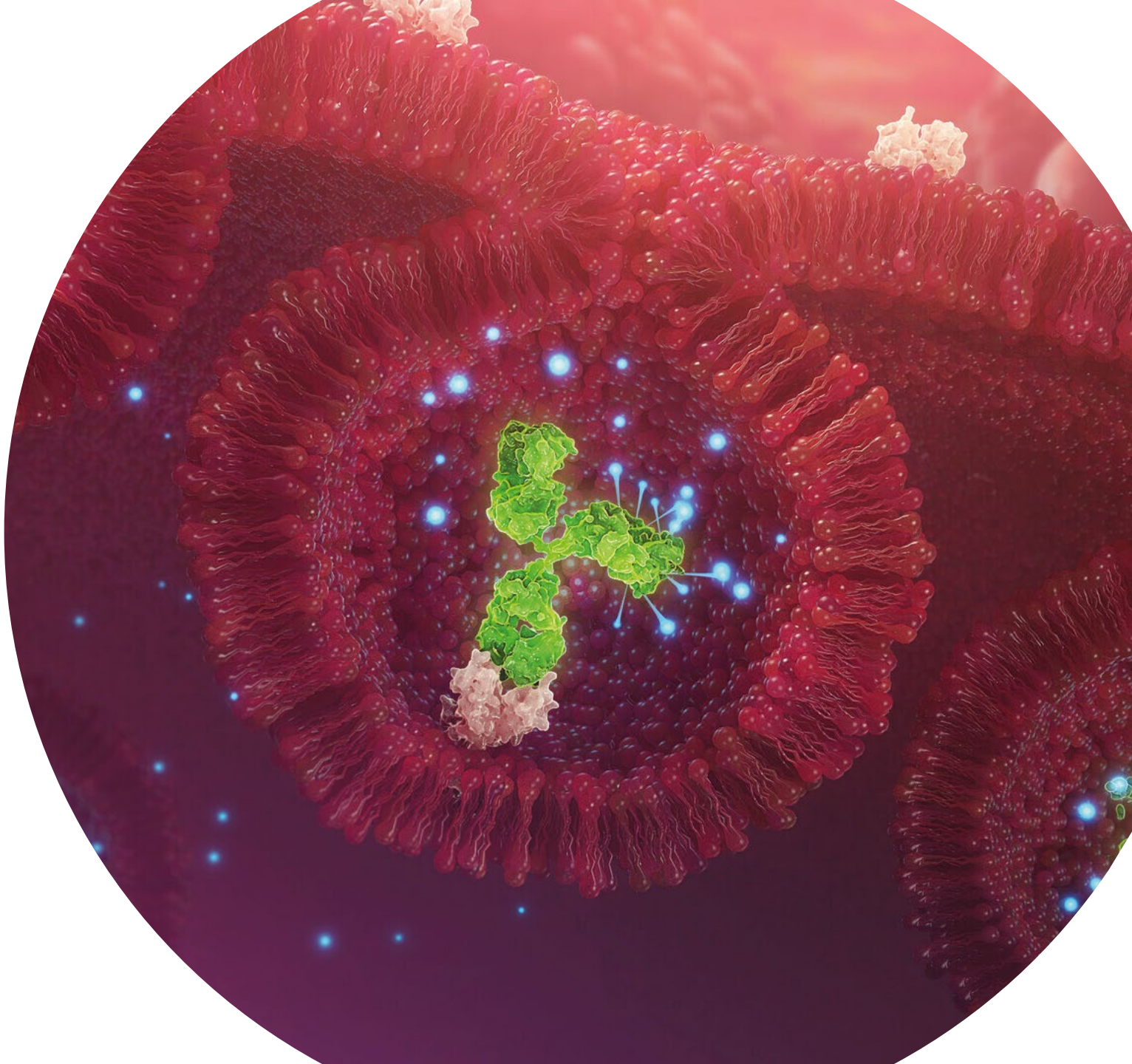
AstraZeneca

Investor science conference call: San Antonio Breast Cancer Symposium (SABCS) 2022

