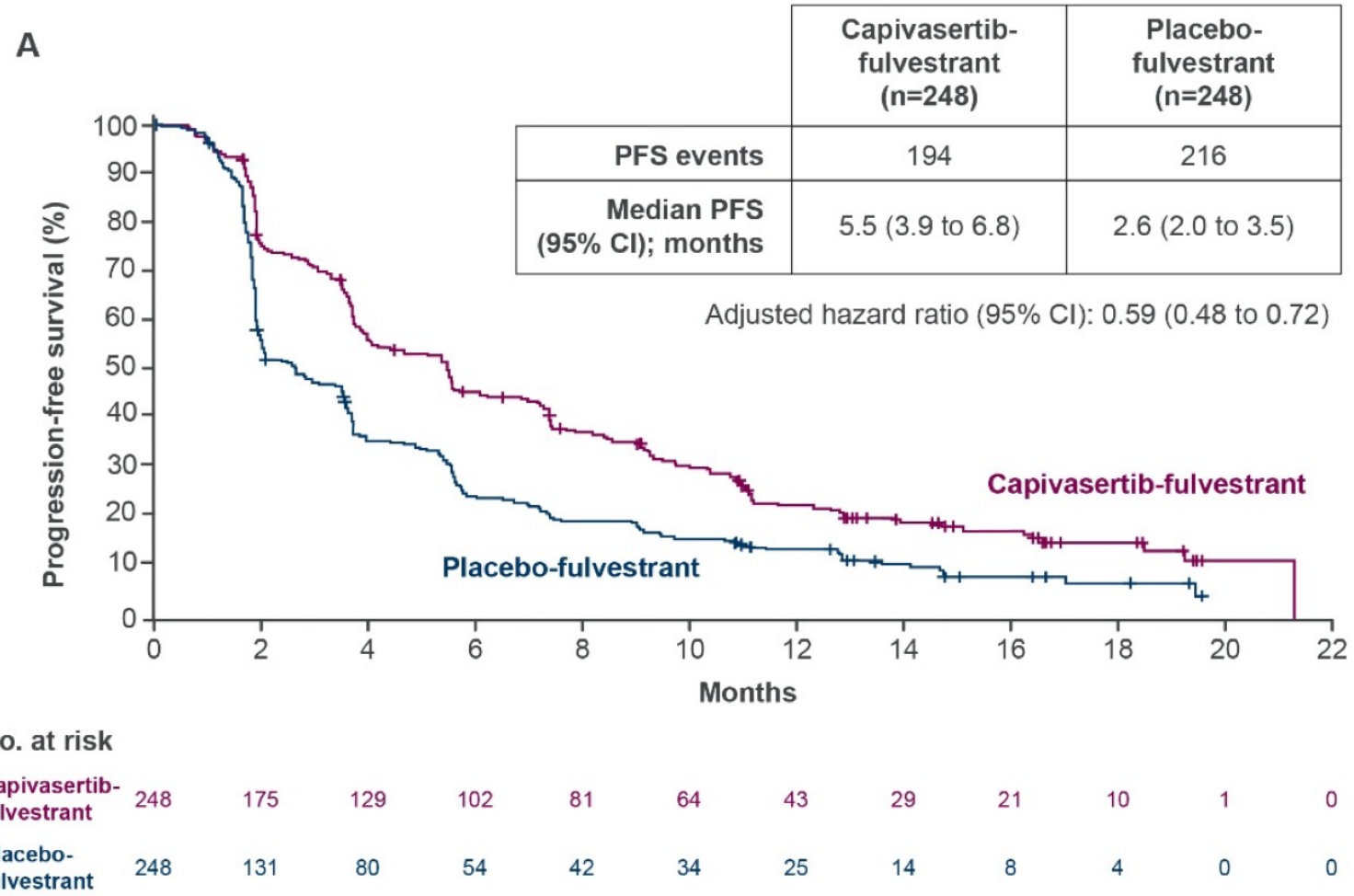
Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65)
P<0.001

No. at Risk

Capivasertib–fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo–fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

Turner NC, NEJM 2023

PFS in CAPItello-291 in patients with prior CDK4/6 inhibitor exposure



Turner NC, NEJM 2023

EMBER-3 Study Design

ER+, HER2- ABC

Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]

R 1:1:1[b]
N=874

- **Imlunestrant 400 mg QD** — A
- **SOC ET[d,e]** Fulvestrant or Exemestane — B
- **Imlunestrant 400 mg QD + abemaciclib[e]** — C[b]

Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

Jhaveri KL et al, SABCS 2024, Jhaveri KL et al, NEJM 2025

Baseline Demographic and Disease Characteristics

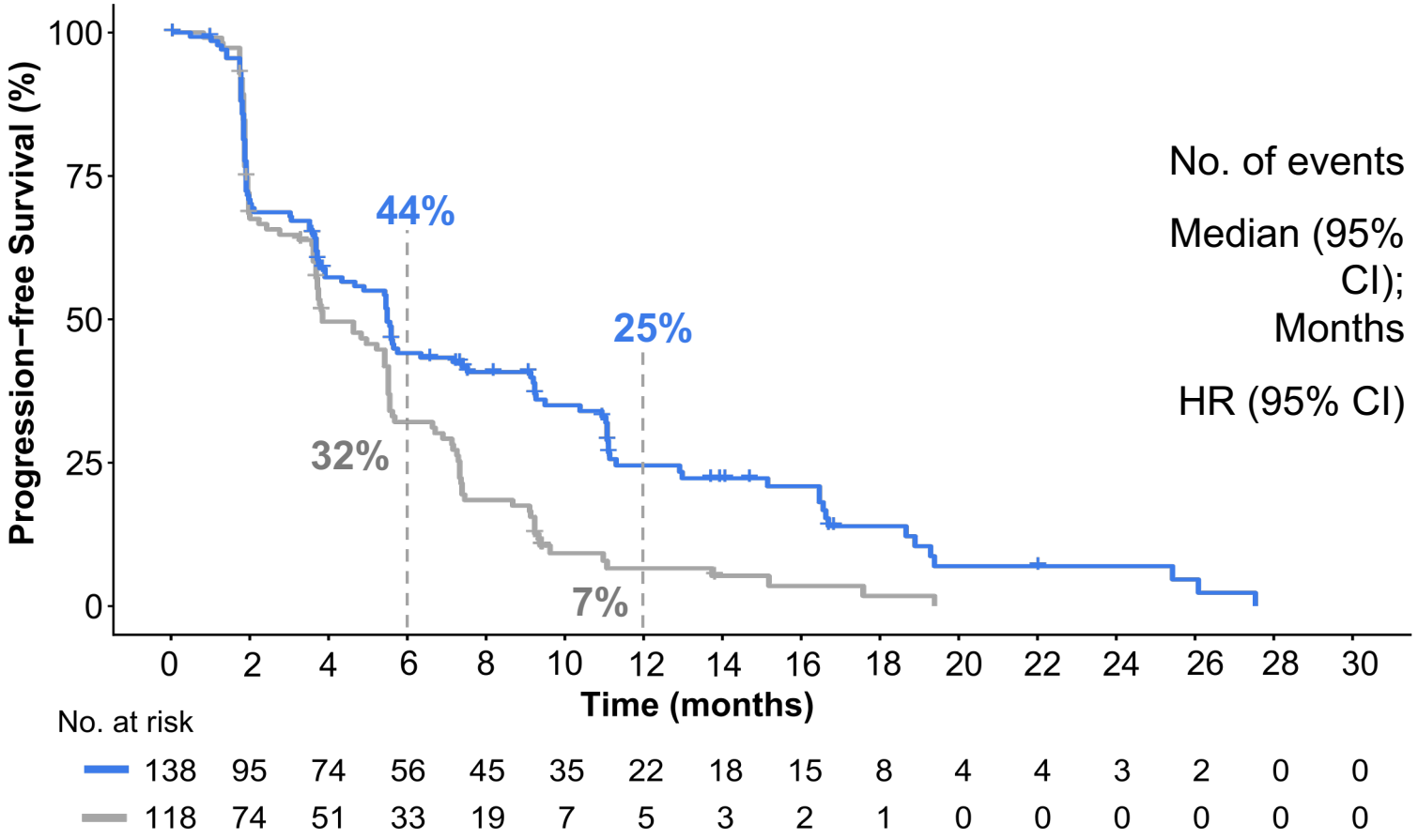
Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

Jhaveri KL et al, SABCS 2024, Jhaveri KL et al, NEJM 2025

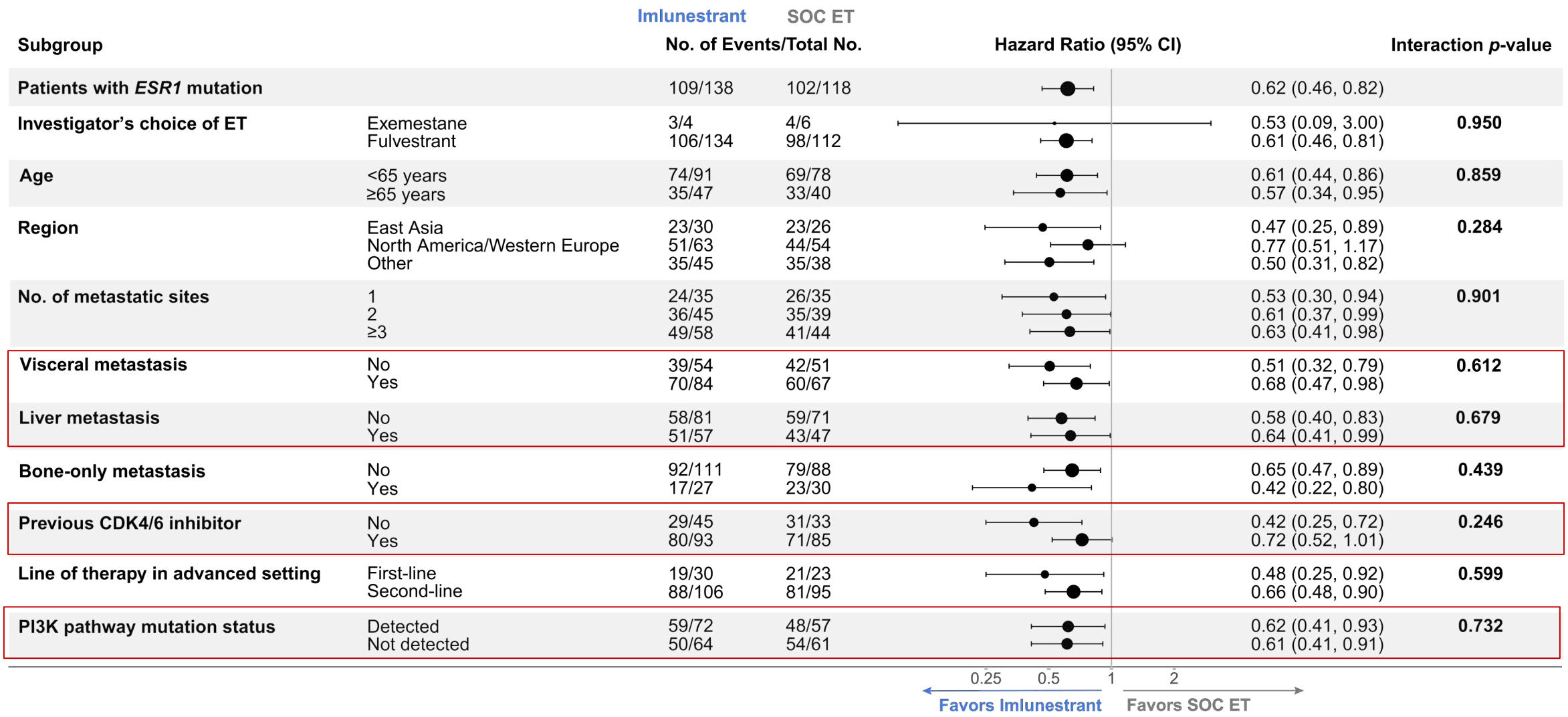
Primary Endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in Patients with *ESR1*m



	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

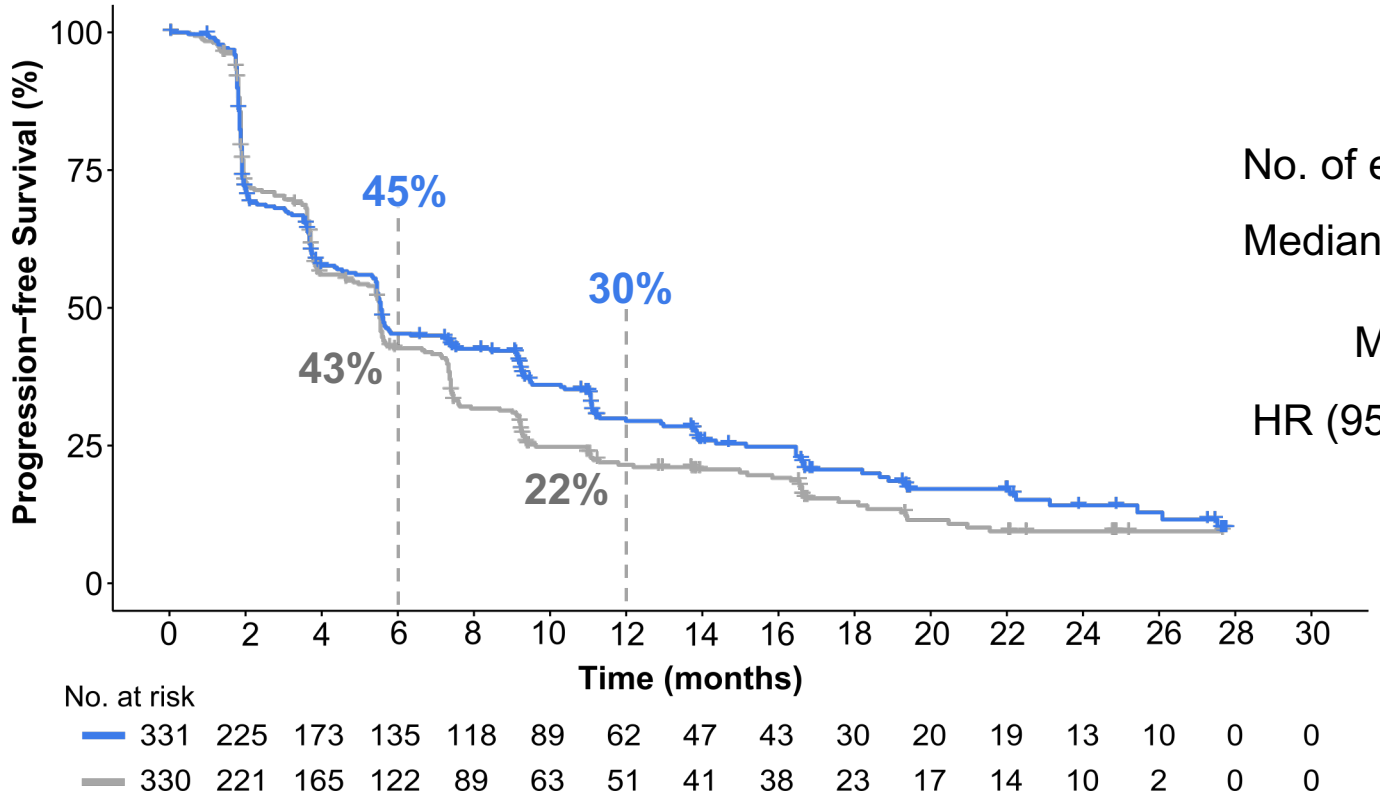
Jhaveri KL et al, SABCS 2024, Jhaveri KL et al, NEJM 2025

Investigator-assessed PFS by Subgroup: Imlunestrant Benefit Across Subgroups in Patients with *ESR1*m



Jhaveri KL et al, SABCS 2024, Jhaveri KL et al, NEJM 2025

Primary Endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in all Patients



	Imlunestrant n=331	SOC ET n=330
No. of events	237	253
Median (95% CI); Months	**5.6** (5.3-7.3)	**5.5** (4.6-5.6)
HR (95% CI)	**0.87 (0.72-1.04)** *p*-value 0.12	

Prespecified Critical HR < 0.84[a]

The majority subgroup of patients without *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79-1.27)[b]

Jhaveri KL et al, SABCS 2024, Jhaveri KL et al, NEJM 2025

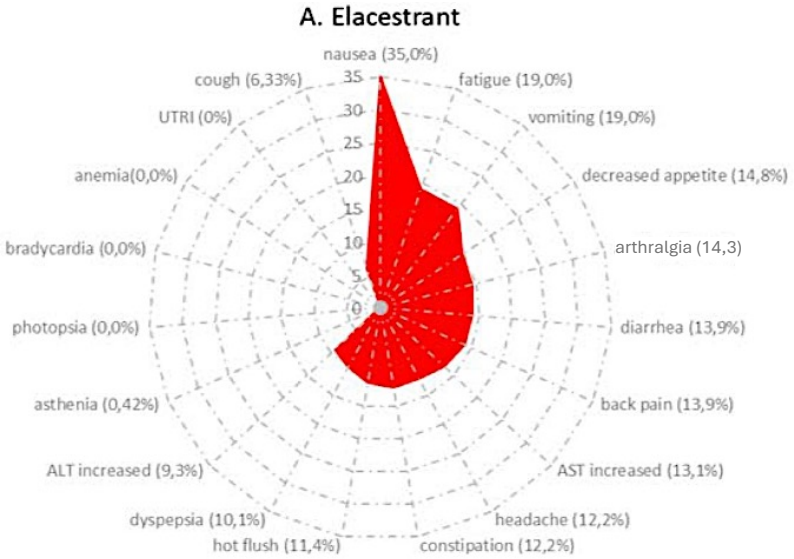
Next Generation Endocrine Therapies that were FDA approved and/ or with positive results from completed Phase III trials

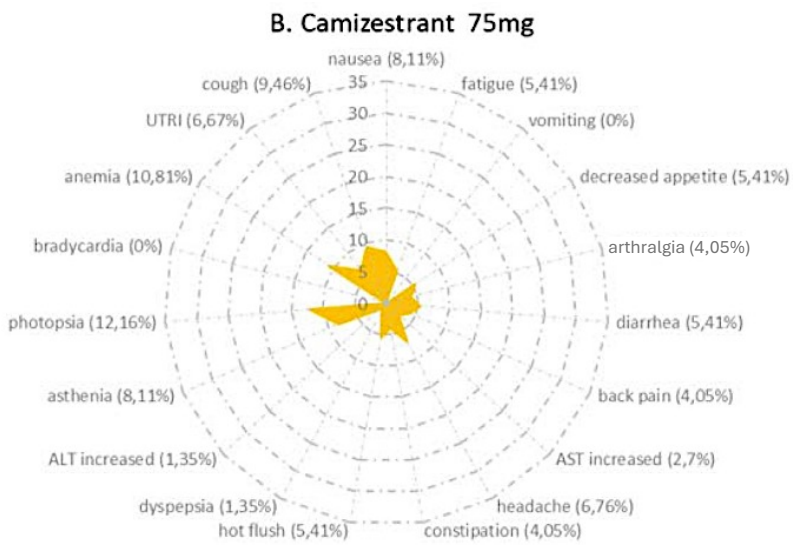
- Elacestrant
- Imlunestrant

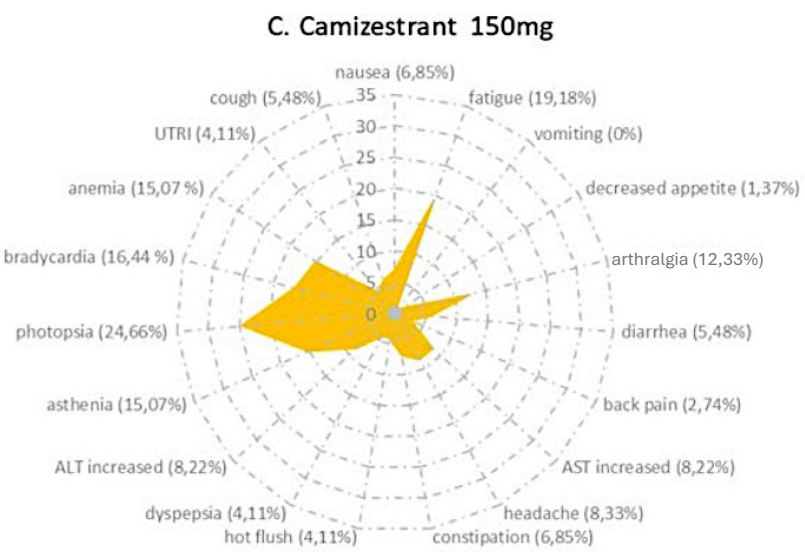
Single agent FDA approved for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced breast cancer with disease progression following at least one line of endocrine therapy

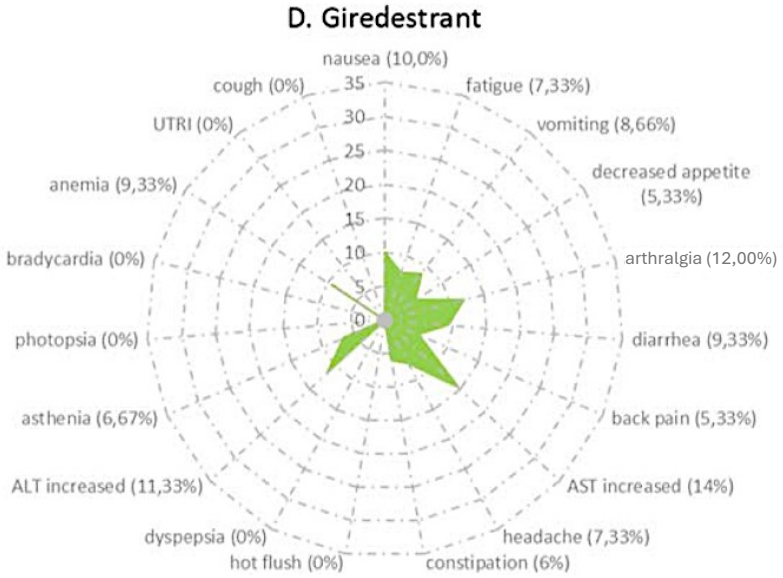
- Camizestrant: Positive phase III trial in combination with a CDK4/6i (SERENA 6,Bidard FC, NEJM 2025)
- Giredestrant : Positive phase III trial in combination with everolimus (evERA, Mayer E, ESMO 2025)
- Vepdegestrant (ER PROTAC): Positive Phase III trial as a single agent (Campone M, NEJM 2025)

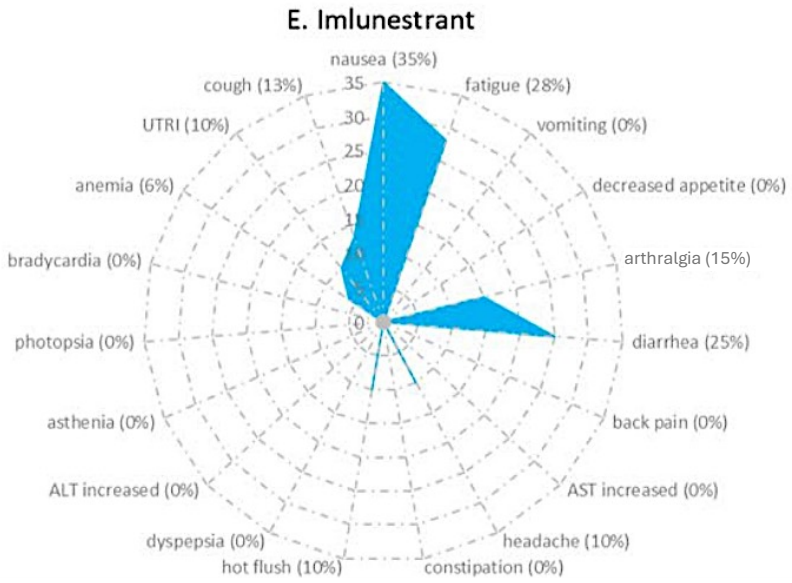
Side effect profiles of new endocrine therapies are different, but mostly low grade

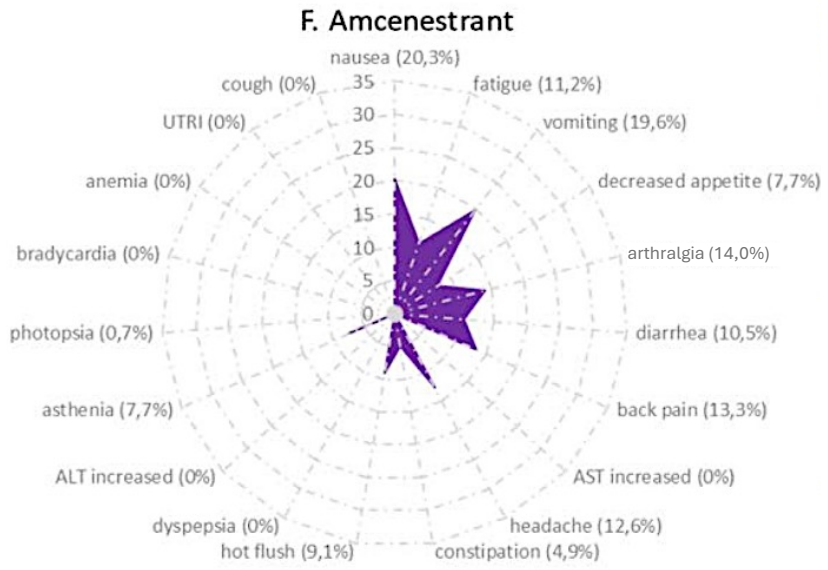










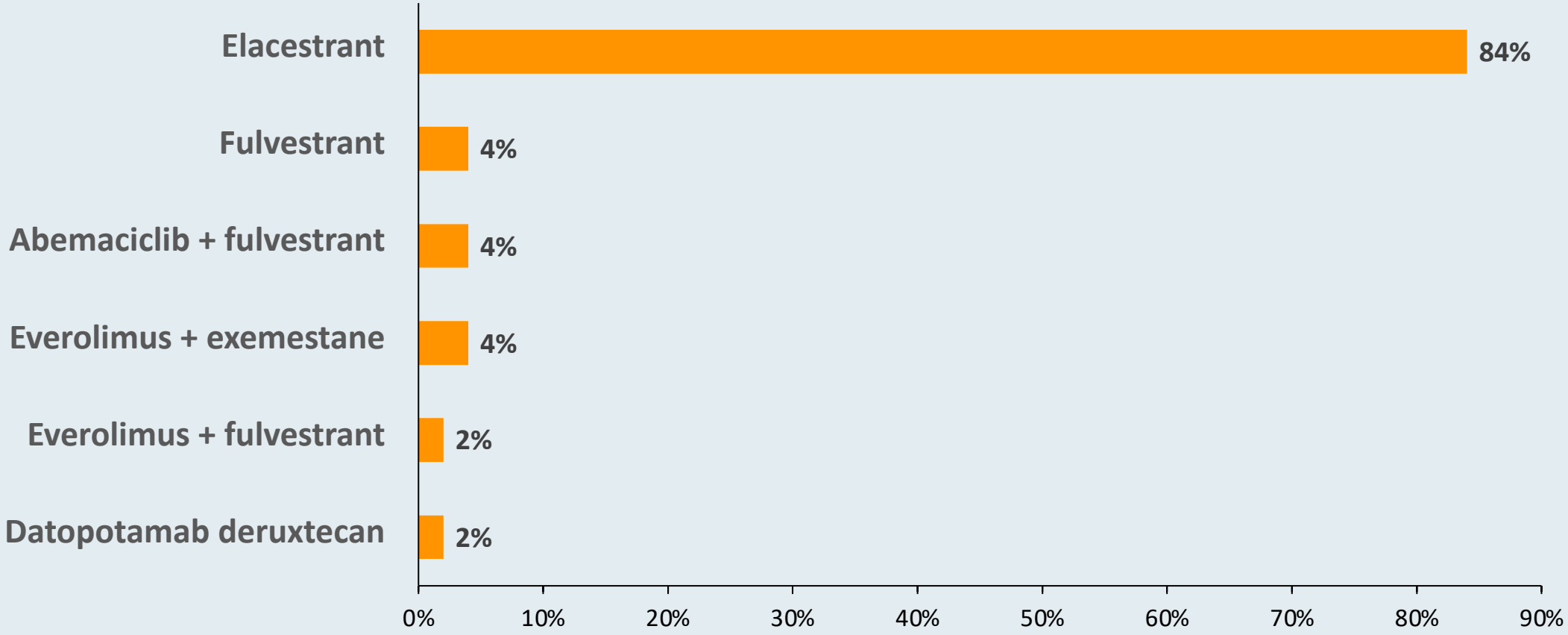


Gheysen M et al, Can Treat Rev 2024

Clinical Scenarios

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple minimally symptomatic bone metastases

ESR1 mutation | **PIK3CA/AKT1/PTEN wild type**



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

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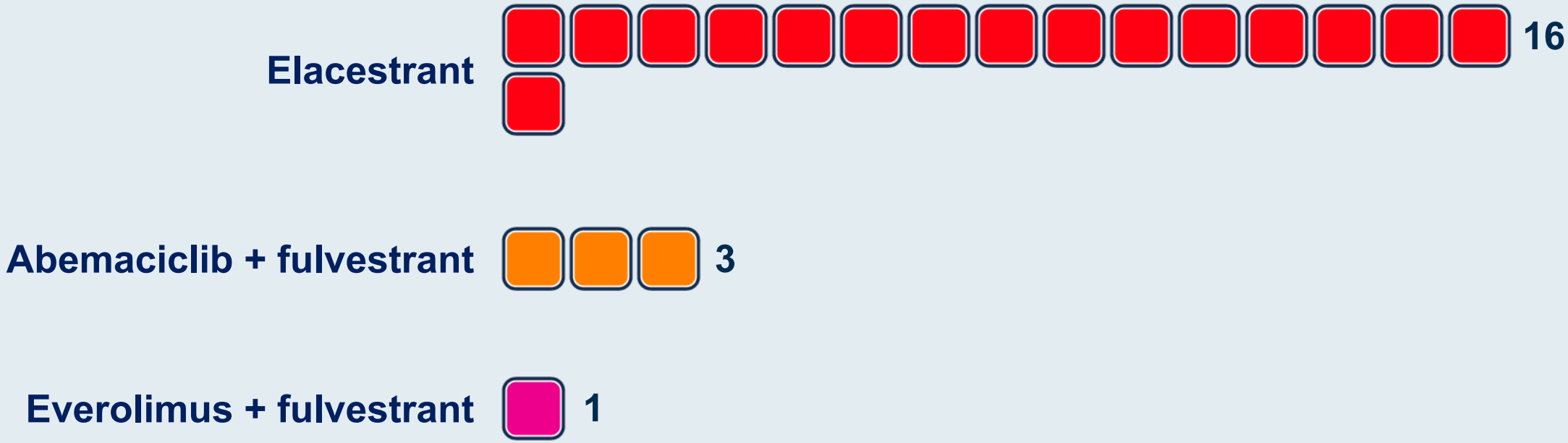
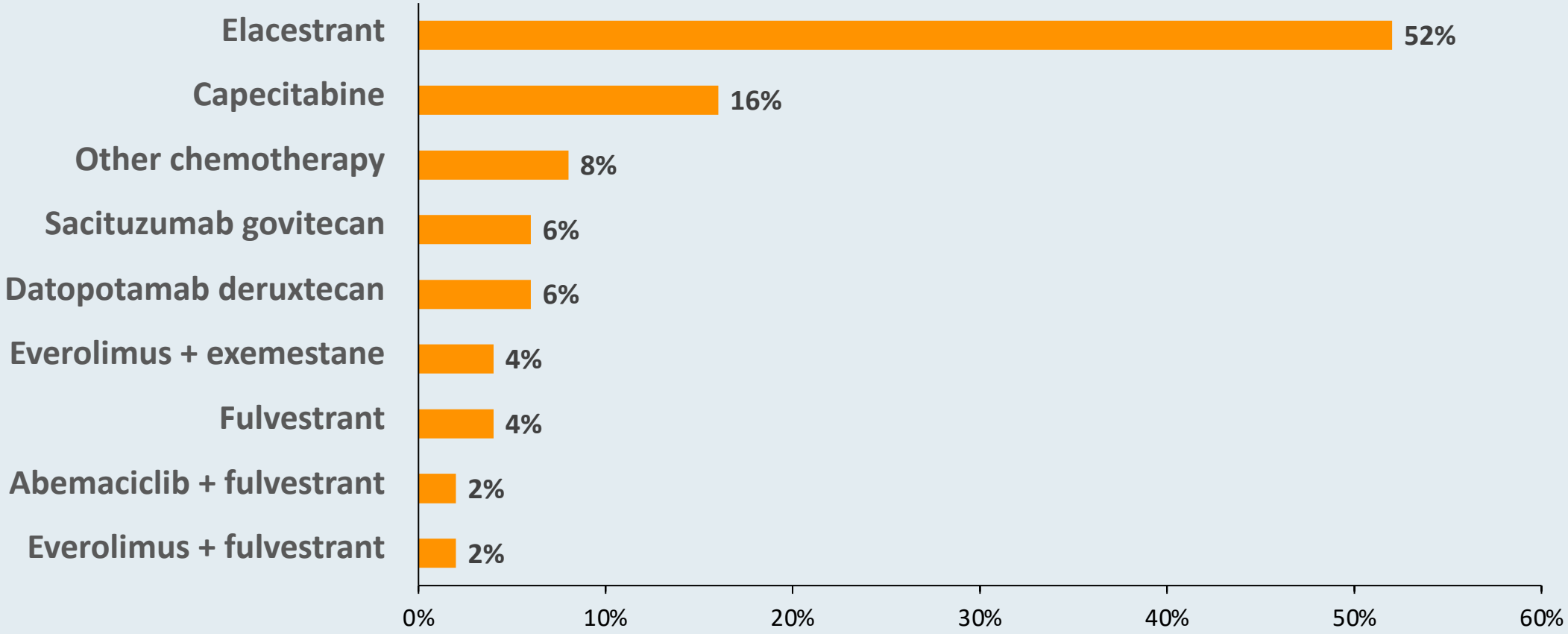


Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 10 months followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

ESR1 mutation | **PIK3CA/AKT1/PTEN wild type**



LFTs = liver function tests

Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 10 months followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

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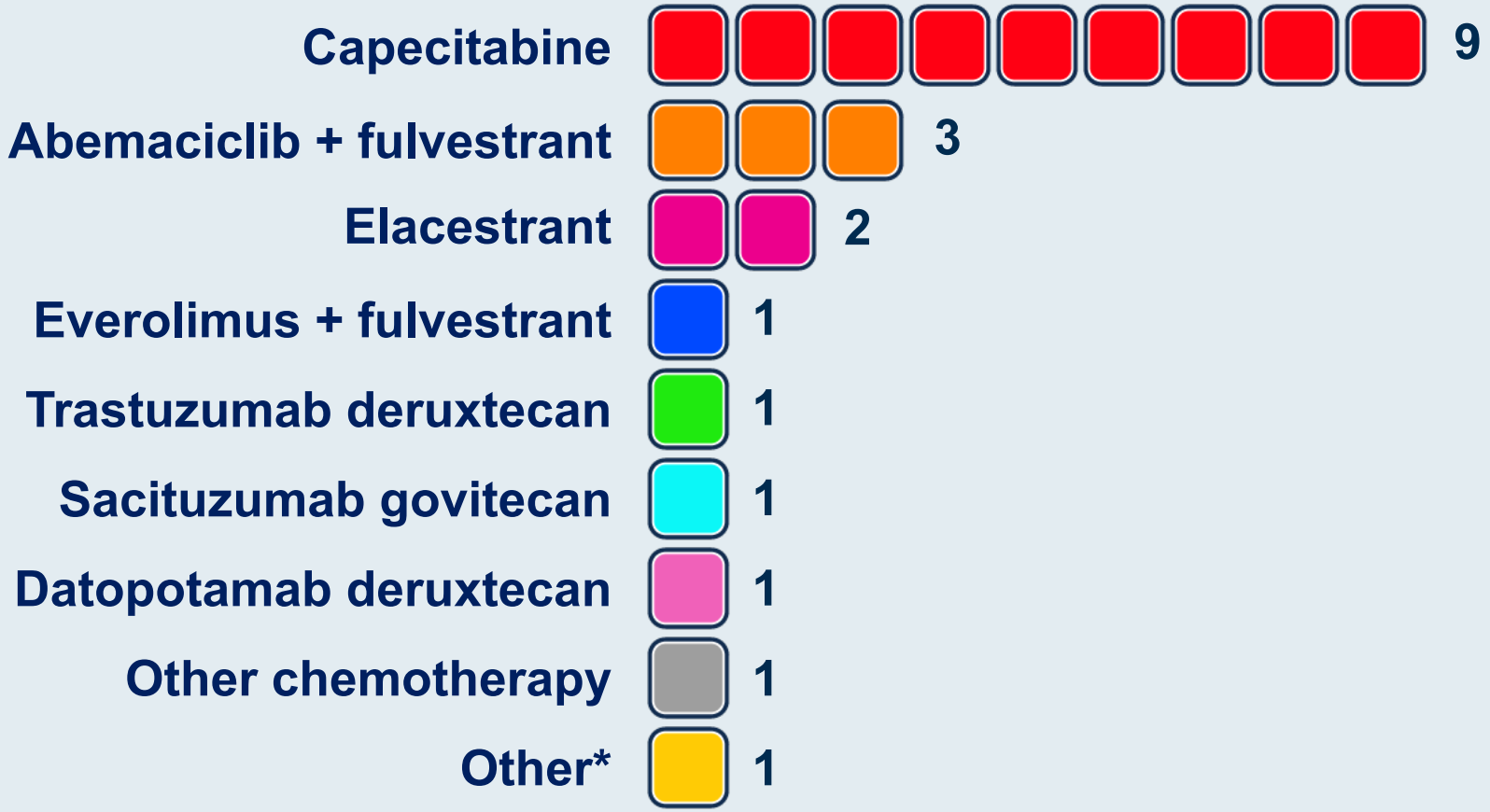


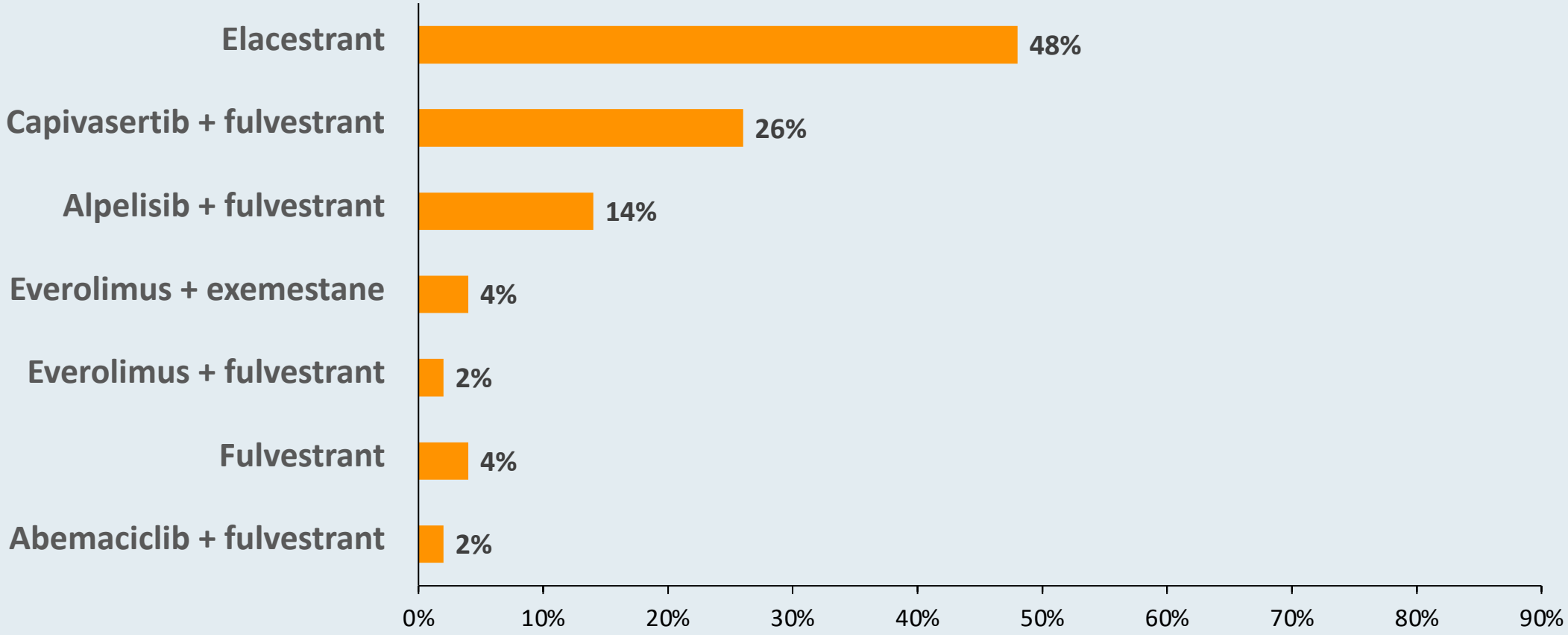
* If the symptoms are mild I would try capecitabine. If more severe I would start with a taxane until we have data from ASCENT-07. If the symptoms were very mild I would try fulvestrant and everolimus

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

An 80-year-old woman (PS 1) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple minimally symptomatic bone metastases

ESR1 mutation **PIK3CA mutation**



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

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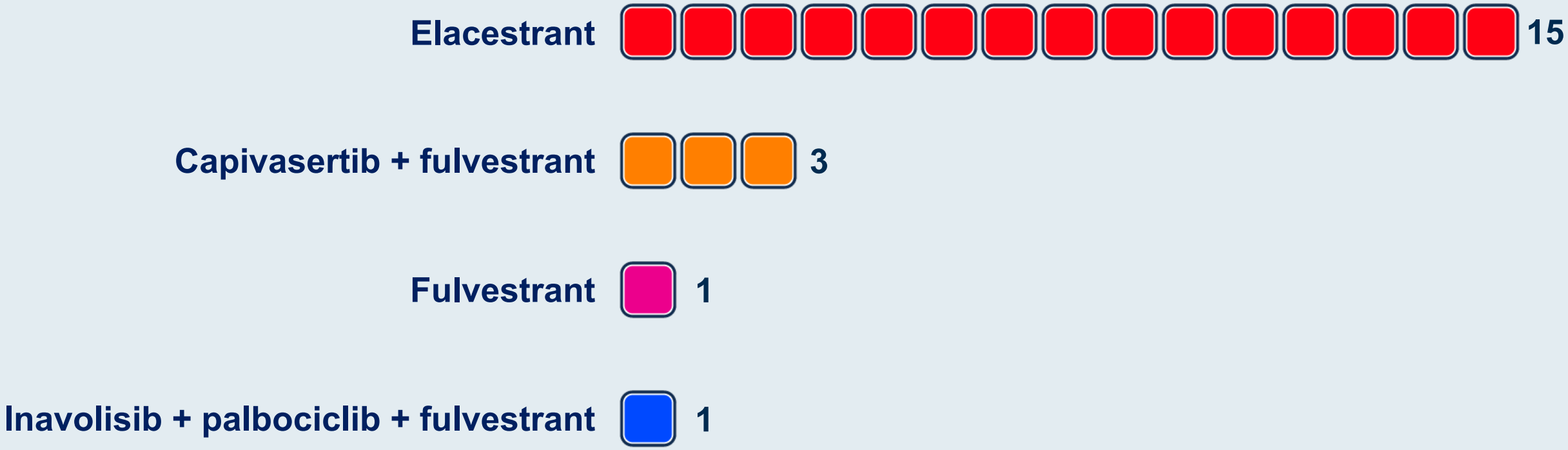

Survey of 20 US-based clinical investigators

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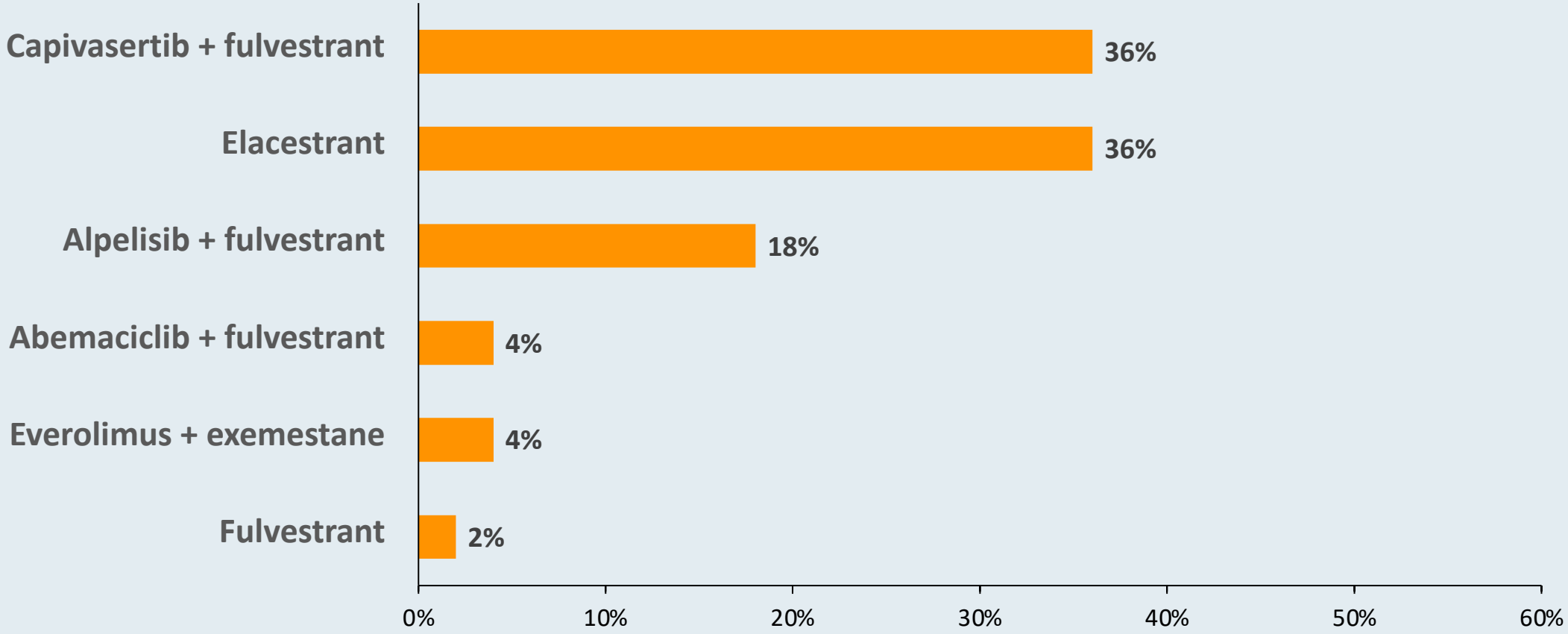

Survey of US-based general medical oncologists

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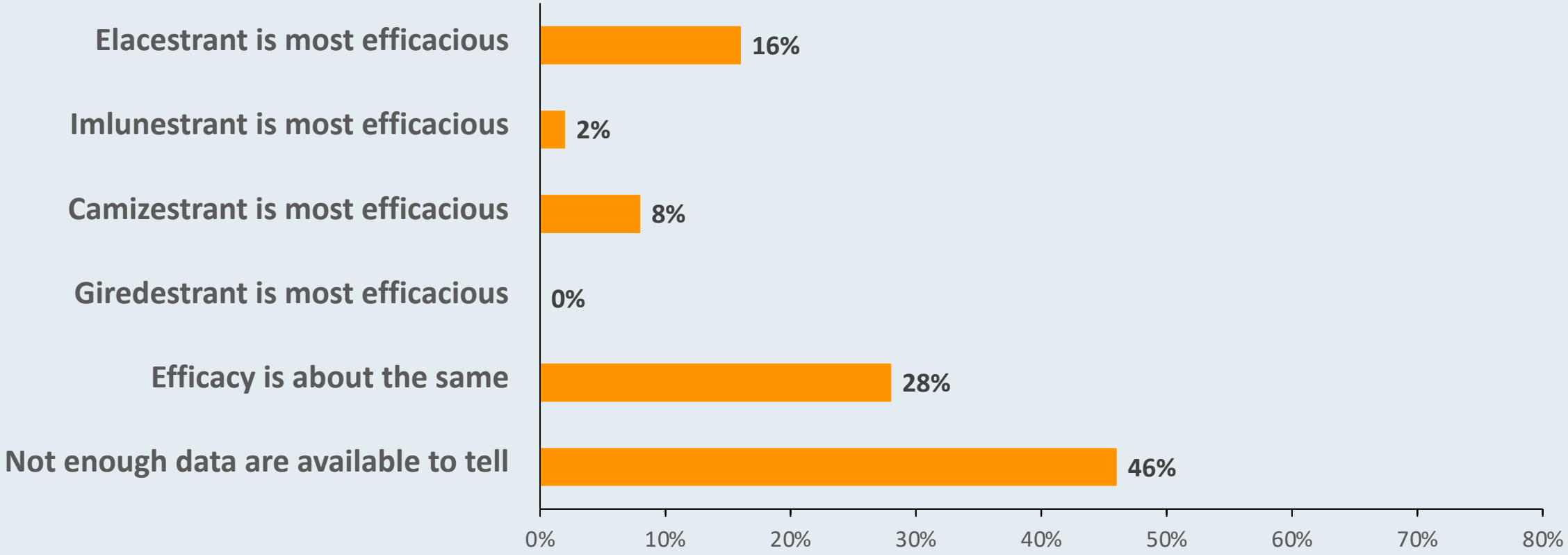
Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

Based on published research data and your own clinical experience, how would you indirectly compare the global efficacy of elacestrant, imlunestrant, camizestrant and giredestrant when administered as monotherapy for endocrine therapy-pretreated ER-positive, HER2-negative mBC with an ESR1 mutation?