Conference call for investors and analysts

08 December 2022



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Speakers and Q&A Panel

Dr. Nicholas Turner

Professor, Institute of Cancer Research, Royal Marsden Hospital, London

Dave Fredrickson

Executive Vice President, Oncology Business

Ingrid Mayer

Global Clinical Strategy Head, Breast Cancer

(for Q&A)

Susan Galbraith

Executive Vice President, Oncology Research and Development

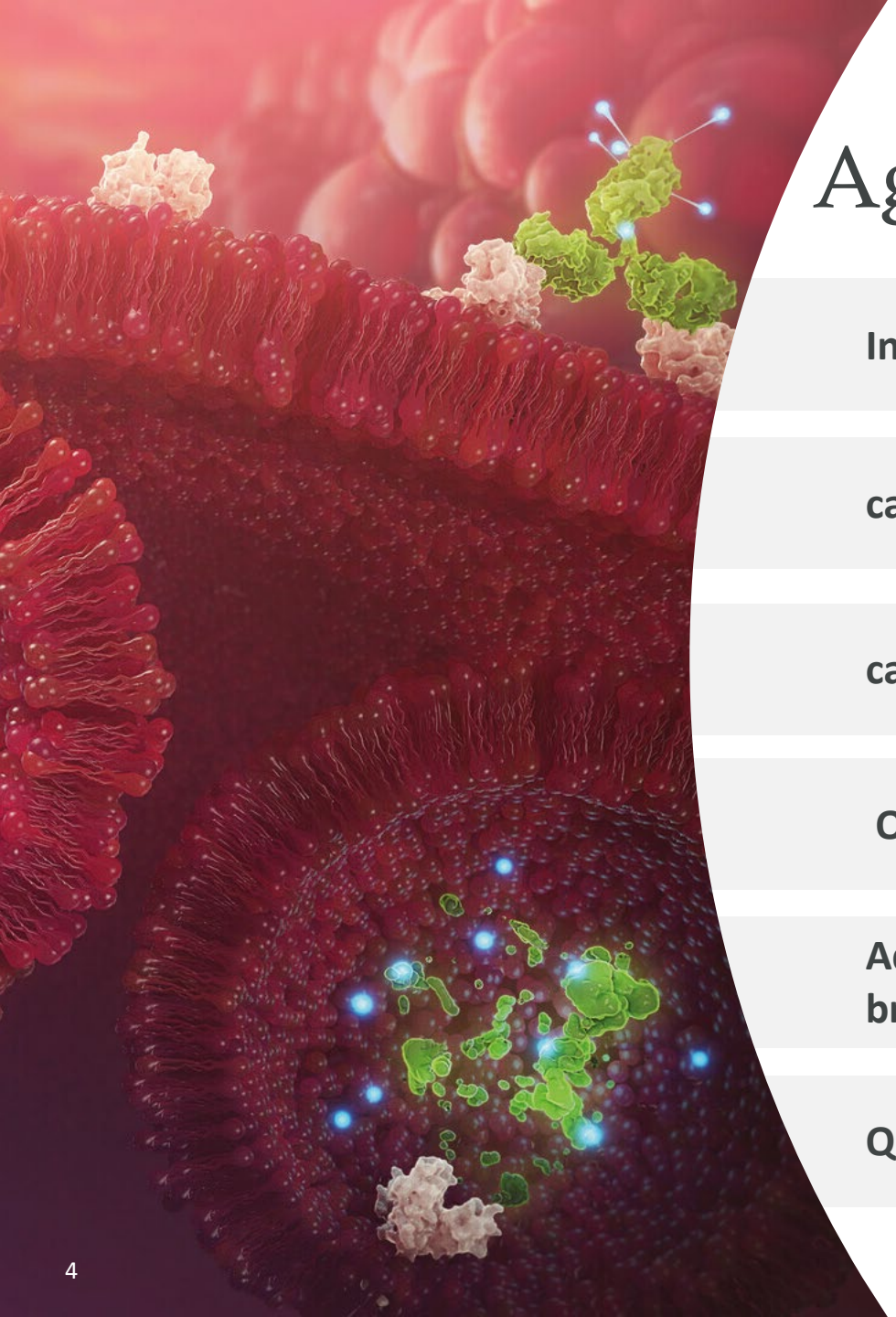
Cristian Massacesi

Chief Oncology Development Officer and Chief Medical Officer

Liz Chatwin

Global Franchise Head, *Enhertu* and Breast Cancer

(for Q&A)



Agenda: SABCS 2022

Introduction	Susan Galbraith, *EVP Oncology R&D*
capivasertib CAPItello-291	Dr. Nicholas Turner, *Professor, Institute of Cancer Research, Royal Marsden Hospital, London*
camizestrant SERENA-2	Cristian Massacesi, *Chief Oncology Development Officer and CMO*
Other key data @ SABCS	Susan Galbraith, *EVP Oncology R&D*
Advancing the treatment paradigm in breast cancer	Dave Fredrickson, *EVP Oncology Business*
Q&A	All

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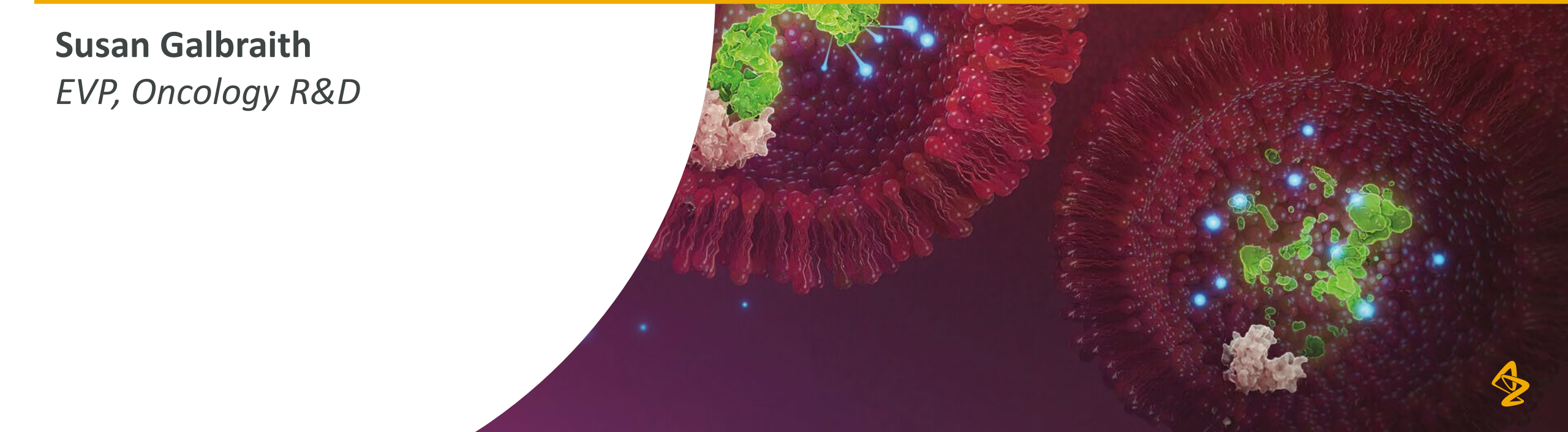
Introduction

Susan Galbraith
EVP, Oncology R&D



AstraZeneca @ SABCS

Key data un-gates potential for novel mechanisms in breast cancer

56 accepted abstracts

across our portfolio

- **5 commercial medicines**
  - *Enhertu, Lynparza, Imfinzi, Faslodex, Koselugo*
- **7 pipeline molecules**
  - capivasertib, camizestrant, Dato-DXd, ceralasertib, adavosertib, monalizumab, AZD1390
- **4 oral presentations (LBA)**

Key data highlights

presented at SABCS 2022

- ***Enhertu* DESTINY-Breast03** (HER2-high)
- ***Enhertu* DESTINY-Breast02** (HER2-high)
- **capivasertib CAPItello-291** (HR+)
- **camizestrant SERENA-2** (HR+)

SABCS = San Antonio Breast Cancer Symposium; LBA = Late breaker abstract; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive.