Survey of US-based general medical oncologists

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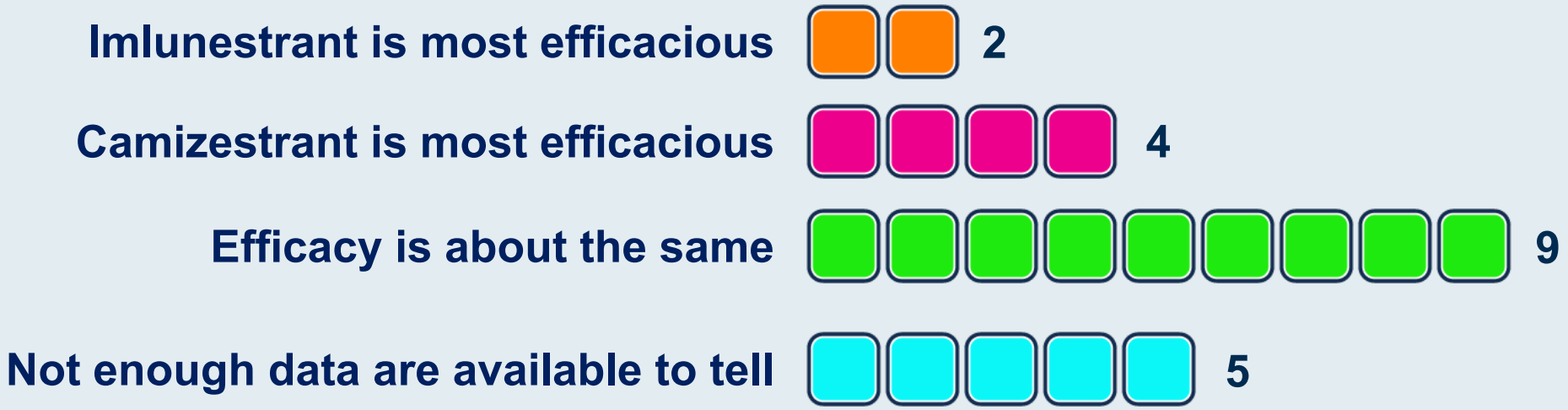

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

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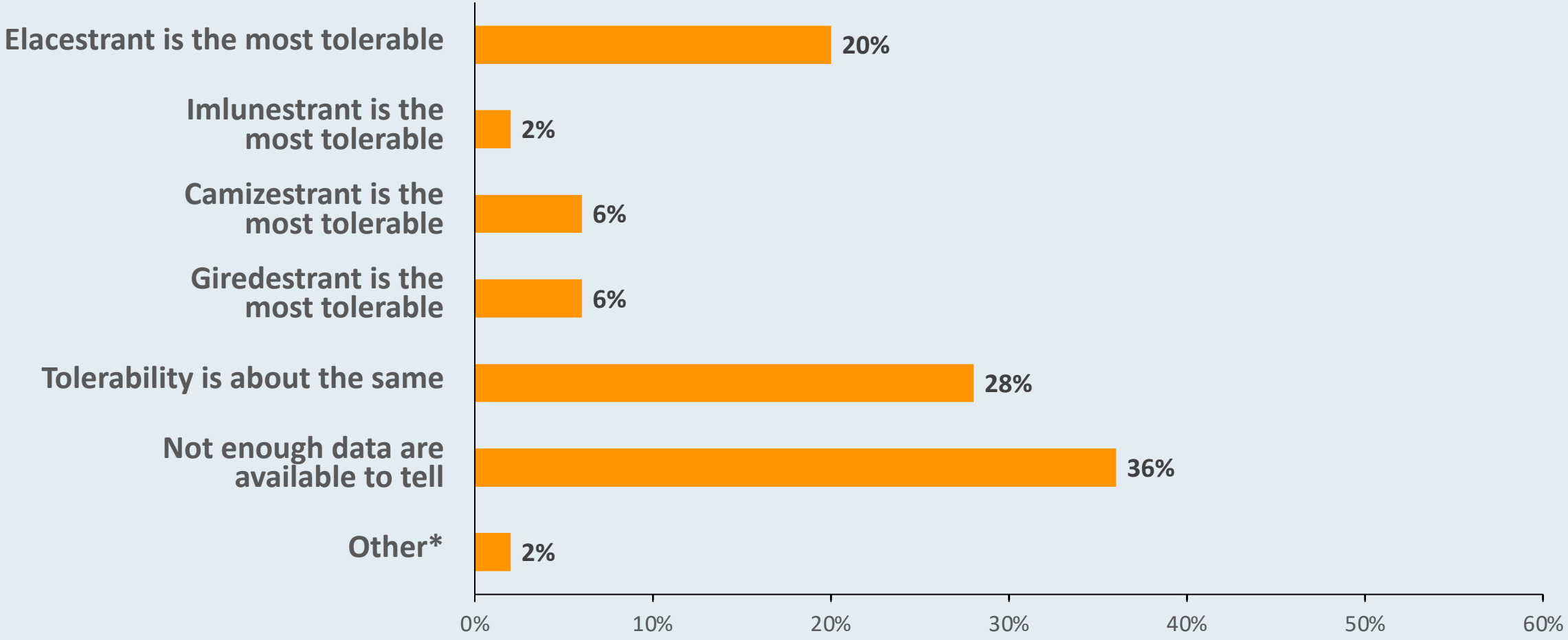
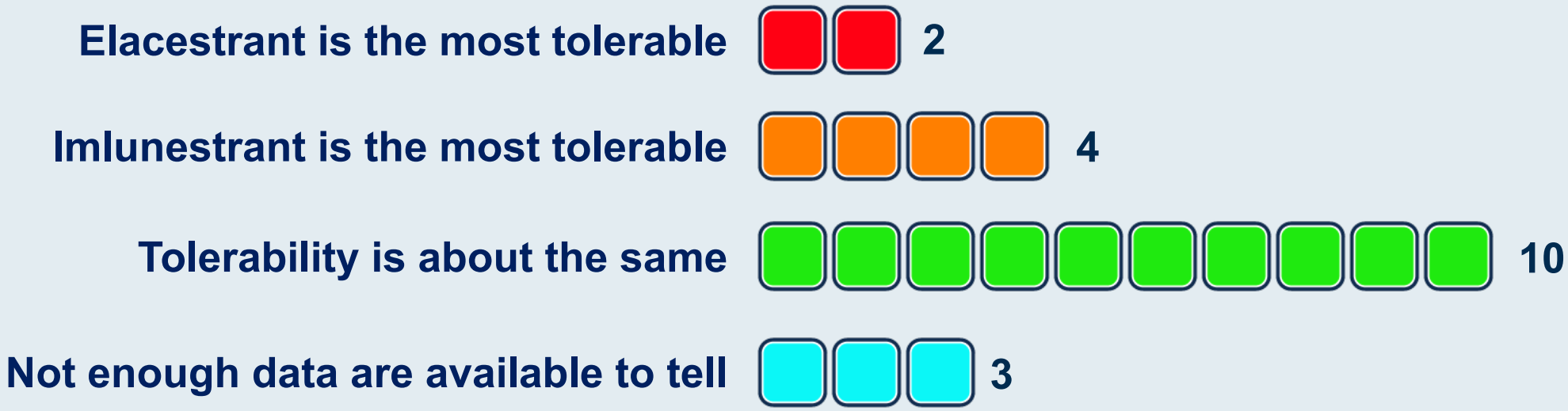


*** I have no idea**

Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

How would you indirectly compare the global tolerability/toxicity of elacestrant, imlunestrant, camizestrant and giredestrant when administered as monotherapy for endocrine therapy-pretreated, ER-positive, HER2-negative mBC with an ESR1 mutation?



N = 19

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

FDA Approves Imlunestrant for Adults with ER-Positive, HER2-Negative, ESR1-Mutated Advanced or Metastatic Breast Cancer

Press Release: September 25, 2025

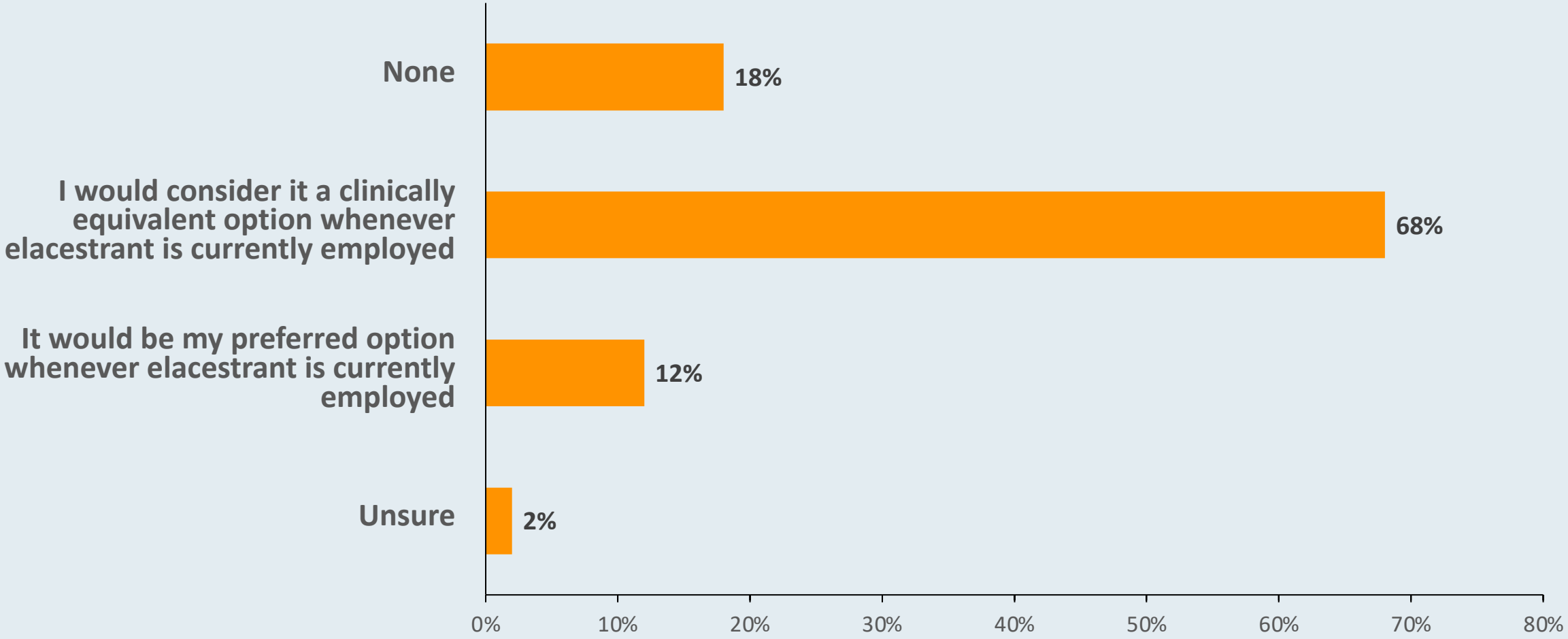
"The FDA has approved imlunestrant, an oral estrogen receptor antagonist, for the treatment of adults with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–), *ESR1*-mutated advanced or metastatic breast cancer (MBC) whose disease progressed after at least one line of endocrine therapy (ET).

In the Phase 3 EMBER-3 trial, imlunestrant reduced the risk of progression or death by 38% versus ET. Among patients with *ESR1*-mutated MBC, imlunestrant significantly improved progression-free survival (PFS) versus fulvestrant or exemestane, with a median PFS of 5.5 months vs 3.8 months (HR = 0.62 [95% CI: 0.46-0.82]); *p*-value = 0.0008."

https://investor.lilly.com/news-releases/news-release-details/us-fda-approves-inluriyo-imlunestrant-adults-er-her2-esr1

RTP RESEARCH TO PRACTICE

If imlunestrant were available, in which situations, if any, would you use this agent as monotherapy?



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

If imlunestrant were available, in which situations, if any, would you use this agent as monotherapy?

I would consider it a clinically equivalent option whenever elacestrant is currently employed

17

It would be my preferred option whenever elacestrant is currently employed

3

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RTP RESEARCH TO PRACTICE

Agenda

Introduction: Oral SERDs for the General Medical Oncologist

Module 1: SERD Monotherapy

Module 2: SERD + CDK Inhibitor Combination — EMBER-3

Module 3: SERD for "Molecular Progression" — SERENA-6

Module 4: Other SERD Issues

The NEW ENGLAND JOURNAL of MEDICINE

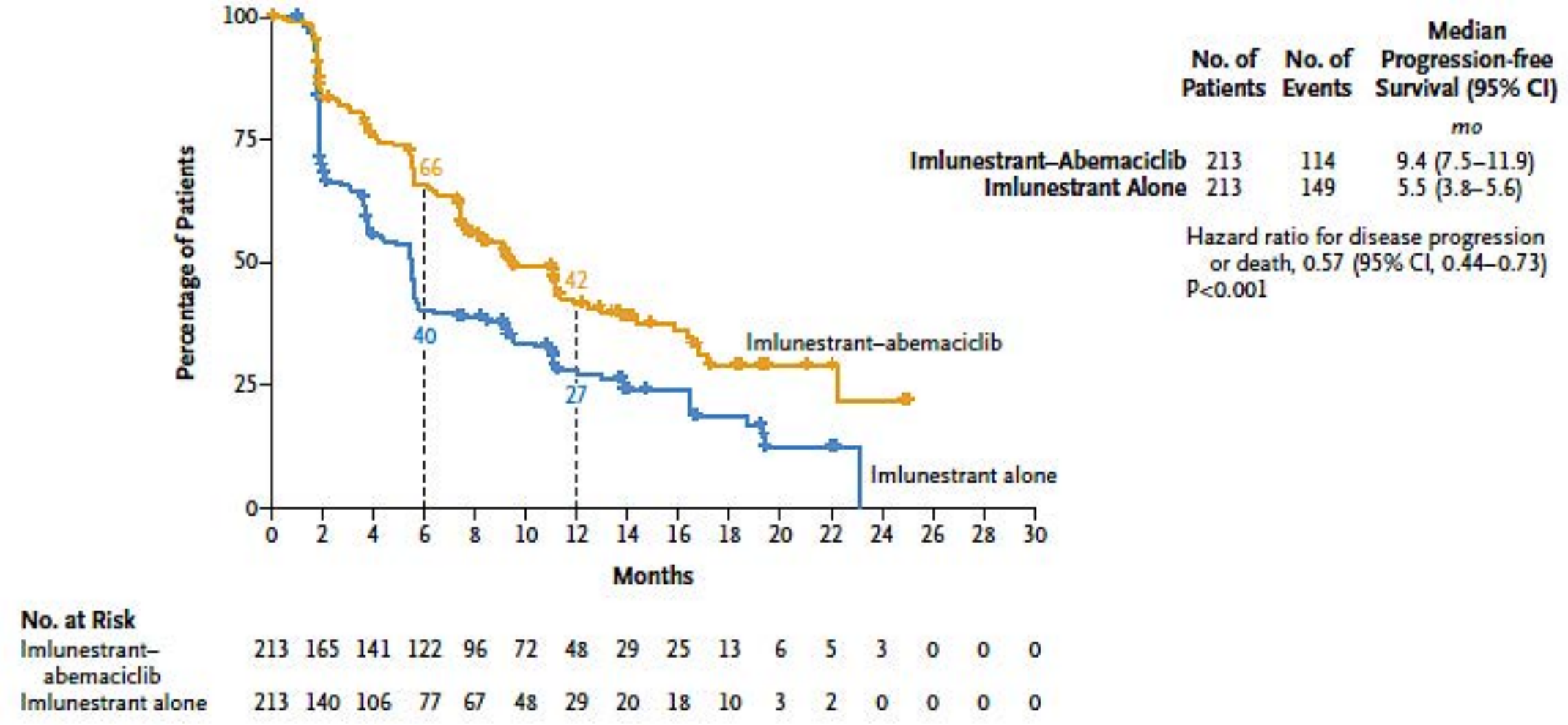
ORIGINAL ARTICLE

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

K.L. Jhaveri,[1] P. Neven,[2] M.L. Casalnuovo,[3] S.-B. Kim,[4] E. Tokunaga,[5] P. Aftimos,[6] C. Saura,[7] J. O'Shaughnessy,[8] N. Harbeck,[9] L.A. Carey,[10] G. Curigliano,[11,12] A. Llombart-Cussac,[13] E. Lim,[14] M.L. García Tinoco,[15] J. Sohn,[16] A. Mattar,[17] Q. Zhang,[18] C.-S. Huang,[19] C.-C. Hung,[20] J.L. Martinez Rodriguez,[21] M. Ruíz Borrego,[22] R. Nakamura,[23] K.R. Pradhan,[24] C. Cramer von Laue,[24] E. Barrett,[24] S. Cao,[24] X.A. Wang,[24] L.M. Smyth,[24] and F.-C. Bidard,[25] for the EMBER-3 Study Group*

***N Engl J Med* 2025;392:1189-202.**

EMBER-3 Trial Progression-Free Survival: Imlunestrant/Abemaciclib versus Imlunestrant Alone — All Patients

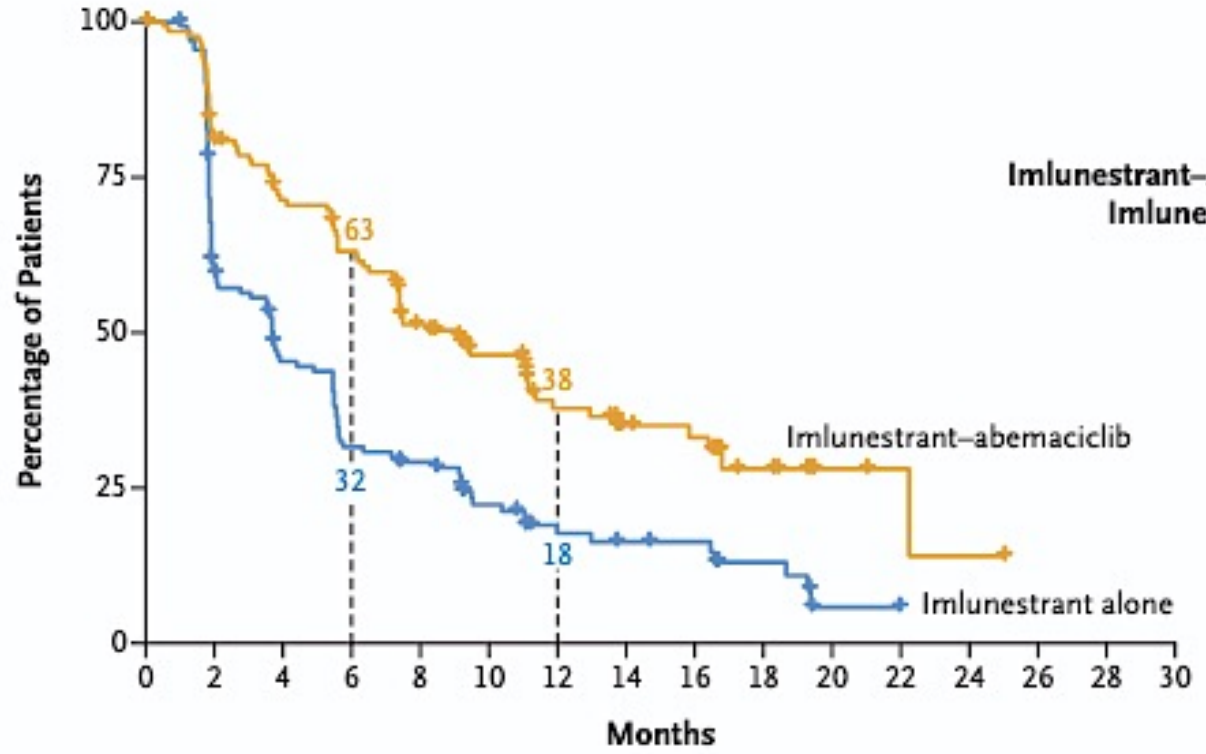


	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

Jhaveri K et al. *N Engl J Med* 2025;392(12):1189-202.

EMBER-3 Progression-Free Survival: Imlunestrant/Abemaciclib versus Imlunestrant Alone — Patients Who Previously Received a CDK4/6 Inhibitor



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

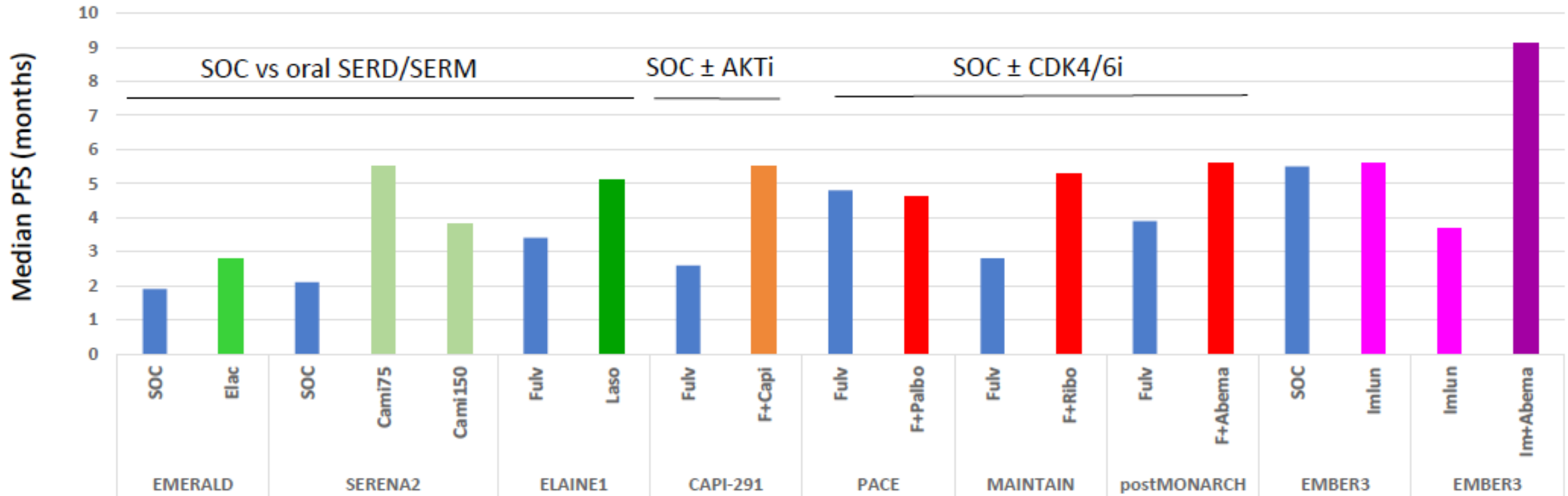
Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

No. at Risk																
Imlunestrant–abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0
Imlunestrant alone	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0

Jhaveri K et al. *N Engl J Med* 2025;392(12):1189-202.

RTP RESEARCH TO PRACTICE

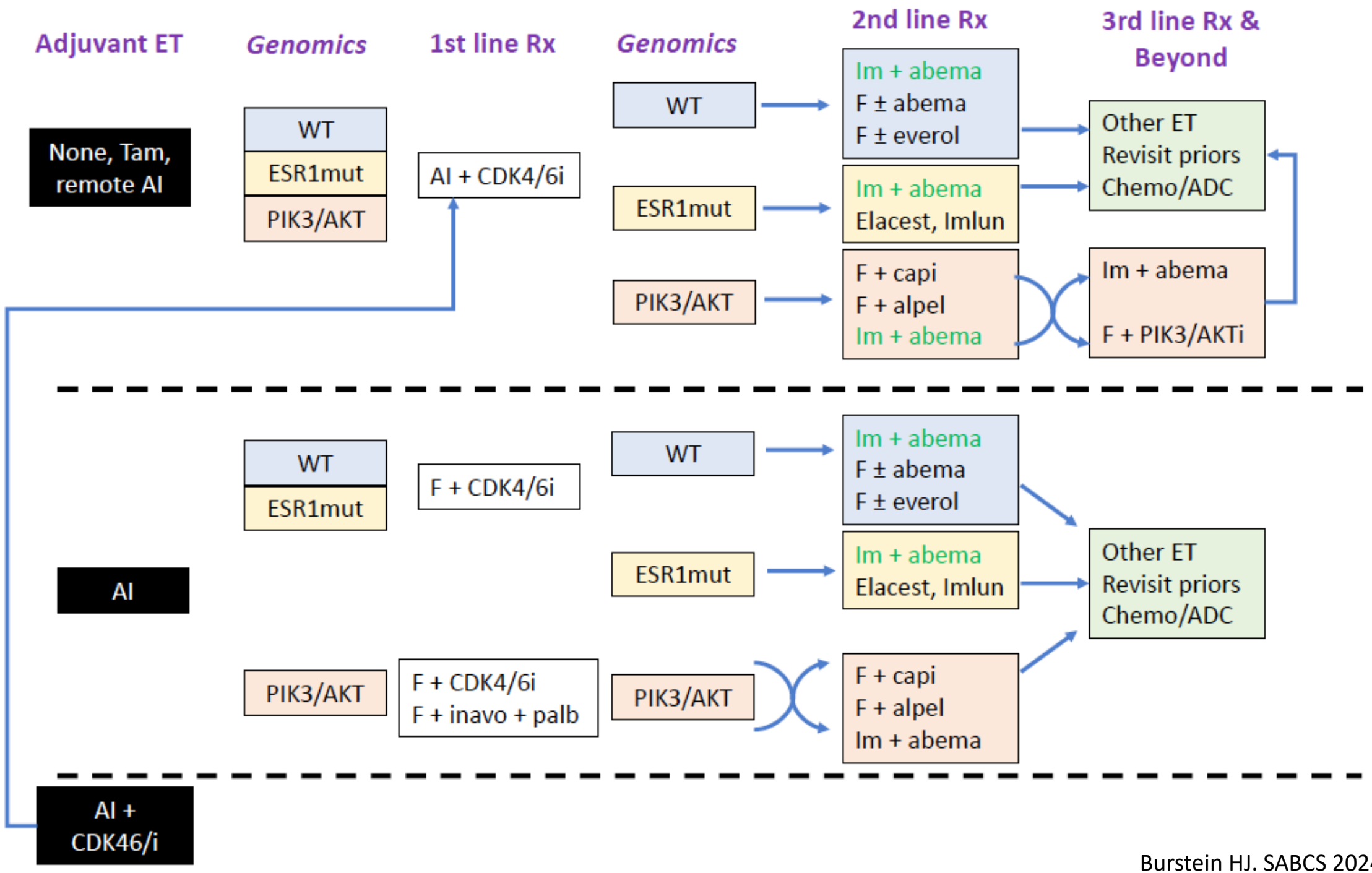
Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy:
*Outcomes among patients with prior CDK4/6 inhibitor treatment**



*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

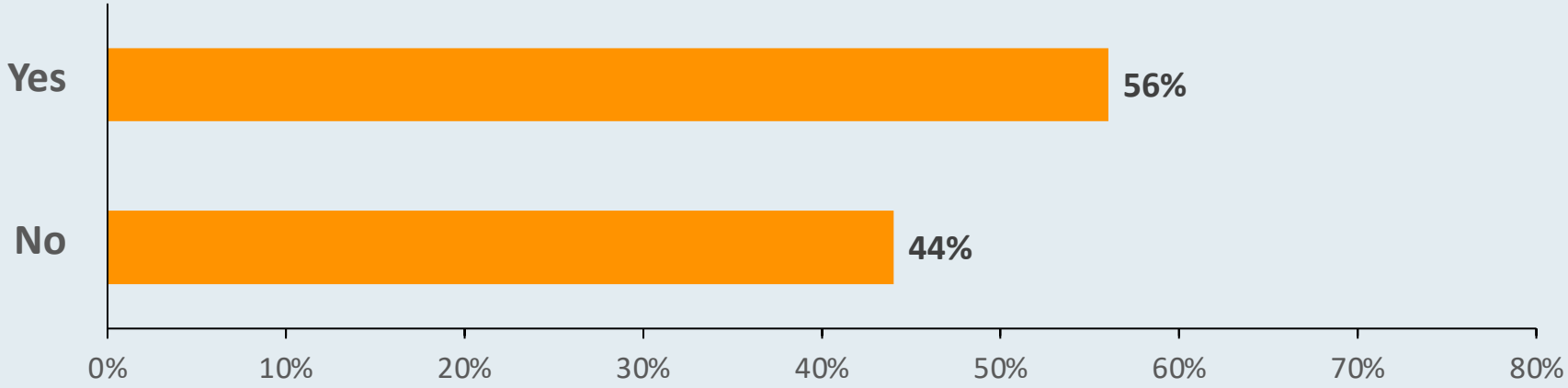
** Denotes subset of larger study cohort

Burstein HJ. SABCS 2024; Discussant.



Burstein HJ. SABCS 2024; Discussant.

Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib as first-line treatment for ER-positive, HER2-negative mBC?



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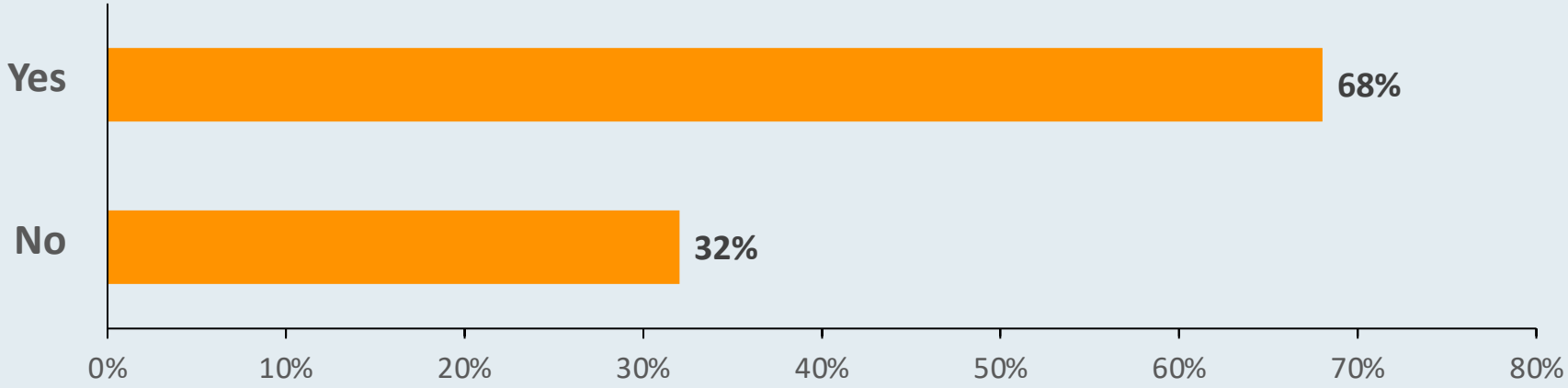

Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

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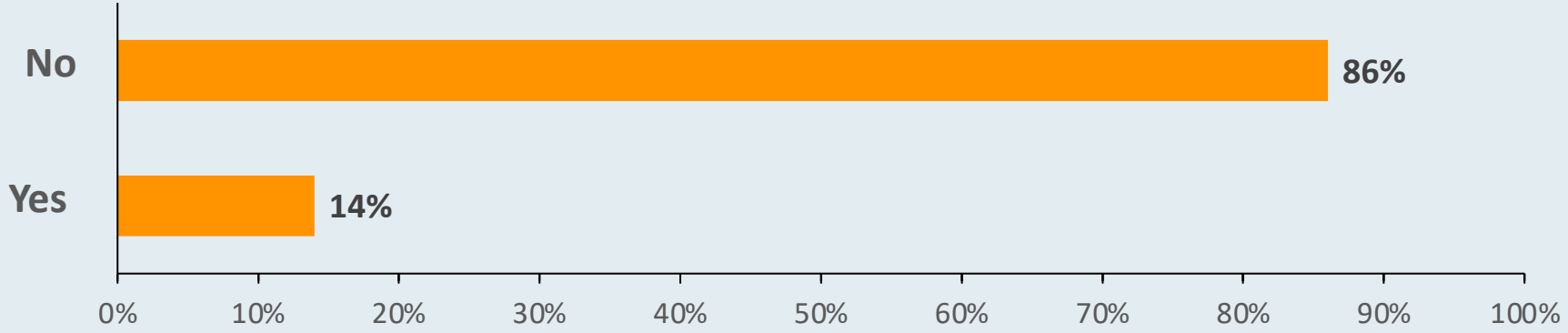
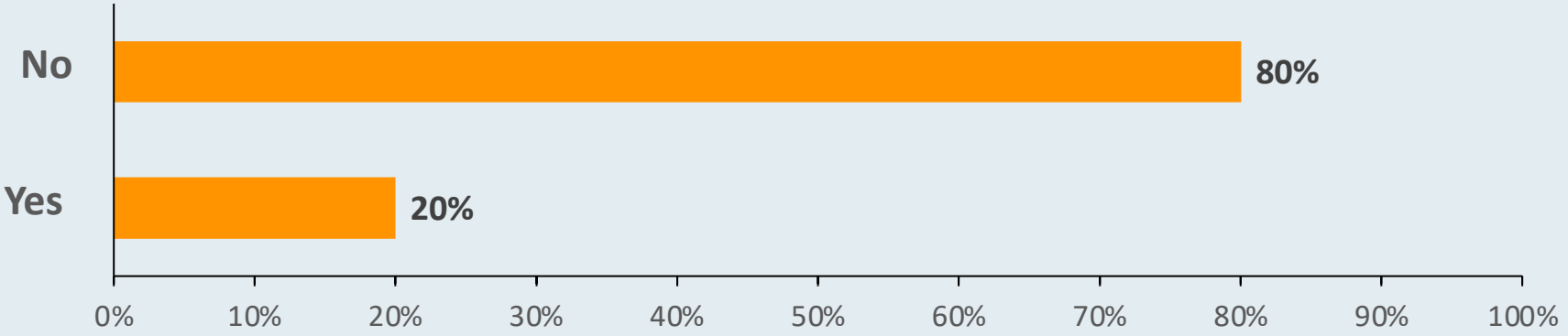
Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you administer an oral selective estrogen receptor degrader (SERD) and CDK4/6 inhibitor combination other than imlunestrant/abemaciclib under any circumstances?



If multiple oral SERDs become available, can you envision any scenario in which you would administer more than one of these agents in sequence to the same patient?



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

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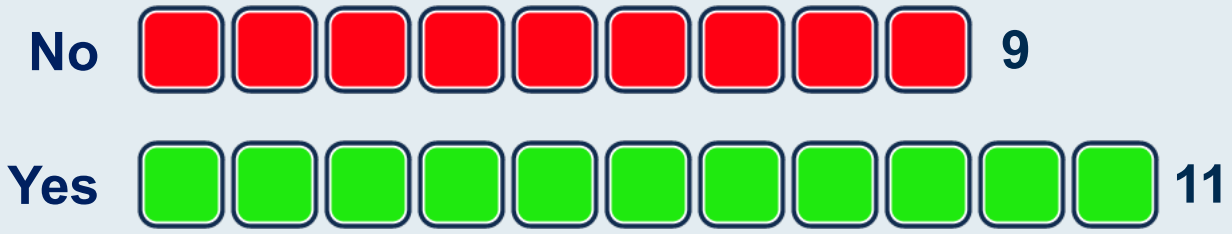

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

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Module 4: Other SERD Issues

Using ctDNA to Direct Changes in Therapy in the Absence of Clinical Progression of HR+ HER2- MBC

Joyce O'Shaughnessy, MD

Baylor University Medical Center, Dallas TX

Texas Oncology

Sarah Cannon Research Institute

CASE: 1L HR+ HER2- MBC

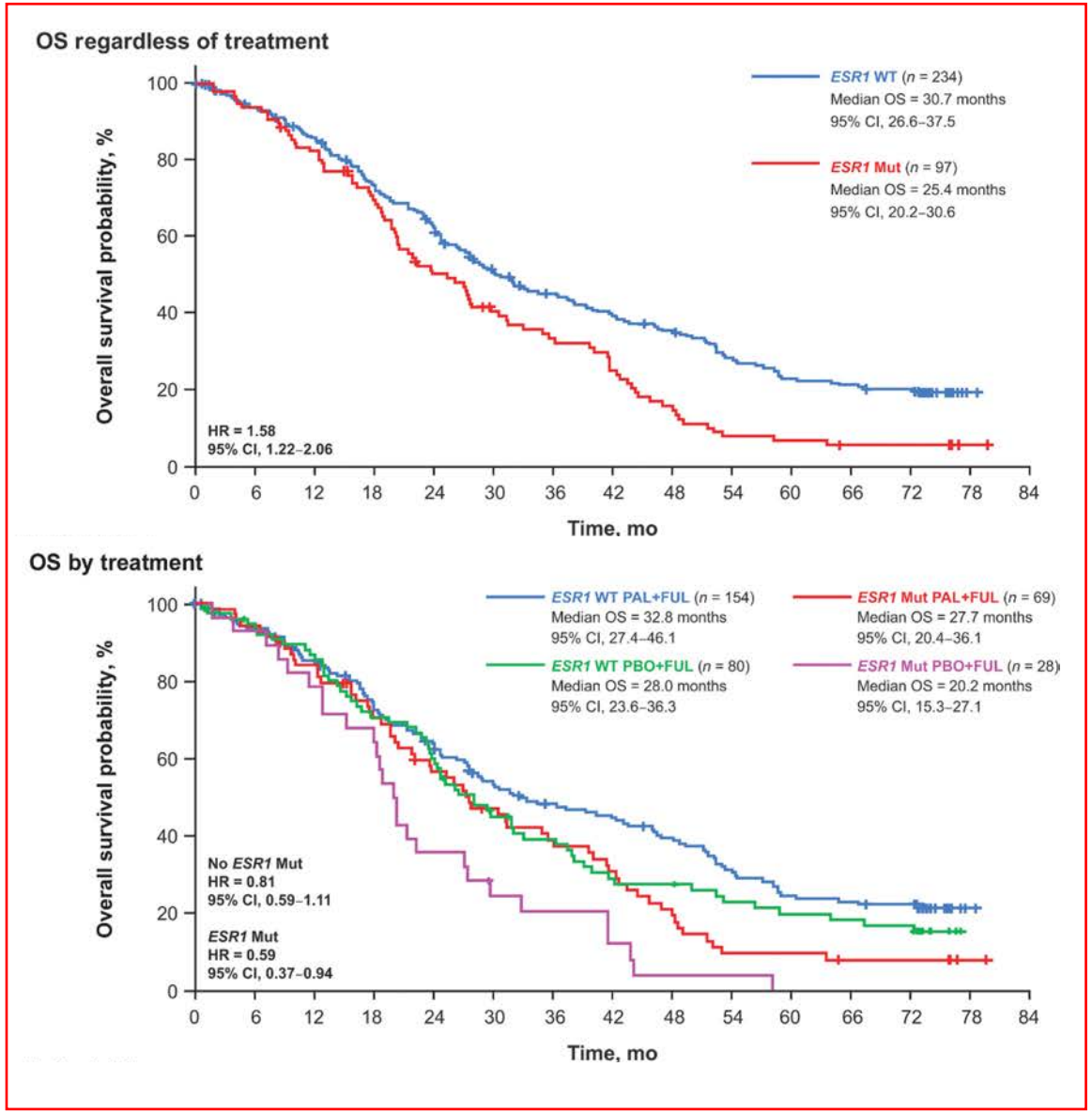
- A 44 yo woman presented with an enlarging right breast mass with axillary adenopathy. Biopsy showed grade 2 IDC, ER 100%, PR 80%, HER2 1+ FISH-, Ki-67 30%
- PET CT scan showed multiple bone metastases and 5 liver metastases with mildly elevated LFTs. She was asymptomatic
- Liver biopsy confirmed HR+ HER2- MBC
- ctDNA and NGS of liver metastasis showed co-amplification of *FGFR1* and *CCND1* genes
- Panel testing showed no germline mutation

CASE: 1L HR+ HER2- MBC

- She was treated with leuprolide, letrozole and abemaciclib. PET CT scan after 4 mos showed complete resolution of liver metastases with improved but residual FDG uptake in multiple bone metastases
- She continued on therapy and began serial ctDNA testing for *ESR1* mutations every 3 mos
- After 16 mos on therapy ctDNA revealed 2 *ESR1* mutations
- PET CT scan now shows continued FDG uptake in several bone metastases without progression
- Her therapy is changed to leuprolide, camizestrant and abemaciclib

Overall Survival with Palbociclib and Fulvestrant in Women with HR$^+$/HER2$^-$ ABC: PALOMA-3 Phase III Randomized Study

Worse overall survival with *ESR1* mutation with fulvestrant + palbociclib



Need combination of CDK4/6i + oral SERD for *ESR1*-mutant MBC

Cristofanilli M, et al. *Clin Cancer Res*. 2022;28(16):3433-3442.

Background: *ESR1*$_{mut}$ & PADA-1 design

***ESR1* mutations**

- are acquired during aromatase inhibitors (AI) therapy in ~40% of ER+ HER2- mBC pts and drive resistance
- can be detected by ctDNA analysis in blood (*bESR1*$_{mut}$)
- retain partial sensitivity to fulvestrant (FUL), a selective estrogen receptor dégrader (SERD)

PADA-1

- Strategy: **targeting rising *bESR1*$_{mut}$ when they become detectable** under AI+Palbociclib (PAL) [1]

[1] Berger *et al.*, BMJ Open 2022

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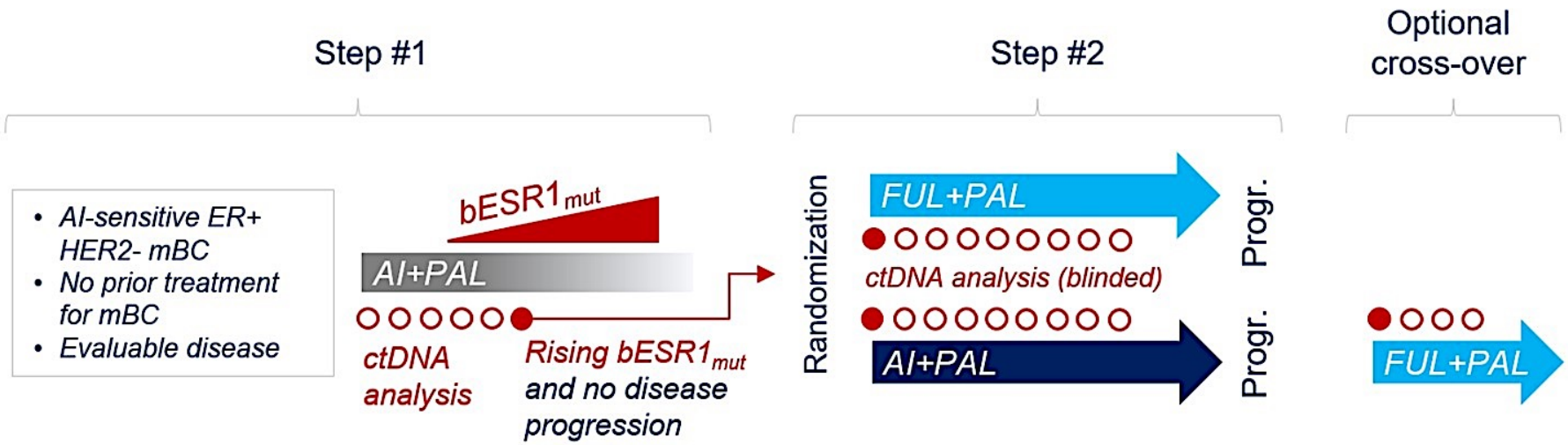


[1] Berger *et al.*, BMJ Open 2022

Updated PFS results – primary endpoint

N= 1,017 pts enrolled in step #1

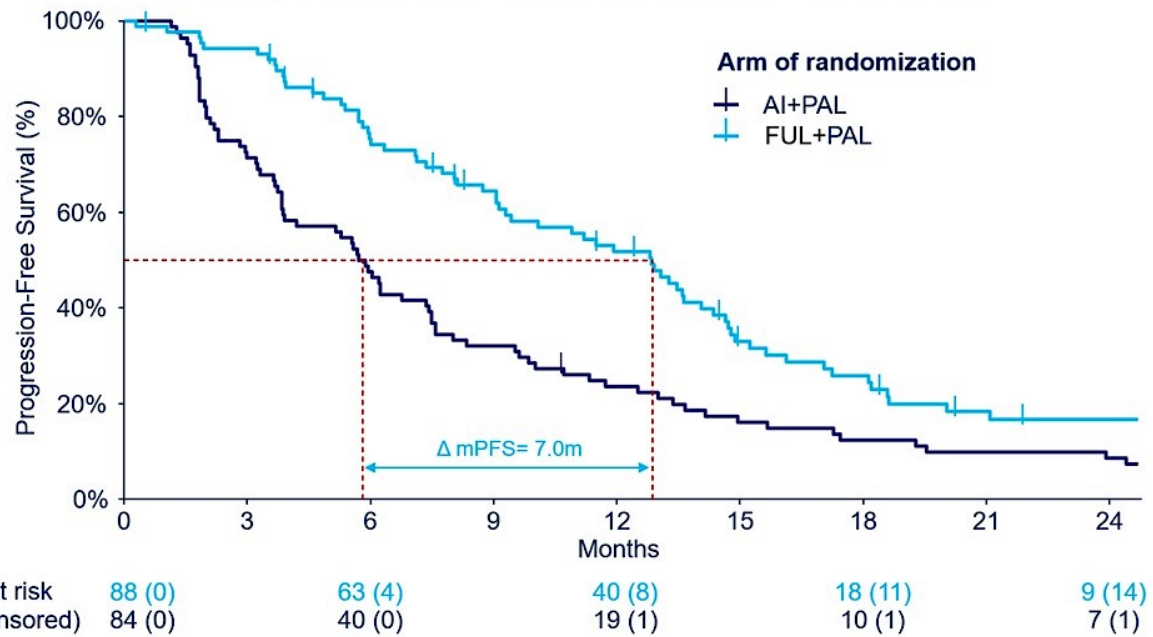
N= 283 pts with a rising *bESR1$_{mut}$*
while the study was ongoing

N= 172 pts randomized

- N= 88 pts allocated to FUL+PAL
- N= 84 pts allocated to AI+PAL

Data cut-off: June 21, 2022 Median FU from randomization: 28.2 months; N= 152 PFS events (89% maturity)

Progression-Free Survival, from randomization



FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

AI+PAL mPFS: 5.8 months, 95%CI [3.9;7.5]

PFS HR= 0.54 [0.38;0.75]

Optional cross-over (N=49 patients)

mPFS: 3.5 months, 95%CI [2.4;5.4]

2021 analysis [2]

N=134 events

11.9 months

5.7 months

0.61

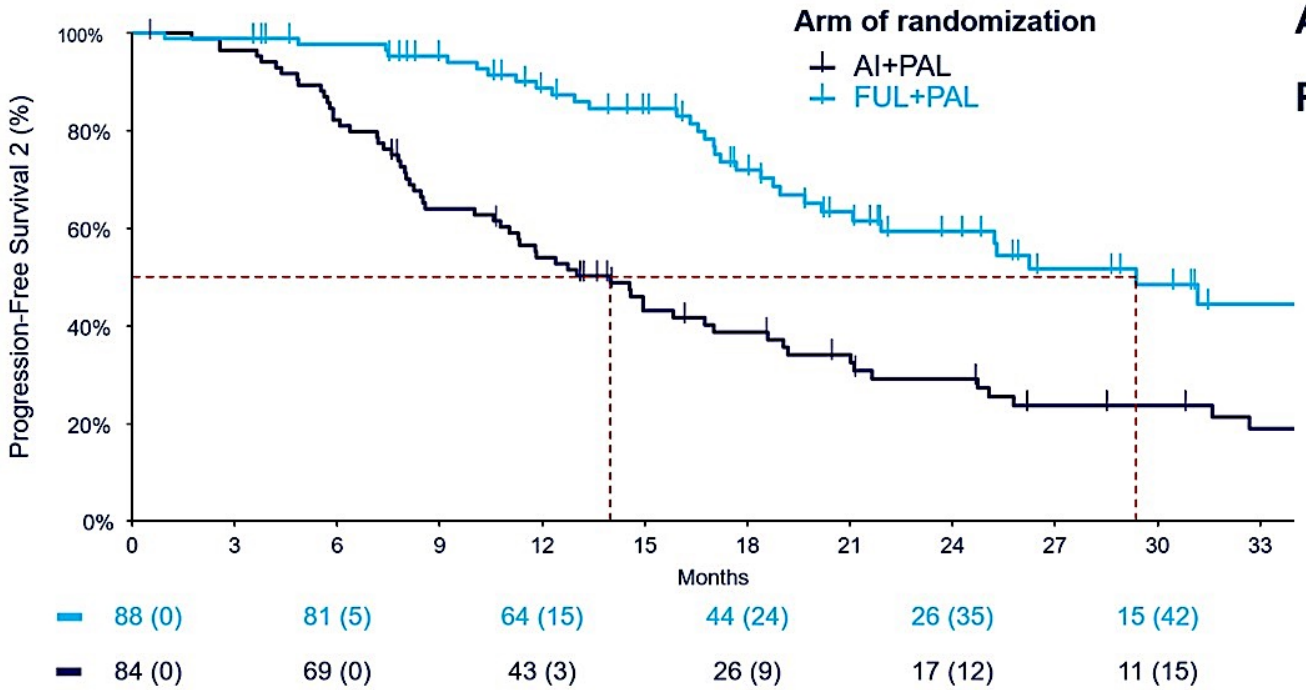
3.5 months

[2] Bidard *et al.*, Lancet Oncol 2022

PFS2 results – secondary endpoint

Data cut-off: June 21, 2022 N= 93 PFS2 events (54% maturity)