AstraZeneca at SABCS 2022

Key data advances our strategic ambitions in breast cancer

HER2-high

Setting new standards of care in HER2-high mBC

- ***Enhertu*** as the foundational therapy across HER2-high mBC, transforming patient outcomes
  - **DESTINY-Breast03**
  - **DESTINY-Breast02**

HR+

Reshaping the treatment of HR+

- Establishing confidence in **camizestrant** as the next generation in ET combinations (**SERENA-2**)
- **capivasertib** extending benefit of ET for ER-driven disease through targeting a key pathway of resistance (**CAPItello-291**)
- Best-in-class ADCs to replace chemotherapy/identifying HER2-low as new targetable sub-type
  - **DESTINY-Breast04**
  - **TROPION-PanTumor01**

gBRCA

Establishing and expanding beyond gBRCA

- Reinforcing and broadening the role of ***Lynparza*** (**OlympiaN TiP**)

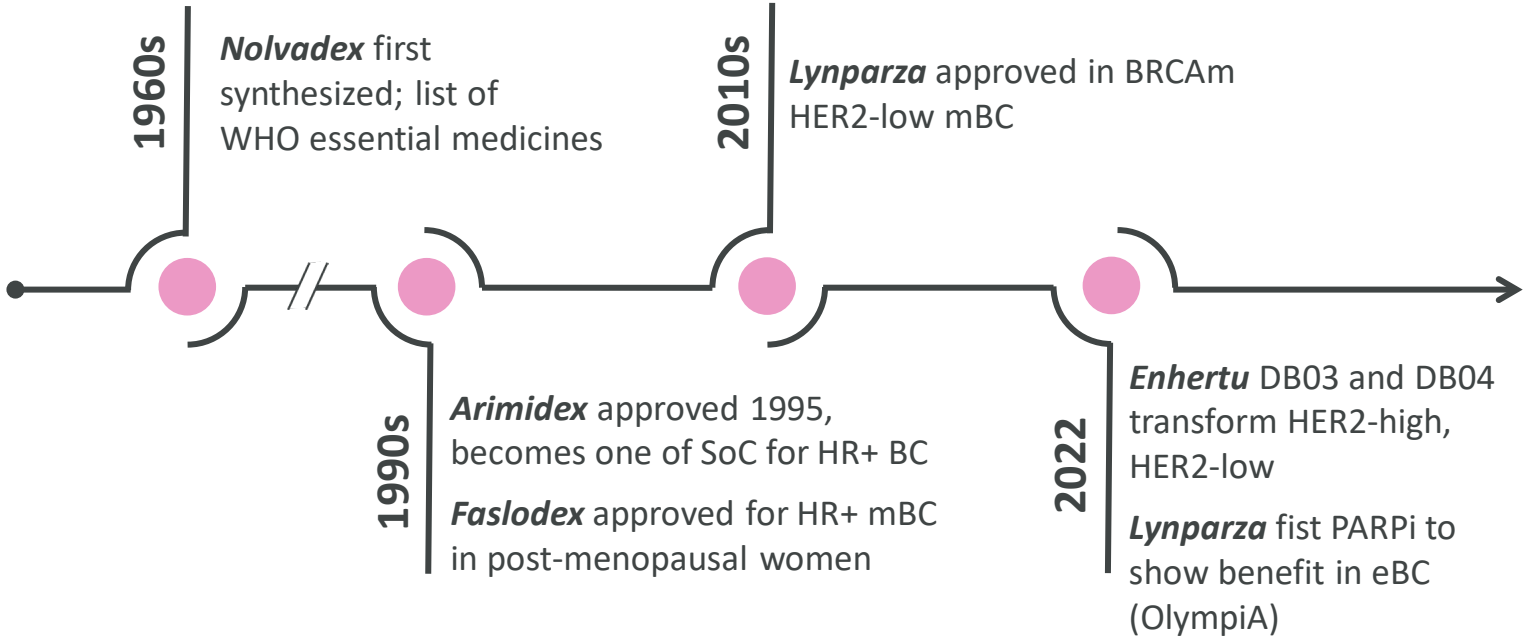
Redefining the treatment and understanding of TNBC

- Improved response rates and durability with best-in-class **ADCs**/in combination with IO **(BEGONIA)**
- Encouraging clinical profile for **Dato-DXd** monotherapy in advanced TNBC monotherapy (**TROPION-PanTumor01**)

SABCS = San Antonio Breast Cancer Symposium; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; ET = endocrine therapy; ER = oestrogen receptor; ADC = antibody drug conjugate; gBRCA = breast cancer gene; TiP = trials in progress poster; IO = immuno-oncology; TNBC = triple negative breast cancer.