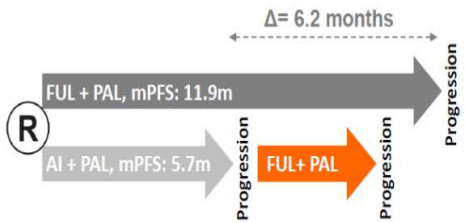
Progression-Free Survival 2, from randomization



FUL+PAL mPFS2: 29.4 months, 95%CI [21.9;NR]

AI+PAL mPFS2: 14.0 months, 95%CI [11.0;18.6]

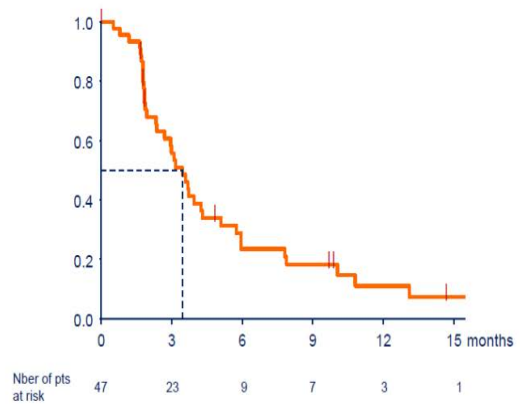
PFS2 HR= 0.37 [0.24;0.56]



As of July 31st, 2021:

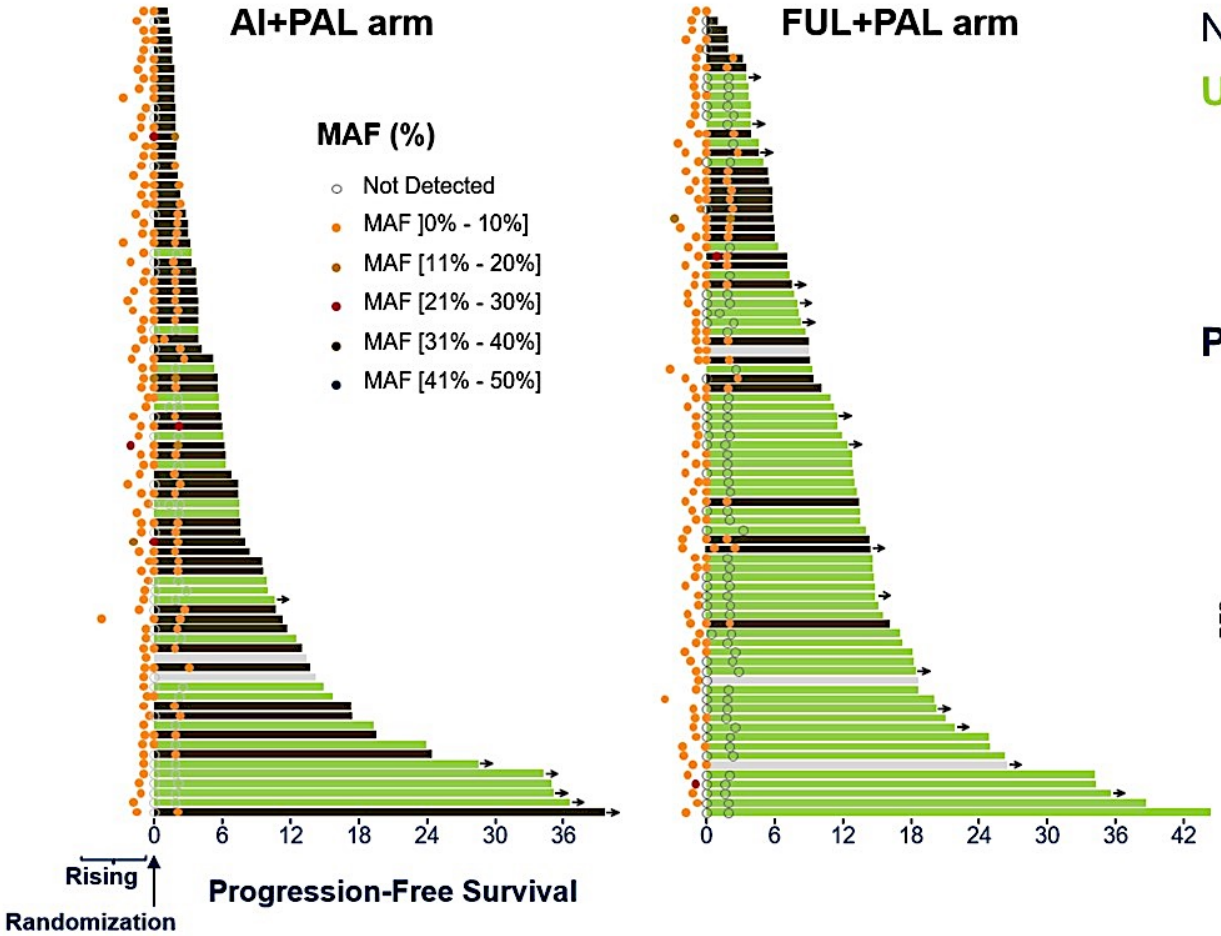
- N= 69 pts had a PD in the AI+PAL arm
- **N= 47 pts participated in the optional 2nd line cross-over cohort**
- Median FU in step #3: 14.7 months (range 0-17.3)
- 37 PFS events observed

Median 2nd line PFS with FUL+PAL
3.5 months 95%CI=[2.7;5.1]



Data cut-off: June 21, 2022; PFS2: time to 2nd progression or death in both arms

bESR1$_{mut}$ after 2 months on therapy



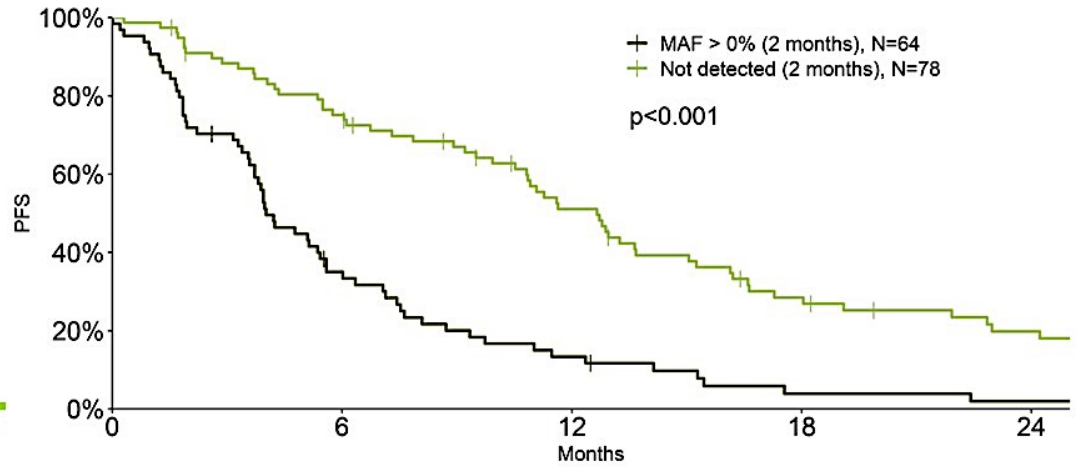
N=163 pts with ctDNA results available at 2 months

Undetectability rate:

FUL+PAL: N=58/85 68.2% [58.3%;78.1%]

AI+PAL: N=25/78 32.1% [21.7%;42.4%]

PFS by mutation status at 2 months (landmark analysis)



SERENA-6 Study (Turner N, ASCO 2025; Bidard FC, NEJM 2025)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1

N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

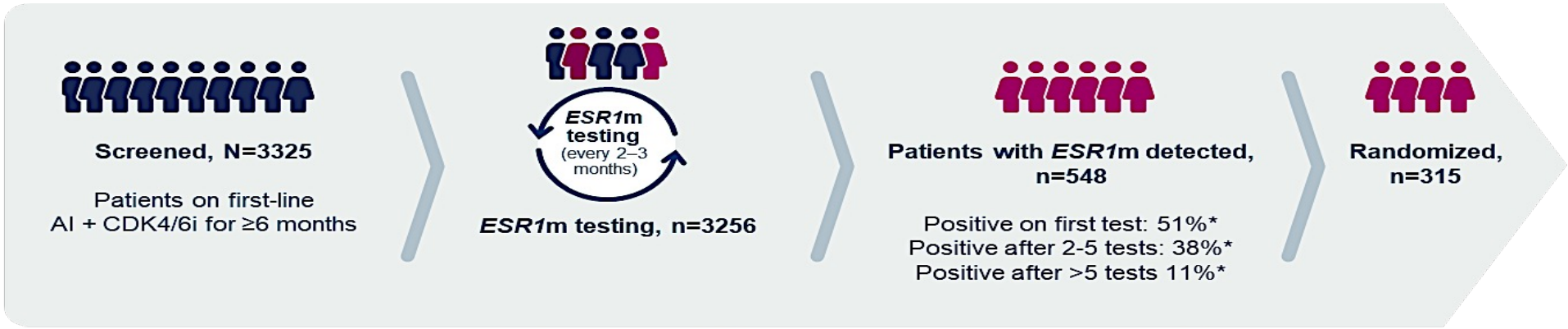
Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2**
- OS**
- Safety
- Patient-reported outcomes



Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

Patients ongoing in surveillance when screening closed, n=1949

Discontinued (n=233) due to:

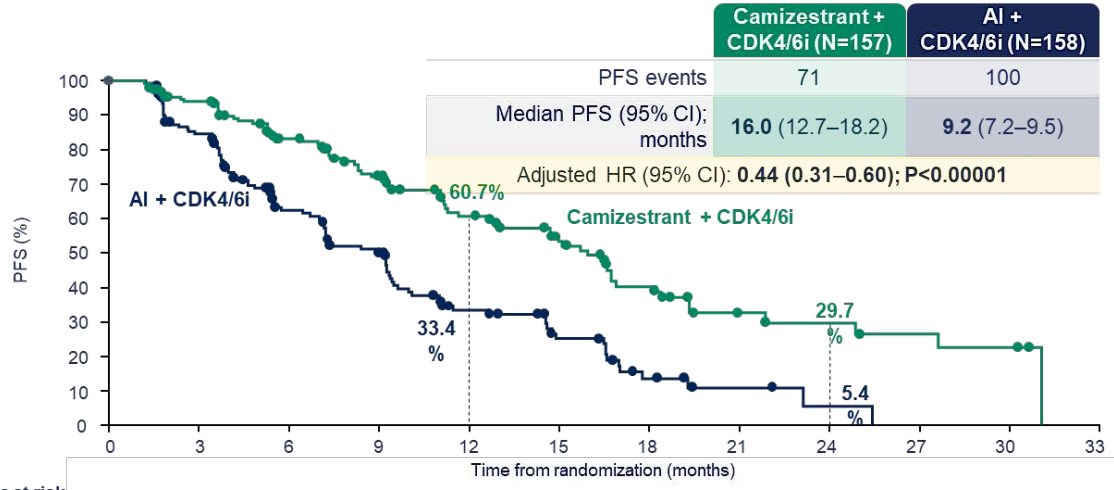
- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

SERENA-6 Study (Turner N, ASCO 2025; Bidard FC, NEJM 2025)

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)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
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)
	Median (range) – months	22 (4–95)	22 (6–96)
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)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

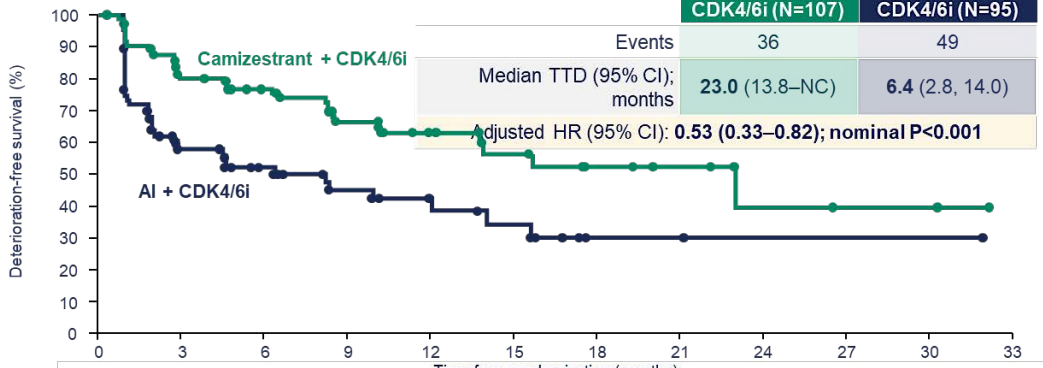
Investigator-assessed PFS



	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		

Number of patients at risk												
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

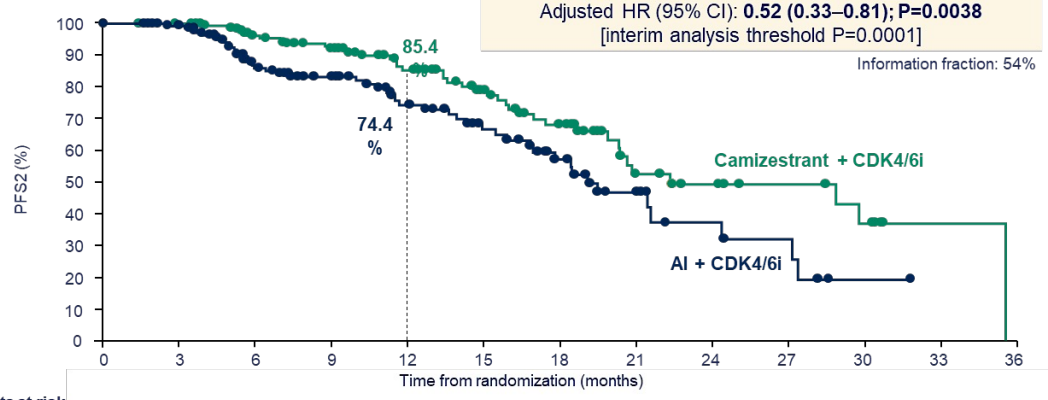
Time to deterioration in global health status/quality of life



	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		

Number of patients at risk												
Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

PFS-2



	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47
Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038** [interim analysis threshold P=0.0001]		
Information fraction: 54%		

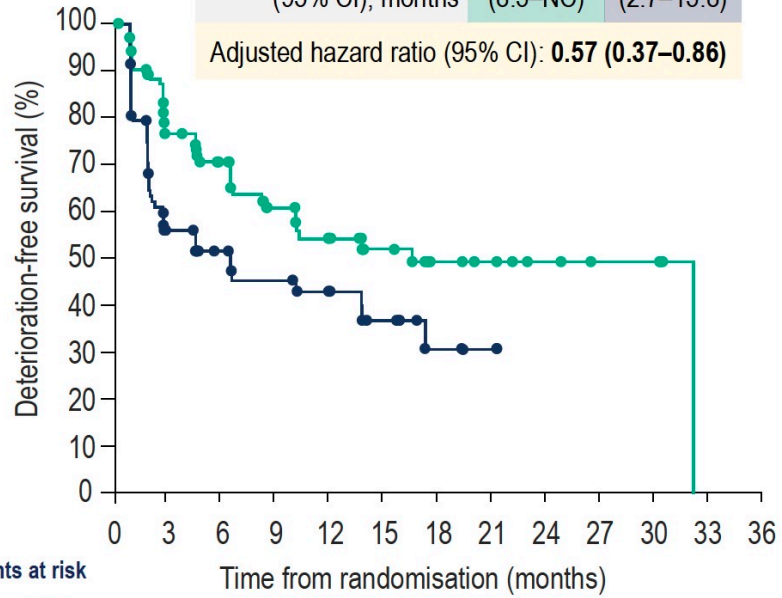
Number of patients at risk													
Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0

SERENA-6: Time to deterioration of patient-reported cancer symptoms

Pain (secondary endpoint)

	CAMI + CDK4/6i	AI + CDK4/6i
Events	42/106	49/94
Median TTD (95% CI); months	**16.6** (8.3–NC)	**6.5** (2.7–13.8)

Adjusted hazard ratio (95% CI): **0.57 (0.37–0.86)**



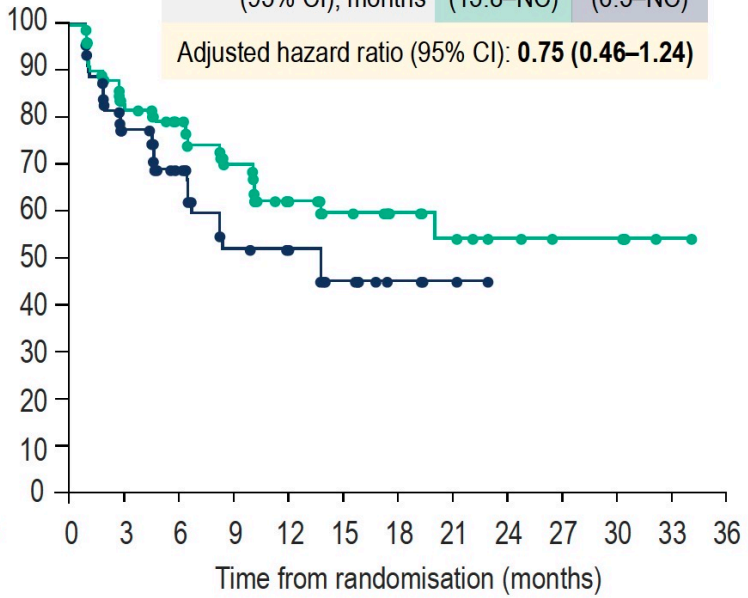
Patients at risk

CAMI + CDK4/6i	106	67	54	39	30	21	11	9	6	4	4	0	0
AI + CDK4/6i	94	39	26	21	14	10	4	2	0	0	0	0	0

Fatigue

	CAMI + CDK4/6i	AI + CDK4/6i
Events	34/104	33/91
Median TTD (95% CI); months	**NR** (13.8–NC)	**13.8** (6.5–NC)

Adjusted hazard ratio (95% CI): **0.75 (0.46–1.24)**

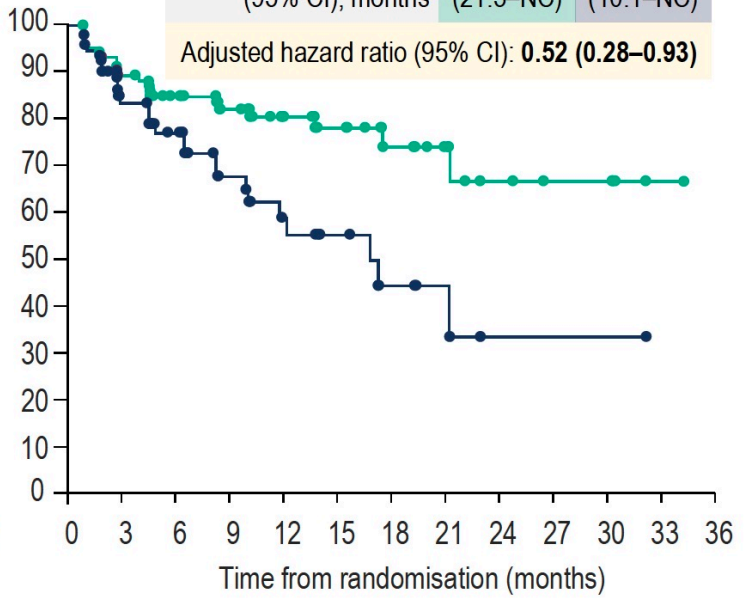


CAMI + CDK4/6i	104	75	64	48	28	21	14	10	7	5	5	1	0
AI + CDK4/6i	91	53	33	20	16	10	4	2	0	0	0	0	0

Shortness of breath/ dyspnoea

	CAMI + CDK4/6i	AI + CDK4/6i
Events	21/105	29/94
Median TTD (95% CI); months	**NR** (21.3–NC)	**16.8** (10.1–NC)

Adjusted hazard ratio (95% CI): **0.52 (0.28–0.93)**



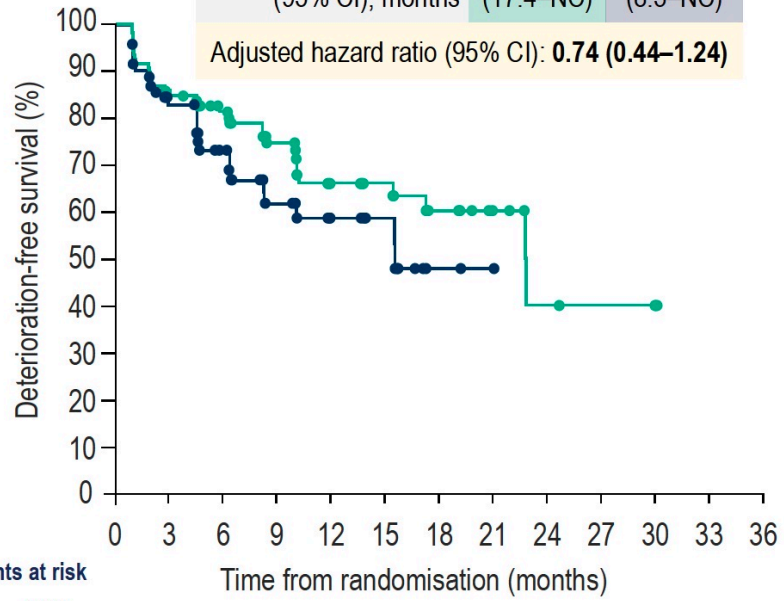
CAMI + CDK4/6i	105	82	70	57	38	28	17	12	7	5	5	1	0
AI + CDK4/6i	94	57	38	25	16	12	6	4	1	1	1	0	0

Mayer E, et al. ESMO 2025. Abstract 486MO.

SERENA-6 : Time to deterioration of patient-reported functioning

Physical: ability to perform everyday physical activities **(secondary endpoint)**

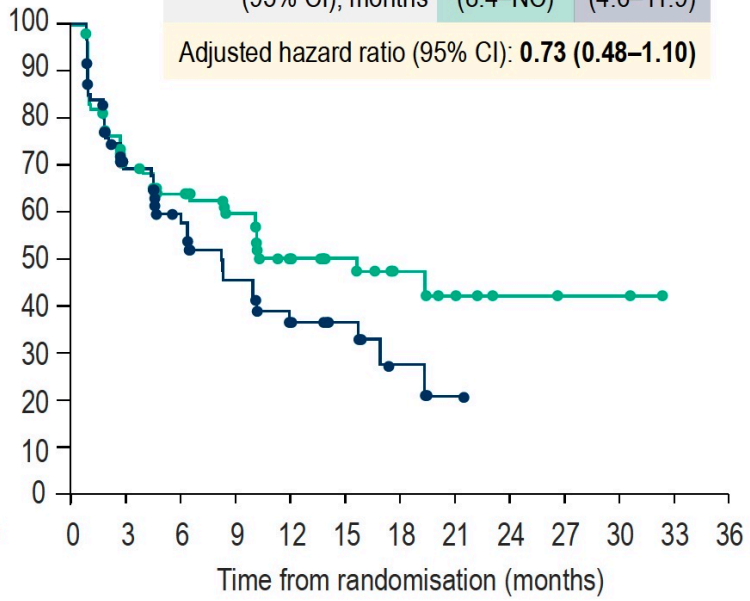
	CAMI + CDK4/6i	AI + CDK4/6i
Events	33/108	29/95
Median TTD (95% CI); months	**23.0** (17.4–NC)	**15.7** (8.3–NC)
Adjusted hazard ratio (95% CI): **0.74 (0.44–1.24)**		



Patients at risk													
CAMI + CDK4/6i	108	81	67	50	31	24	14	9	4	3	3	0	0
AI + CDK4/6i	95	56	36	24	15	11	2	1	0	0	0	0	0

Role: impact of health on work and daily activities

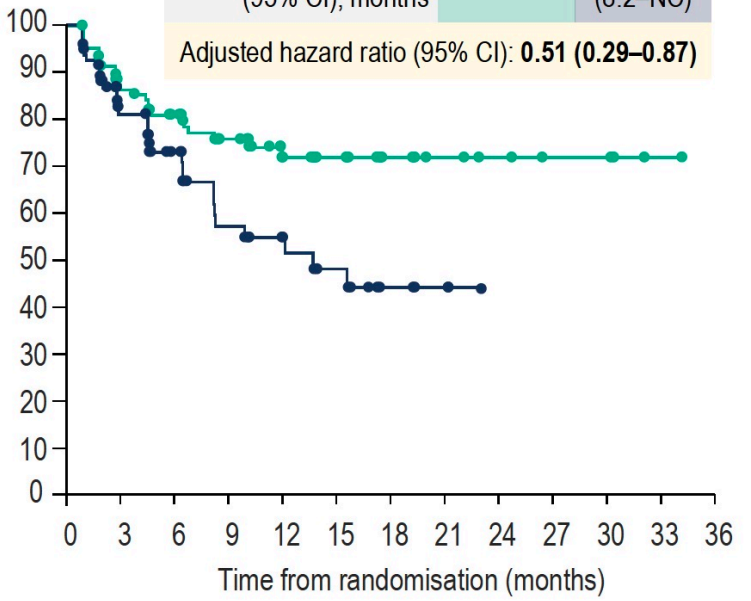
	CAMI + CDK4/6i	AI + CDK4/6i
Events	48/108	47/94
Median TTD (95% CI); months	**15.6** (8.4–NC)	**8.2** (4.6–11.9)
Adjusted hazard ratio (95% CI): **0.73 (0.48–1.10)**		



CAMI + CDK4/6i	108	66	52	41	25	18	9	5	3	2	2	0	0
AI + CDK4/6i	94	46	31	21	14	10	4	1	0	0	0	0	0

Emotional: feelings of anxiety, depression and irritability

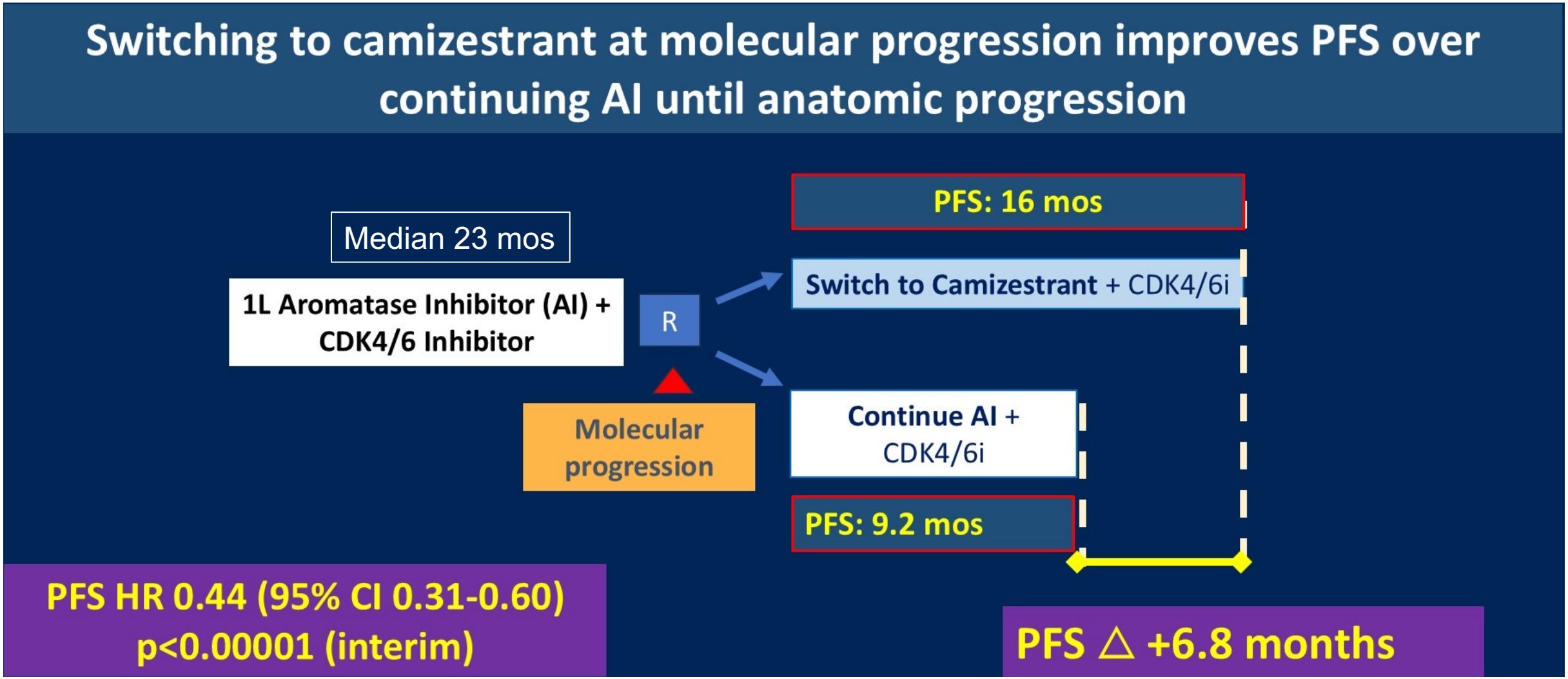
	CAMI + CDK4/6i	AI + CDK4/6i
Events	25/107	32/95
Median TTD (95% CI); months	**NR**	**13.7** (8.2–NC)
Adjusted hazard ratio (95% CI): **0.51 (0.29–0.87)**		



CAMI + CDK4/6i	107	82	69	52	32	23	12	8	6	4	4	1	0
AI + CDK4/6i	95	54	36	24	17	12	5	3	0	0	0	0	0

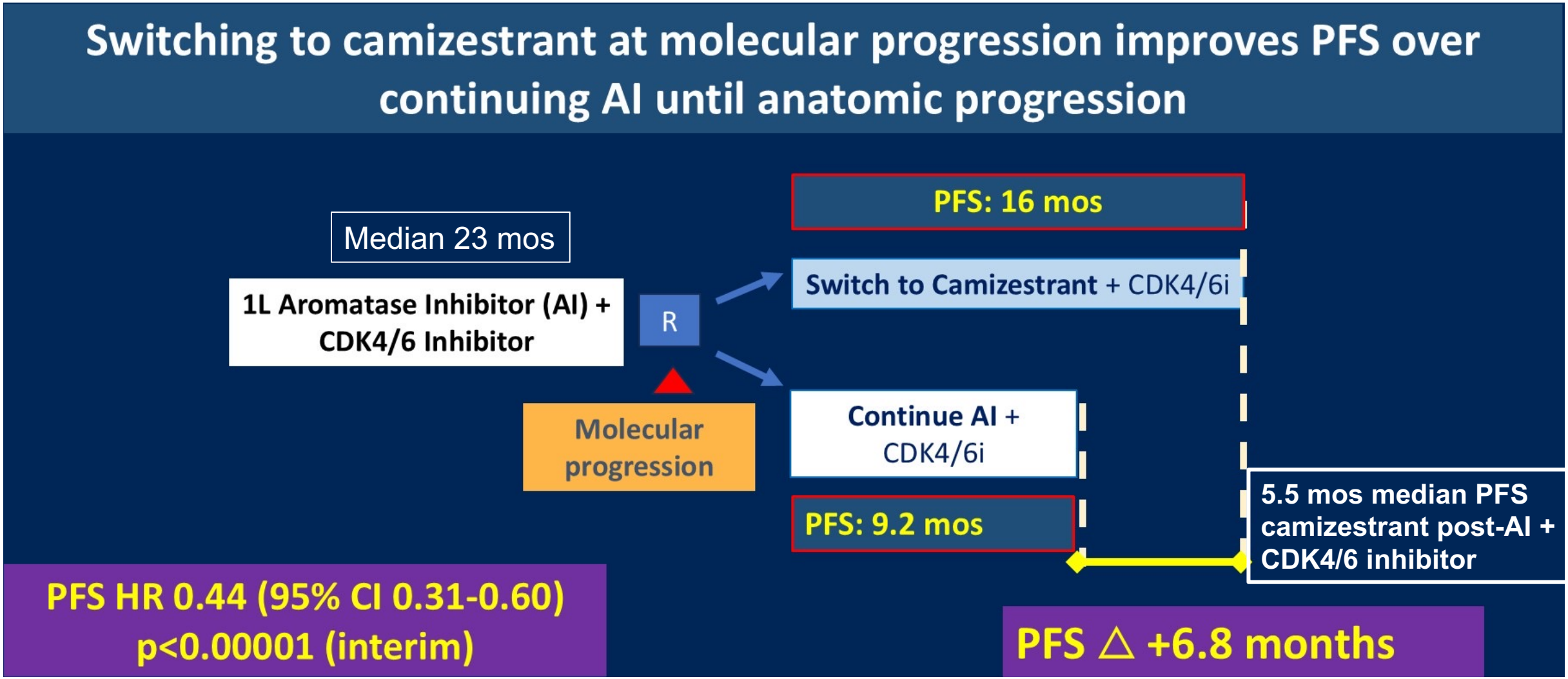
Mayer E, et al. ESMO 2025. Abstract 486MO.

SERENA-6 Met Primary Endpoint



DeMichele A, et al. Presented at: ASCO Annual Meeting; 2025.

SERENA-6 Met Primary Endpoint

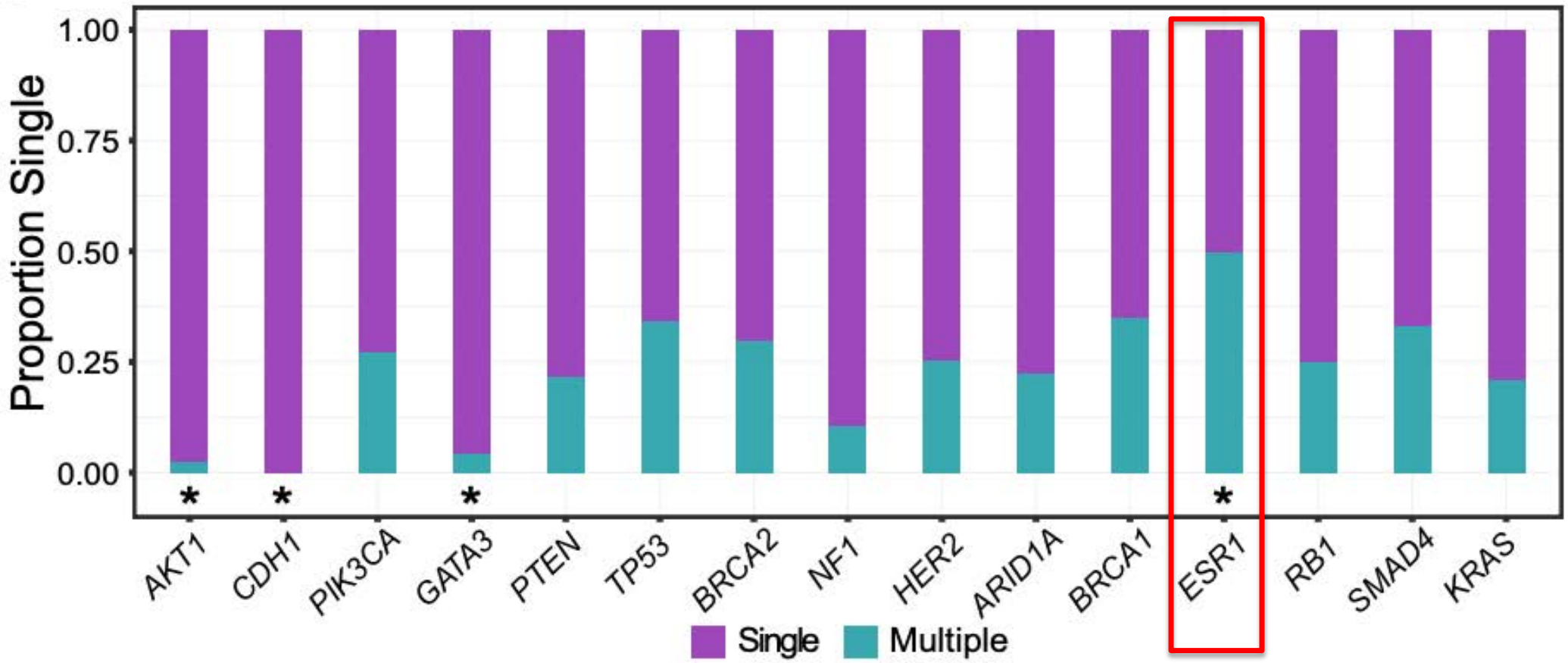


DeMichele A, et al. Presented at: ASCO Annual Meeting; 2025. Oliveira M, et al. *Lancet Oncol*. 2024;25(11):1424-1439.

Is Early Switch to Oral SERD Better than Sequential Therapy?

- In SERENA-6, *ESR1* mutation detection occurred between 4 mos to 8 years after initiation of AI + CDK4/6 inhibitor therapy
- Would benefit from camizestrant have been greater if switch occurred at earliest and lowest detectable level of *ESR1* mutation?
- Probably, as all our best therapies are most effective in treating MRD or early 1L MBC

Multiple ESR1 Mutations with Acquired AI Resistance



Kingston B, et al. *Nat Commun*. 2021;12(1):4479.

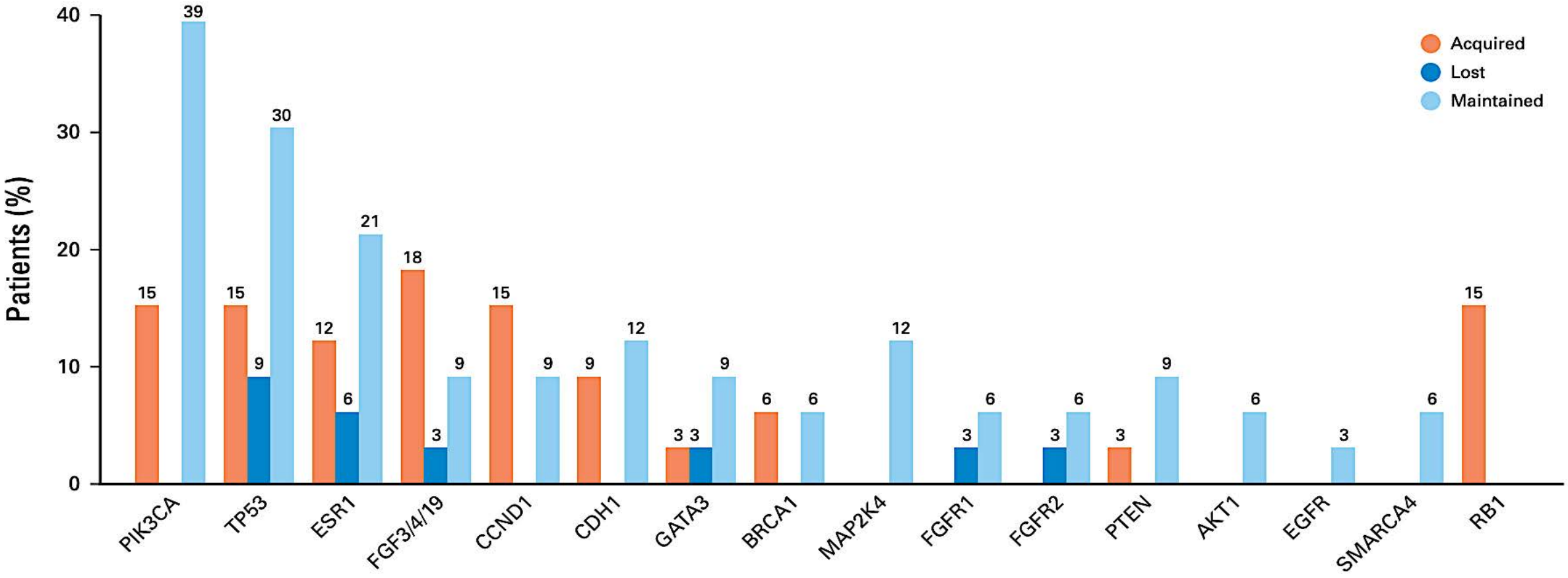
SERENA-2: 2L Camizestrant for *ESR1*m MBC – Does the Number of *ESR1*m Impact Oral SERD Efficacy? YES!!

	CAMI (n=147), No. (%)	CAMI mPFS, (90% CI), mo	FUL (n=73), No. (%)	FUL mPFS (90% CI), mo	CAMI vs FUL PFS HR (90% CI)
***ESR1*m detected**	48 (33)	8.0 (4.5, 12.0)	35 (48)	2.2 (1.9, 3.8)	0.44 (0.28, 0.68)
1 *ESR1*m variant detected	21 (44)	12.9 (4.5, 14.7)	17 (49)	2.2 (1.9, 9.3)	0.52 (0.28, 0.97)
> 1 *ESR1*m variant detected	27 (56)	4.7 (2.0, 11.1)	18 (51)	2.3 (1.9, 3.8)	0.45 (0.25, 0.81)
D538G detected	28 (58)	4.5 (2.0, 9 1)	23 (66)	2.2 (1.9, 3.8)	0.61 (0.36, 1.03)
Y537C/D/N/S detected	33 (69)	9.1 (3.9, 12.7)	23 (66)	2.3 (1.9, 5.6)	0.46 (0.28, 0.76)

The greatest mPFS improvement was seen in patients where a single *ESR1*m variant was detected, suggesting that early intervention upon detection of *ESR1*m may provide maximum patient benefit

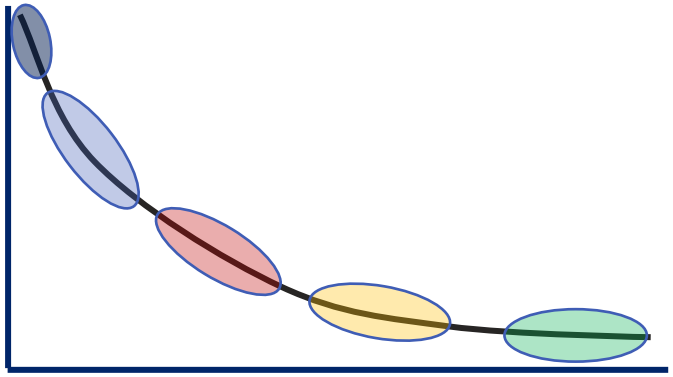
Oliveira M, et al. *J Clin Oncol*. 2023;41(16 Suppl):1066.

Acquired Mutations Cause ET-Resistance Post-Progression on AI + CDK4/6 Inhibitor



Hattori M, et al. *JCO Precis Oncol*. 2024;8:e2300647.

Intercepting Molecular Resistance with Switch to Oral SERD Prior to Radiologic Progression



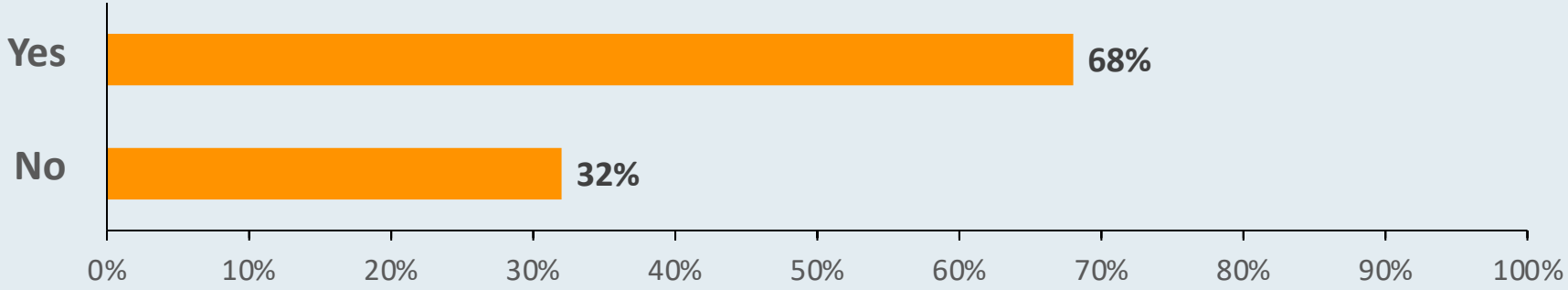
Switching Therapy at Molecular Progression: The Way Forward

- Early treatment with oral SERD to inhibit the driving mutant *ESR1* that is causing AI resistance
- Longer AI therapy leads to acquired polyclonal mutant *ESR1* – and less benefit from oral SERD therapy
- Longer AI therapy – more acquired aggressive mutations/biology and ET/CDK4/6i resistance

- Earliest detection of *ESR1* mutation with lowest metastatic and mutation burden with early switch from AI to oral SERD will optimize and prolong benefit from oral SERD + CDK4/6i in MBC

Regulatory and reimbursement issues aside, do you believe that the results from the SERENA-6 study justify the routine use of serial ctDNA monitoring for early detection of ESR1 mutations in patients with ER-positive, HER2-negative mBC receiving first-line therapy?

General Medical Oncologists

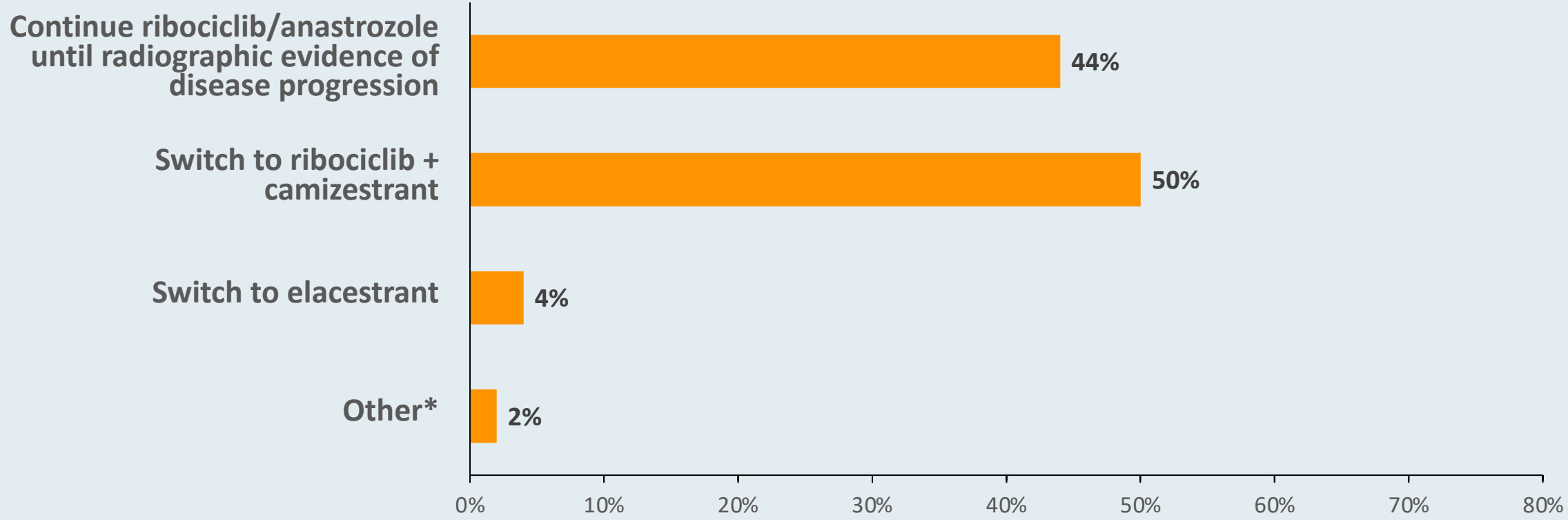


Clinical Investigators

Survey of 20 US-based clinical investigators and 50 general medical oncologists

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0/null) mBC with multiple minimally symptomatic bone metastases. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. She is started on ribociclib with anastrozole and followed with serial ctDNA testing for ESR1 mutations. After 1 year she is found to have an ESR1 mutation without radiographic evidence of disease progression. Regulatory and reimbursement issues aside, what would you most likely recommend?

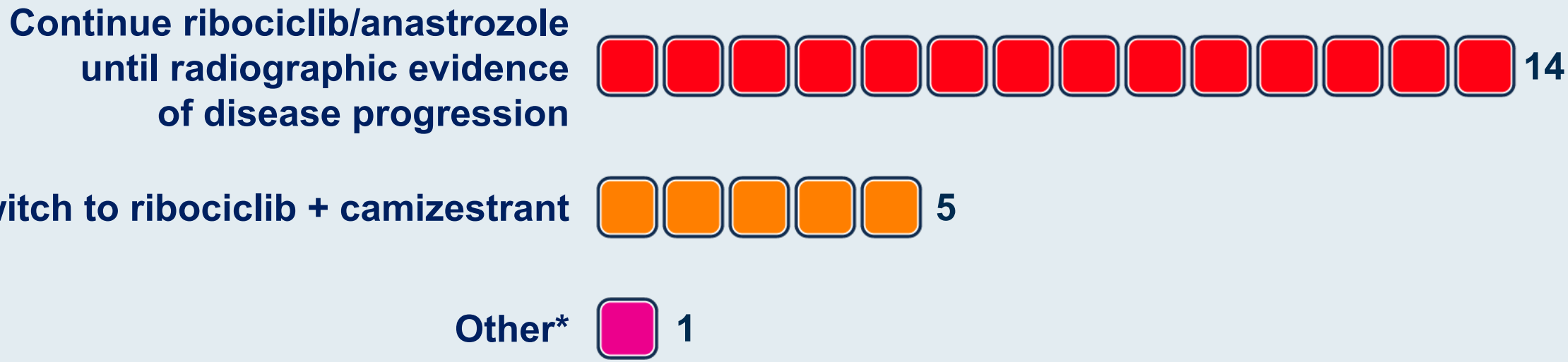


*** Combination of radiologic, biochemical and symptomatic progression**

Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0/null) mBC with multiple minimally symptomatic bone metastases. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. She is started on ribociclib with anastrozole and followed with serial ctDNA testing for ESR1 mutations. After 1 year she is found to have an ESR1 mutation without radiographic evidence of disease progression. Regulatory and reimbursement issues aside, what would you most likely recommend?

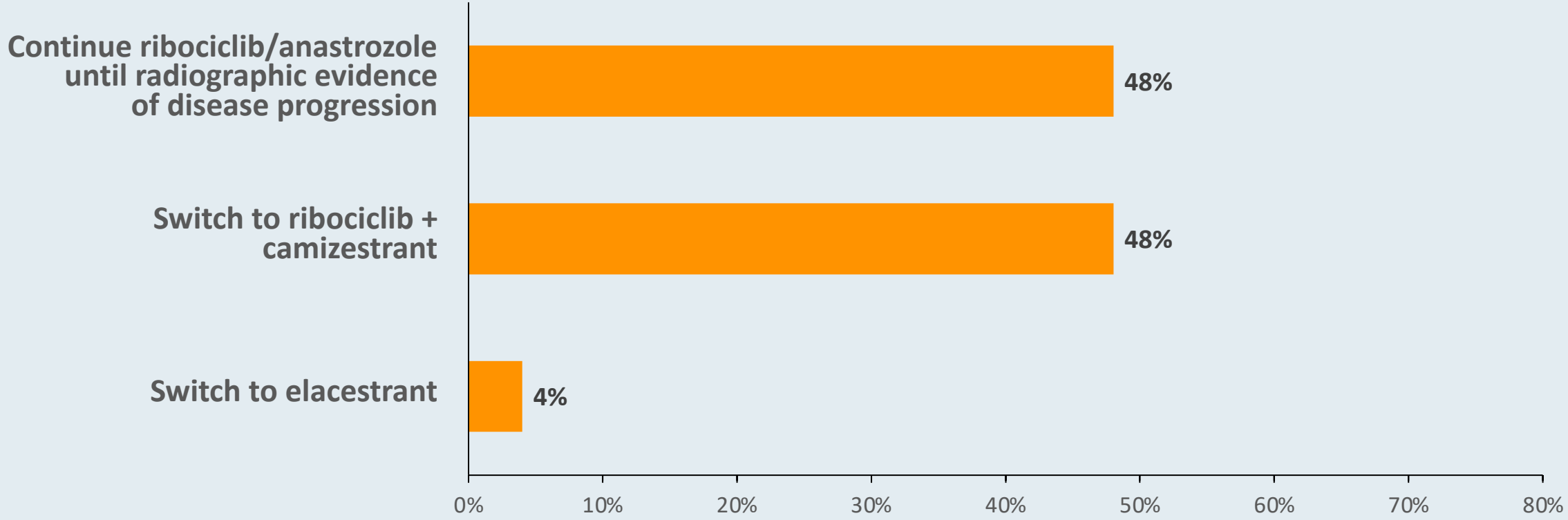


* I would wait for some change based on only the current data, emergence of pain without progression on imaging for example, or rising tumor markers, or rising ctDNA.

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0/null) mBC with multiple minimally symptomatic bone metastases. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. She is started on ribociclib with anastrozole and followed with serial ctDNA testing for ESR1 mutations. After 2 years, she is found to have an ESR1 mutation without radiographic evidence of disease progression. Regulatory and reimbursement issues aside, what would you most likely recommend?



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

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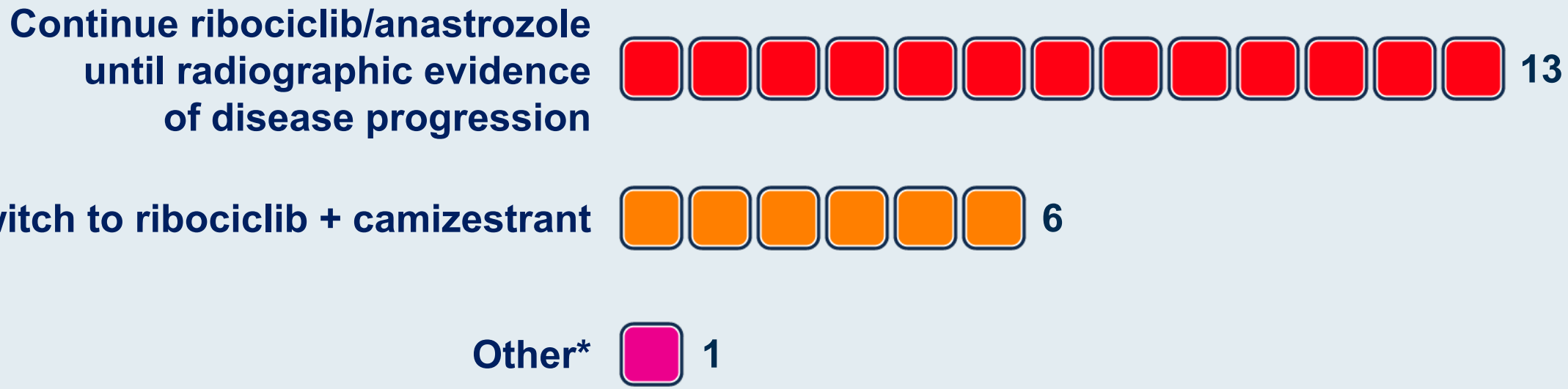

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Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

Agenda

Introduction: Oral SERDs for the General Medical Oncologist

Module 1: SERD Monotherapy

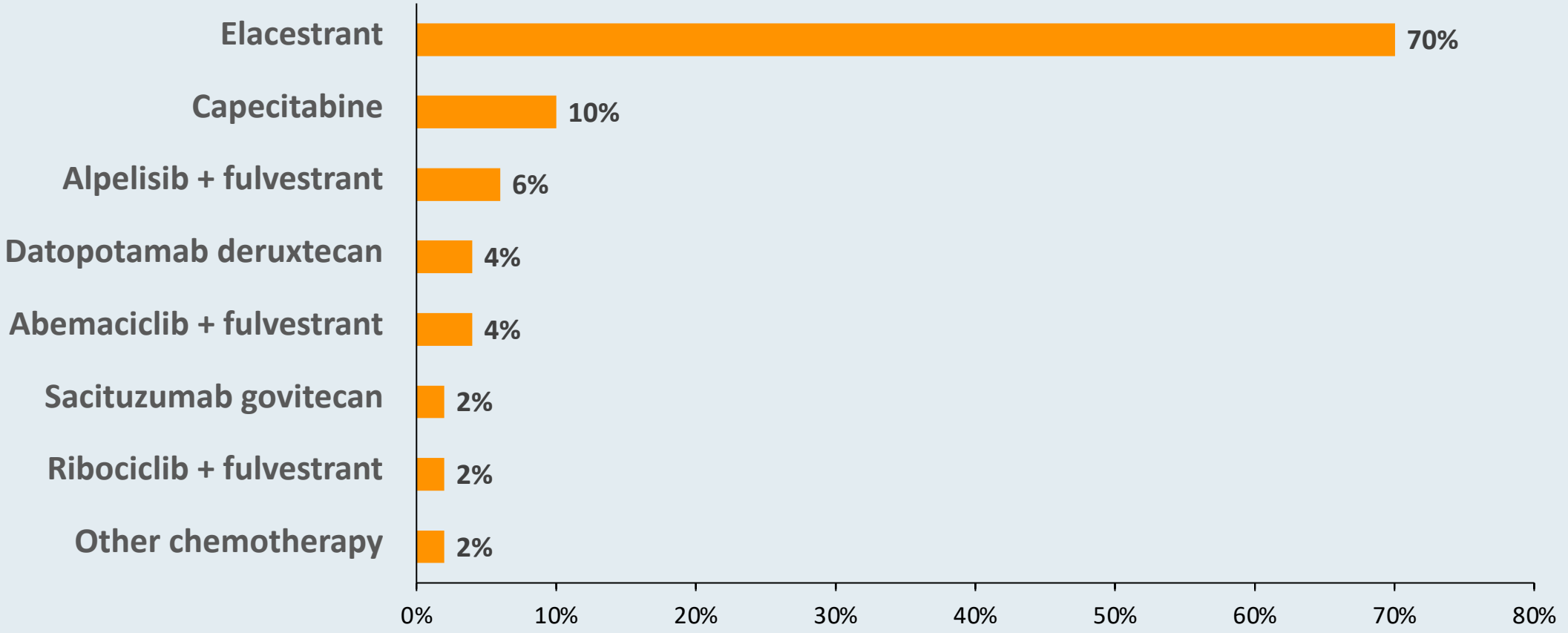
Module 2: SERD + CDK Inhibitor Combination — EMBER-3

Module 3: SERD for "Molecular Progression" — SERENA-6

Module 4: Other SERD Issues

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) breast cancer with a PIK3CA mutation who develops metastatic disease after 2 years of adjuvant anastrozole receives inavolisib + palbociclib + fulvestrant for 10 months followed by disease progression with multiple minimally symptomatic bone metastases

Persistent PIK3CA mutation | **New ESR1 mutation**



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RTP RESEARCH TO PRACTICE

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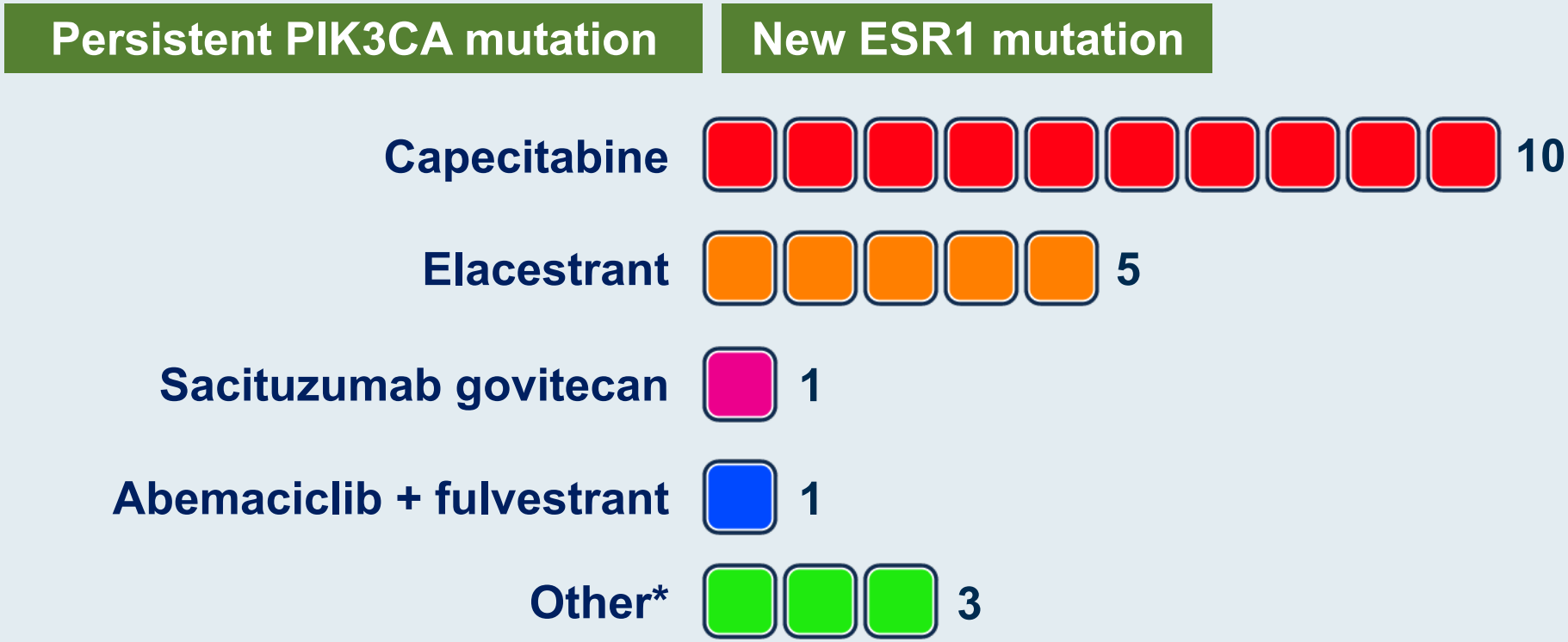

* Elacestrant + abemaciclib; clinical trial of oral SERD + CDK2,4,6 inhibitor or oral SERD plus KAT6 inhibitor or fulvestrant plus gedatolisib; clinical study with elacestrant and alpelisib

Survey of 20 US-based clinical investigators

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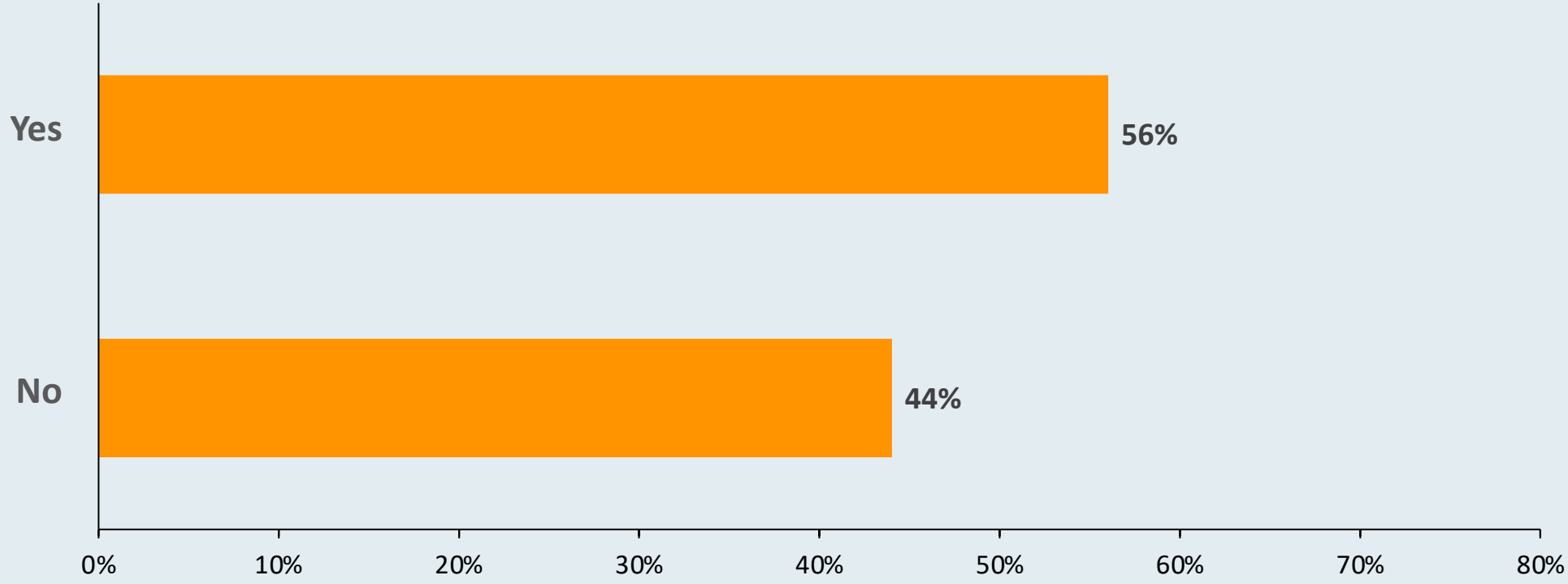
In general, are there clinical situations in which you are adding palbociclib to anti-HER2 therapy and maintenance endocrine therapy after first-line induction therapy for your patients with HR-positive, HER2-positive mBC as in the PATINA study?



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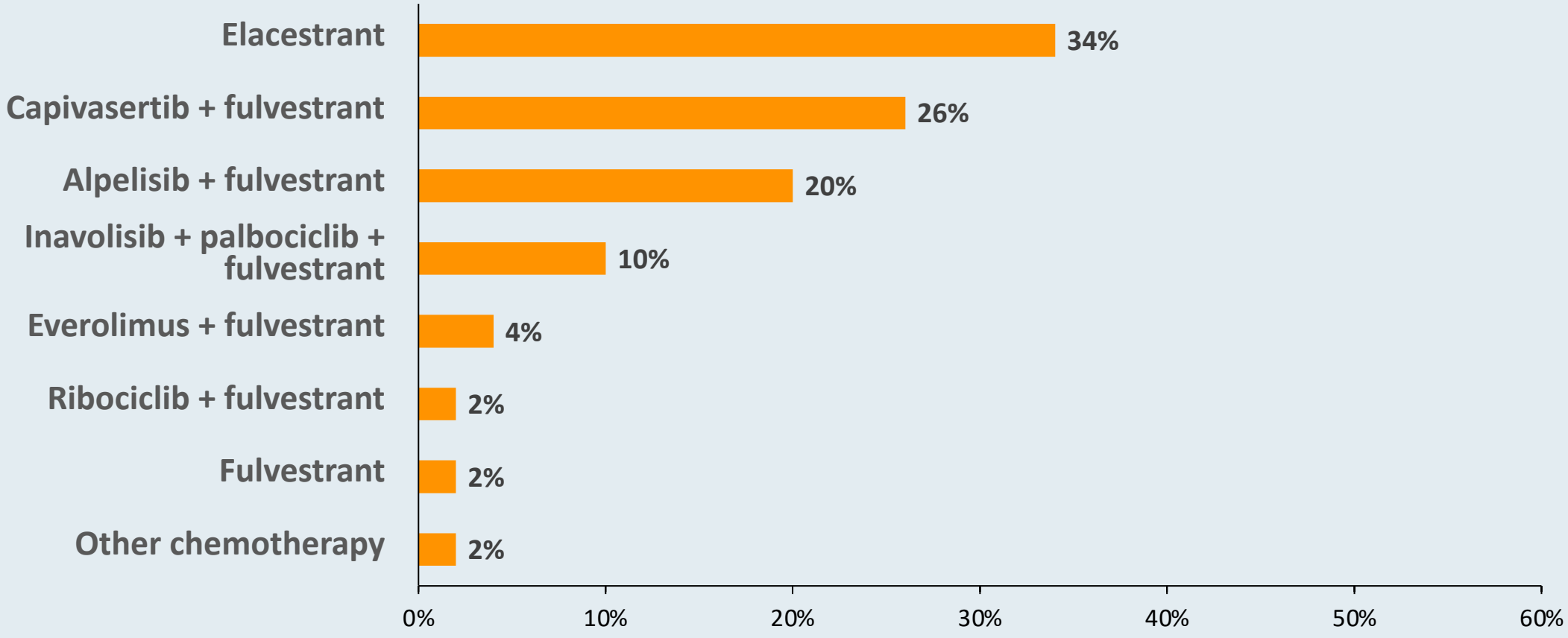
Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) breast cancer receives adjuvant abemaciclib + anastrozole for 2 years followed by development of biopsy-confirmed ER-positive, HER2-negative (IHC 0/null) metastatic disease with multiple minimally symptomatic bone metastases

ESR1 mutation **PIK3CA mutation**



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ESR1 mutation **PIK3CA mutation**

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RTP RESEARCH TO PRACTICE

evERA Study Design

Key eligibility criteria*

- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

Enrolment period: August 2022 to October 2024

N = 373*

R 1:1

- **Giredestrant (30 mg) + everolimus (10 mg)†**
- **SOC ET‡ + everolimus (10 mg)†**
  ‡Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

Stratification factors

- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

Co-primary endpoints (RECIST v1.1)

- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

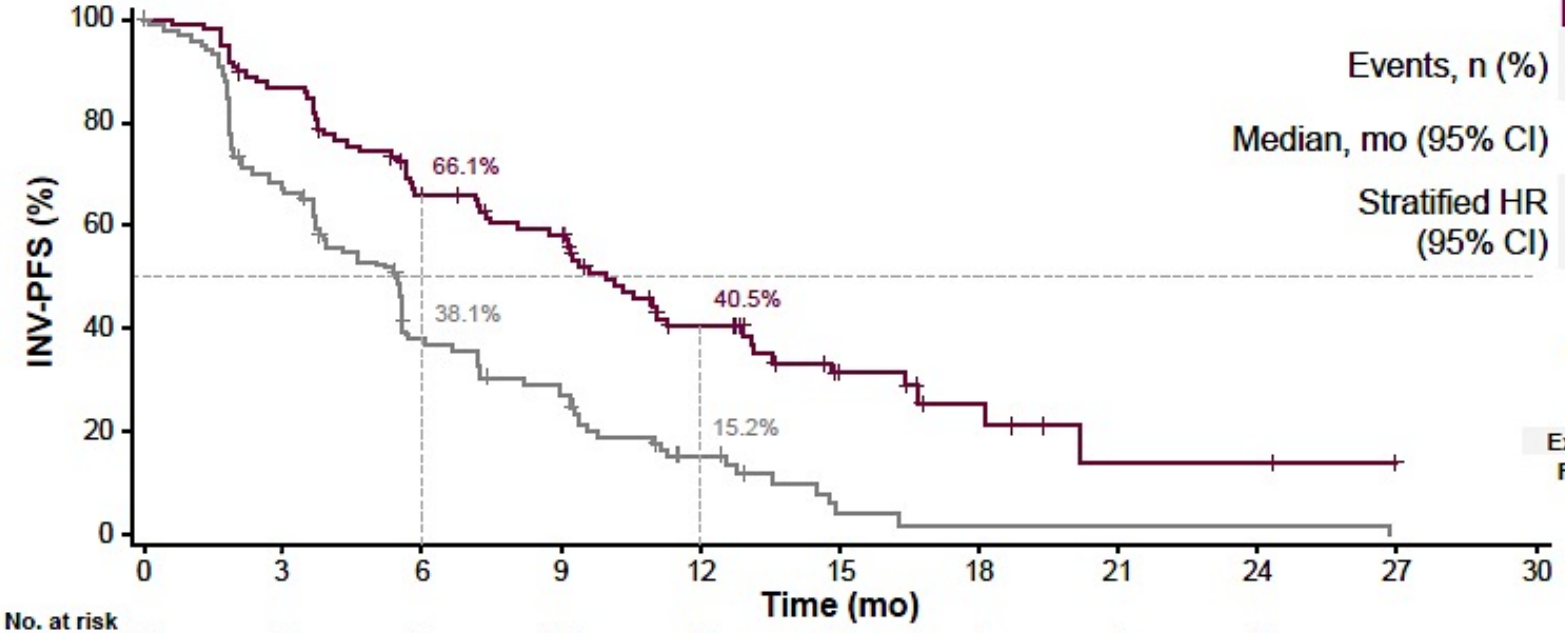
Key secondary endpoints

- OS
- INV-assessed ORR, DoR

ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission.
1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.
1. Rugo HS, *et al. Lancet Oncology* 2017; 18:654–662.

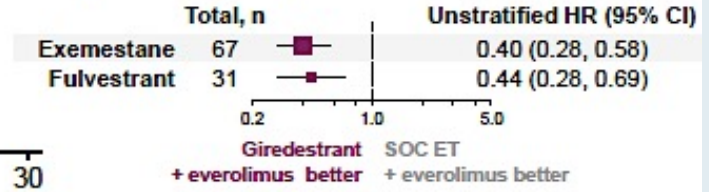
Mayer E et al. ESMO 2025;Abstract LBA16.

evERA Coprimary Endpoint: PFS for Patients with ESR1 Mutations



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

Exploratory analysis: INV-PFS by SOC ET

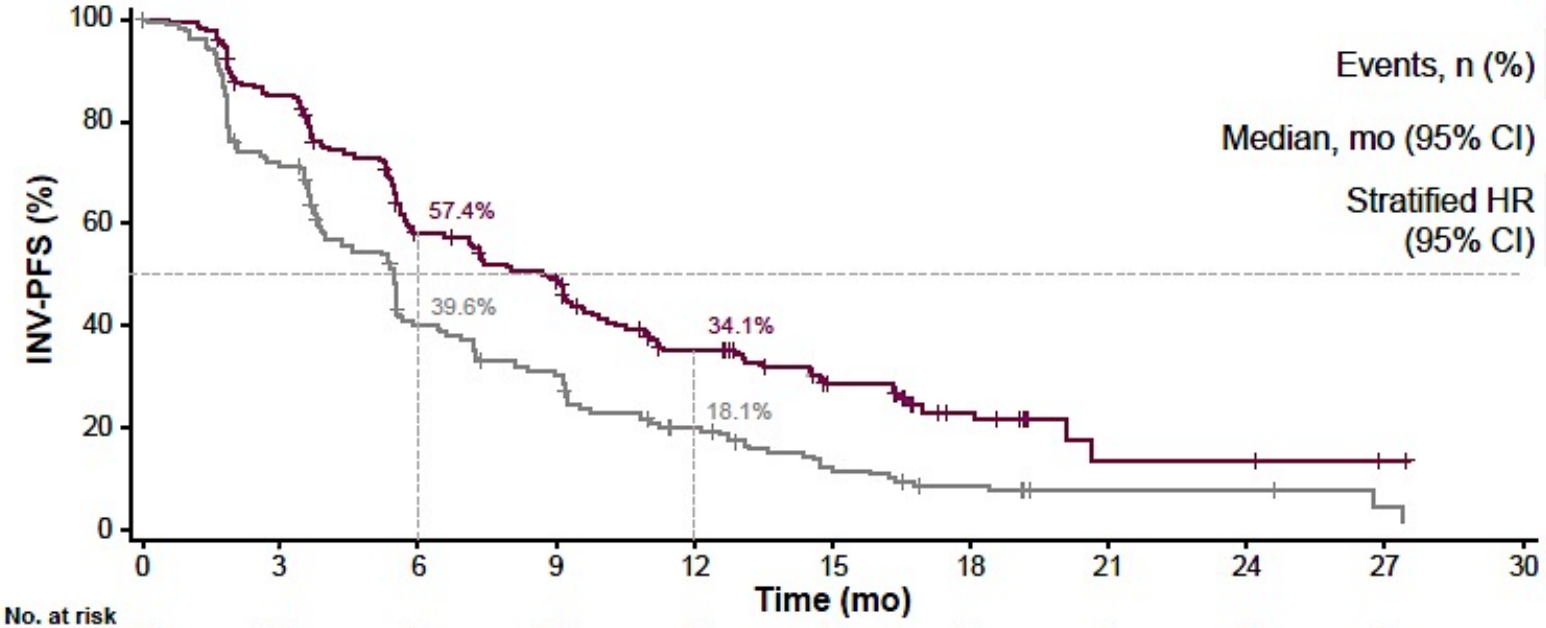


Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71.
CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Mayer E et al. ESMO 2025;Abstract LBA16.

evERA Coprimary Endpoint: PFS in the ITT Population



	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	

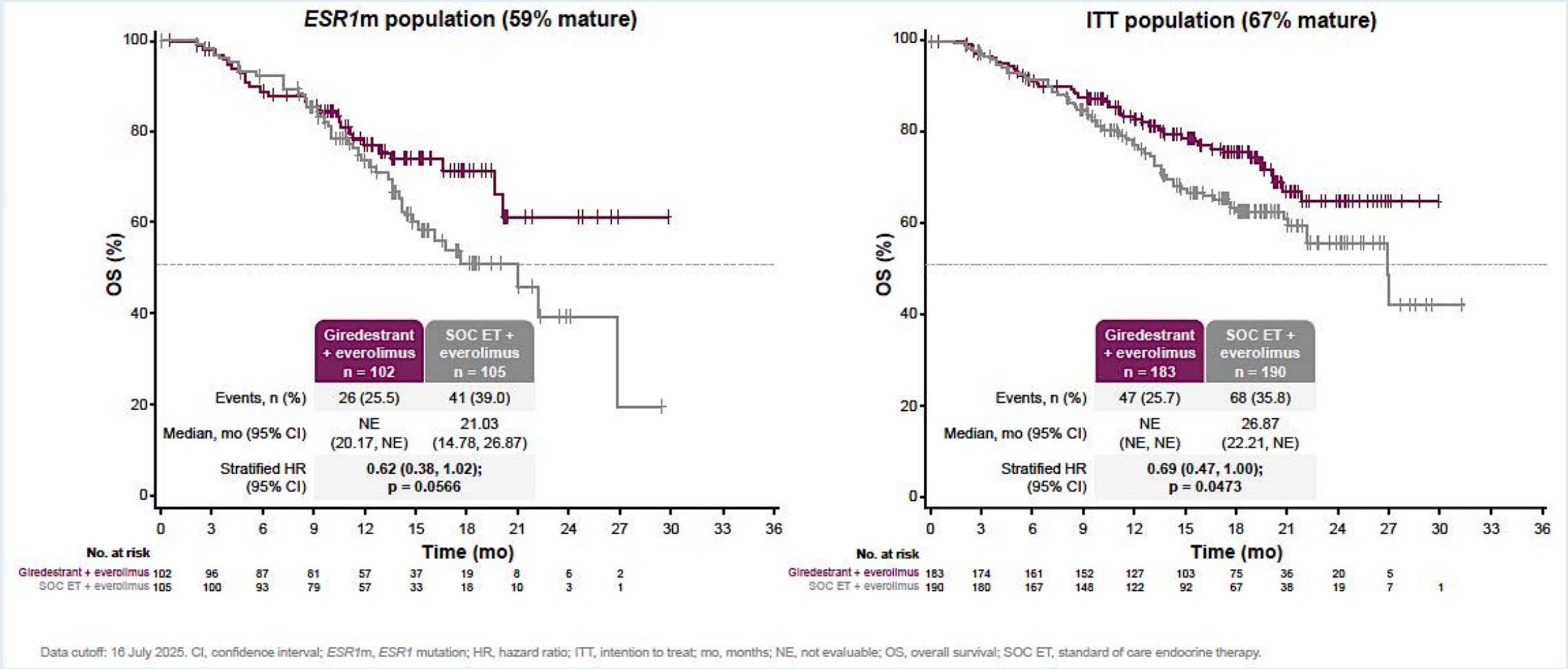
No. at risk										
Giredestrant + everolimus	183	149	95	70	47	29	14	3	3	1
SOC ET + everolimus	190	131	68	50	27	14	7	3	3	1

Combination therapy with giredestrant + everolimus led to a clinically meaningful 44% reduction in the risk of progression or death in patients in the ITT population

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 10.32 mo (giredestrant + everolimus) and 7.26 mo (SOC ET + everolimus); stratified HR, 0.66; 95% CI: 0.50, 0.87.
CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; ITT, intention to treat; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Mayer E et al. ESMO 2025;Abstract LBA16.

evERA: Interim OS in the ESR1-Mutation and ITT Populations



Data cutoff: 16 July 2025. CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; ITT, intention to treat; mo, months; NE, not evaluable; OS, overall survival; SOC ET, standard of care endocrine therapy.

Mayer E et al. ESMO 2025;Abstract LBA16.

Join Us In Person or Virtually

Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

Saturday, November 8, 2025

Lung Cancer

Faculty

Justin F Gainor, MD

Corey J Langer, MD

Chronic Lymphocytic Leukemia

Faculty

Kerry A Rogers, MD

Moderator

Stephen “Fred” Divers, MD

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Ovarian Cancer

Faculty

Gottfried E Konecny, MD

Gastroesophageal Cancers

Faculty

Manish A Shah, MD

Moderator

Stephen “Fred” Divers, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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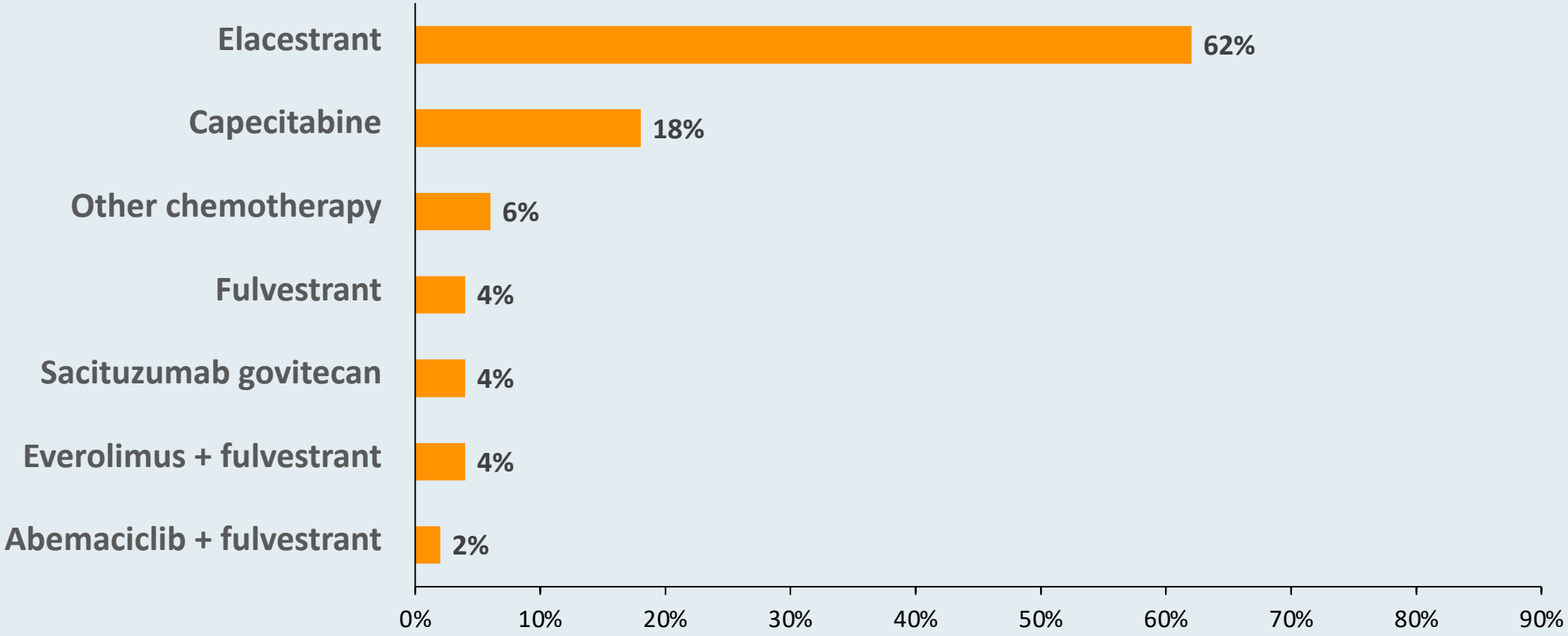
Appendix

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

ESR1 mutation | **PIK3CA/AKT1/PTEN wild type**



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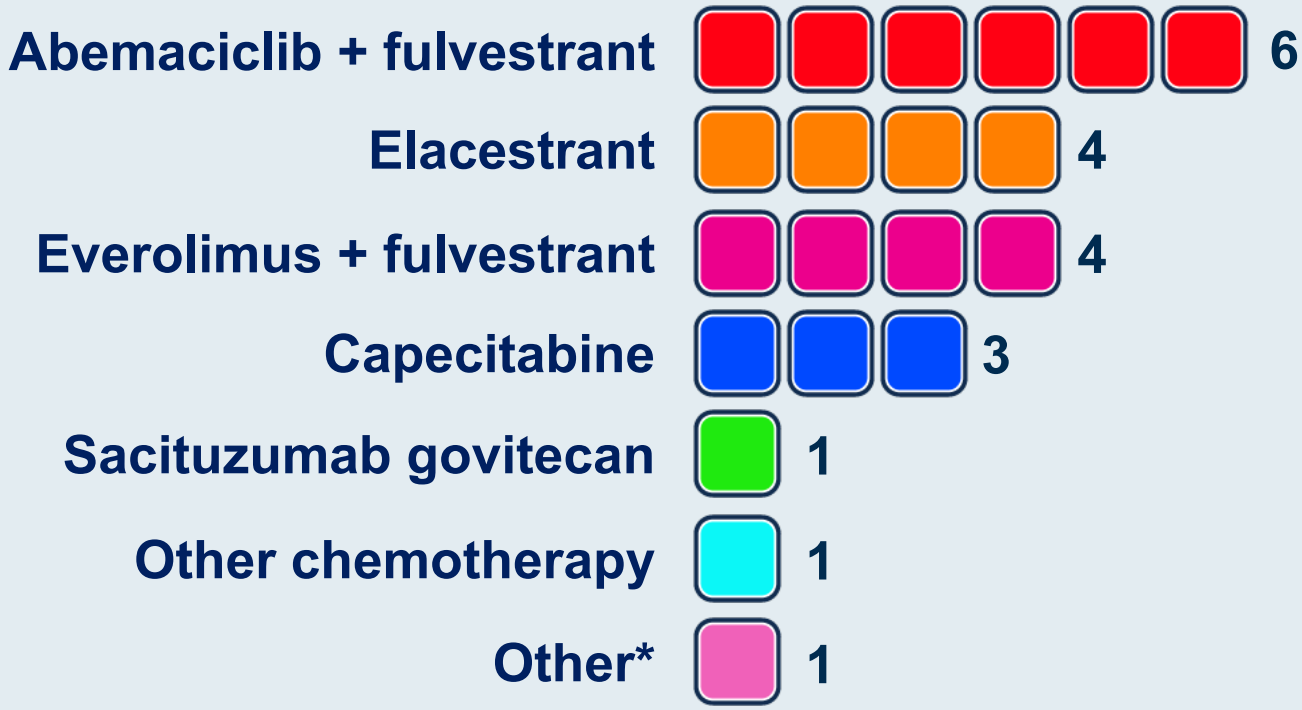

* Very much depends on what the symptoms are. Would start with capecitabine if quite symptomatic, or if modest to minimal and no hypoxia would try everolimus and fulvestrant

Survey of 20 US-based clinical investigators

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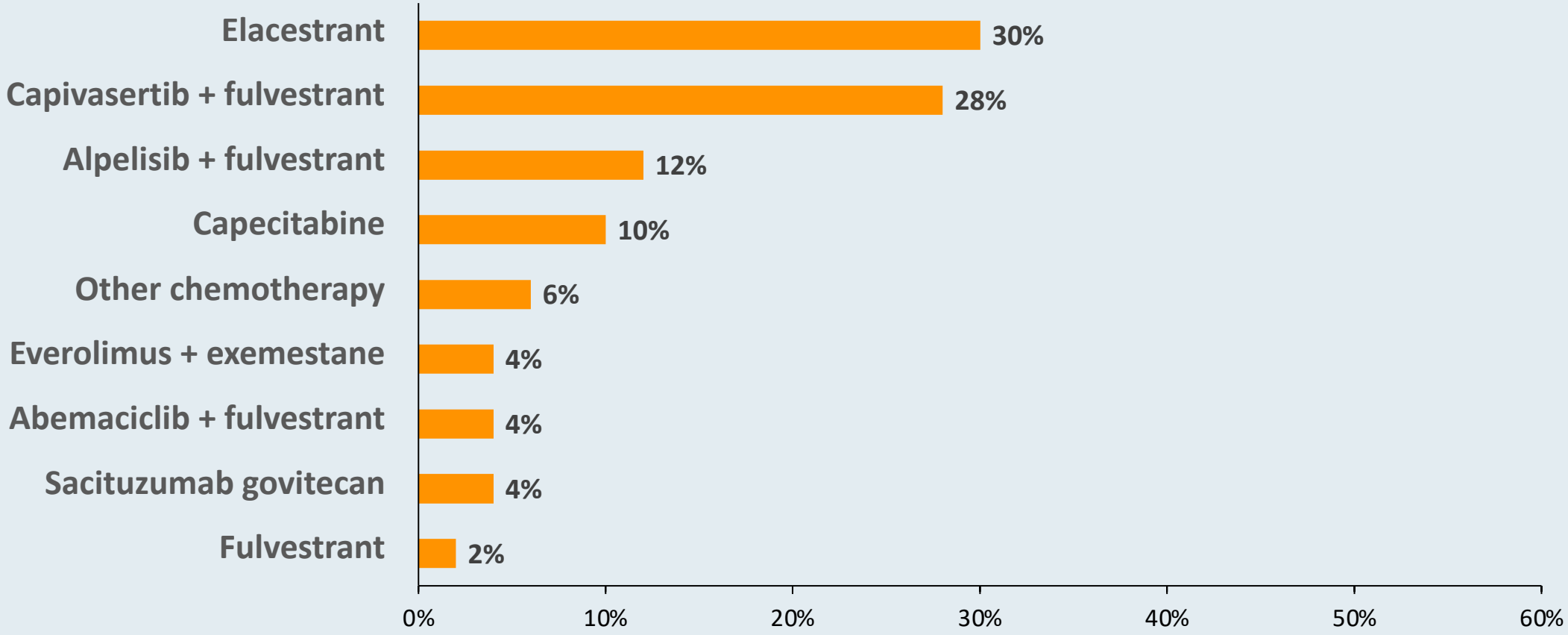

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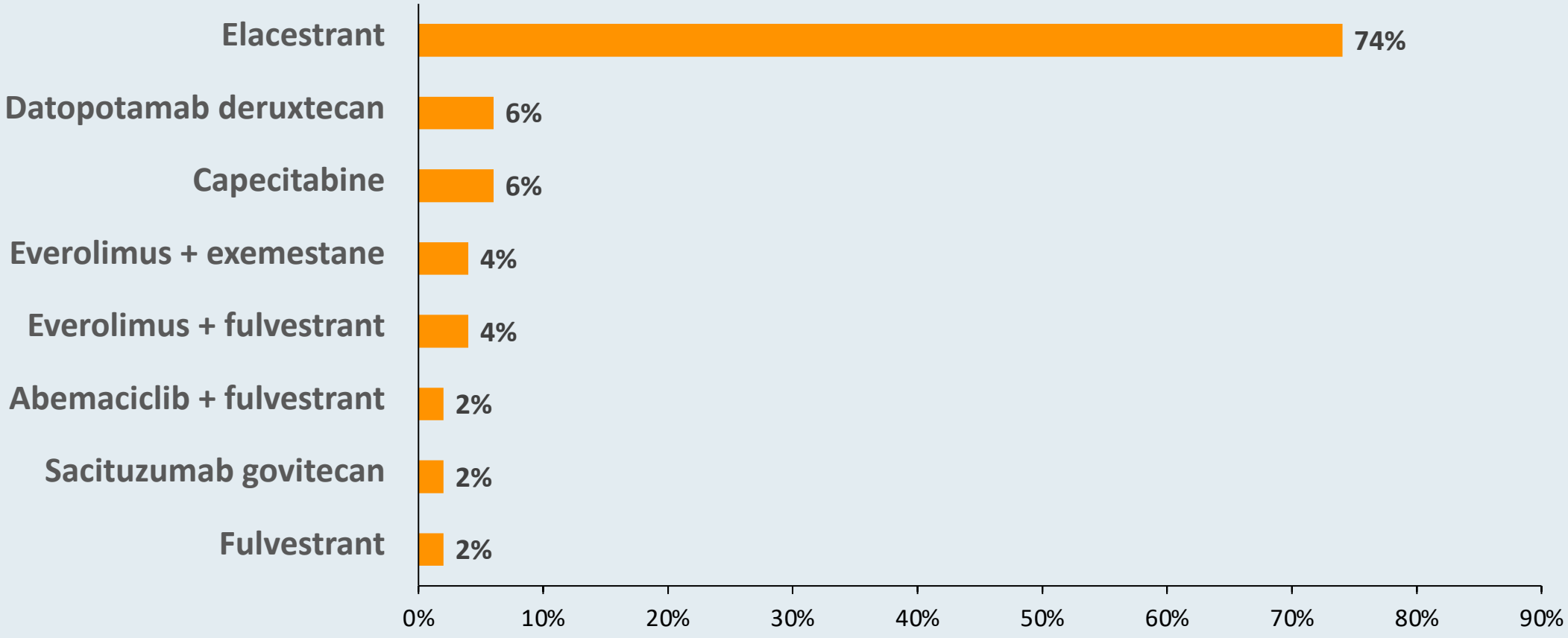

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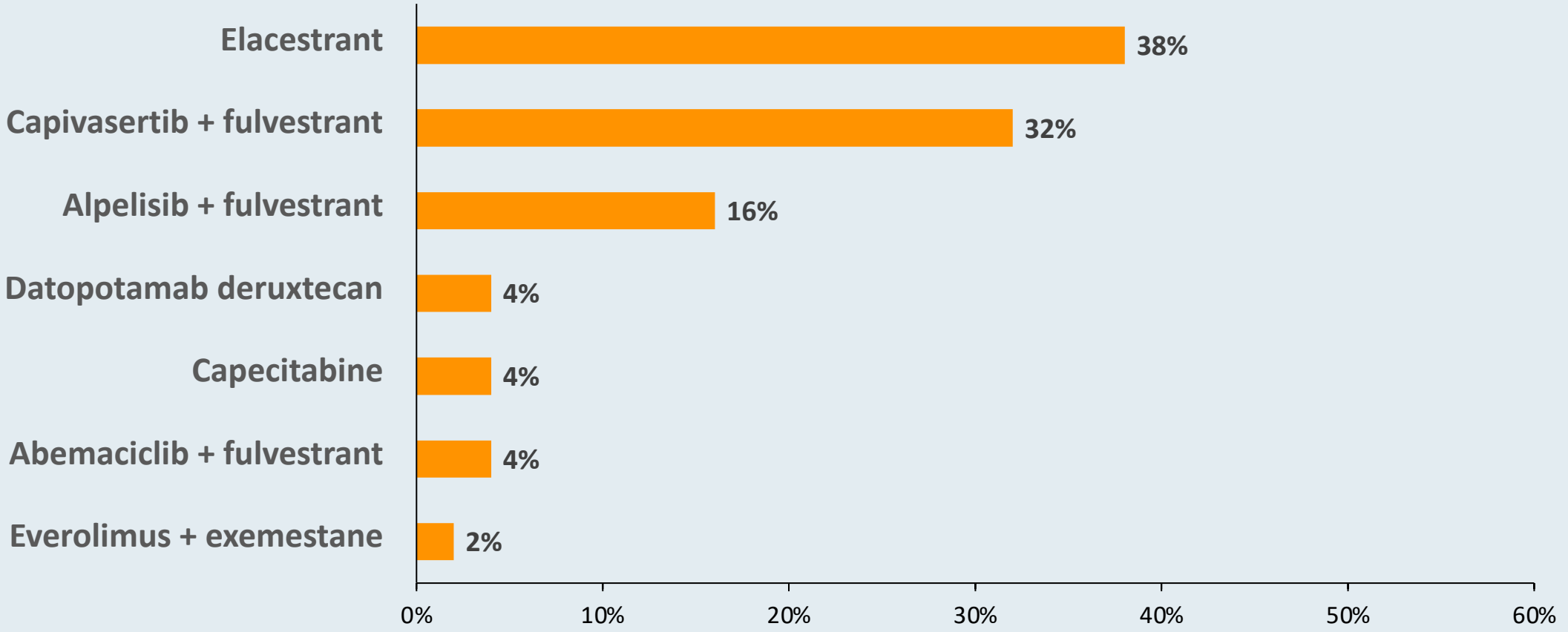

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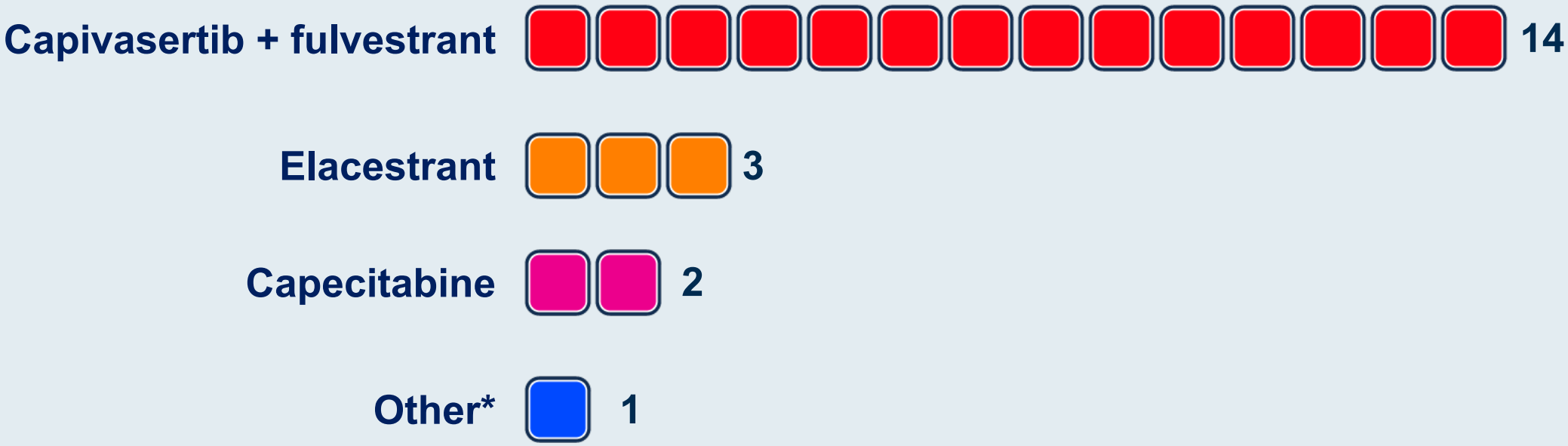

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