AstraZeneca: Leaders in Breast Cancer treatment

Innovative portfolio of medicines, built on foundational history



Future state: Continuing to transform the treatment paradigm

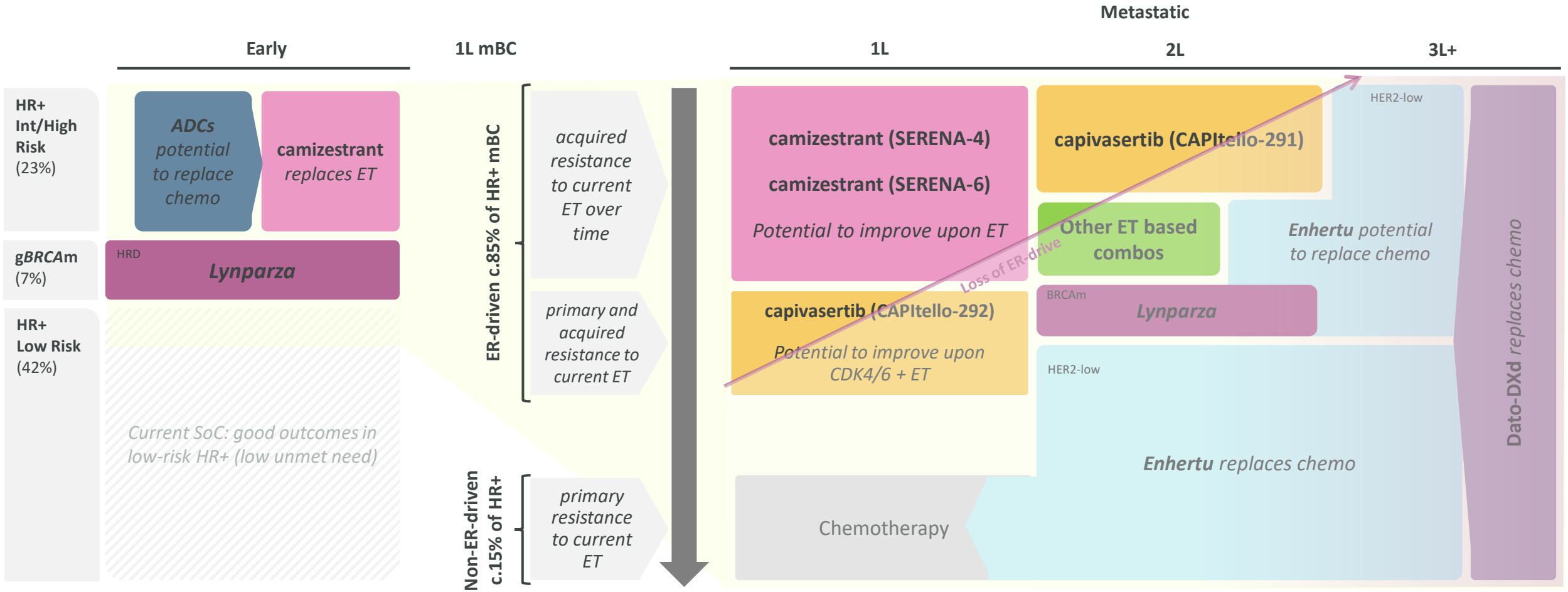
- Next-generation oral SERD (**camizestrant**) ongoing Phase IIIs
- **Capivasertib** CAPItello-291 regulatory filing H1 2023
- ***Enhertu*** moving earlier and in combinations (DB06, DB09)
- TROP2-targeted therapy (**Dato-DXd**)
- Pursuing novel next-gen combos

Leading innovation in breast cancer with >15 Phase III trials underway

1. breastcancer.org, statistics specific to women in US; 2. GLOBOCAN 2020; SoC = standard of care; PARPi = poly(ADP-ribose) polymerases inhibition therapy; HER2 = human epidermal growth factor receptor 2; eBC = early breast cancer; HLR = high level results; TROP2 = tumour-associated calcium signal transducer 2.

Reshaping HR+ Breast Cancer

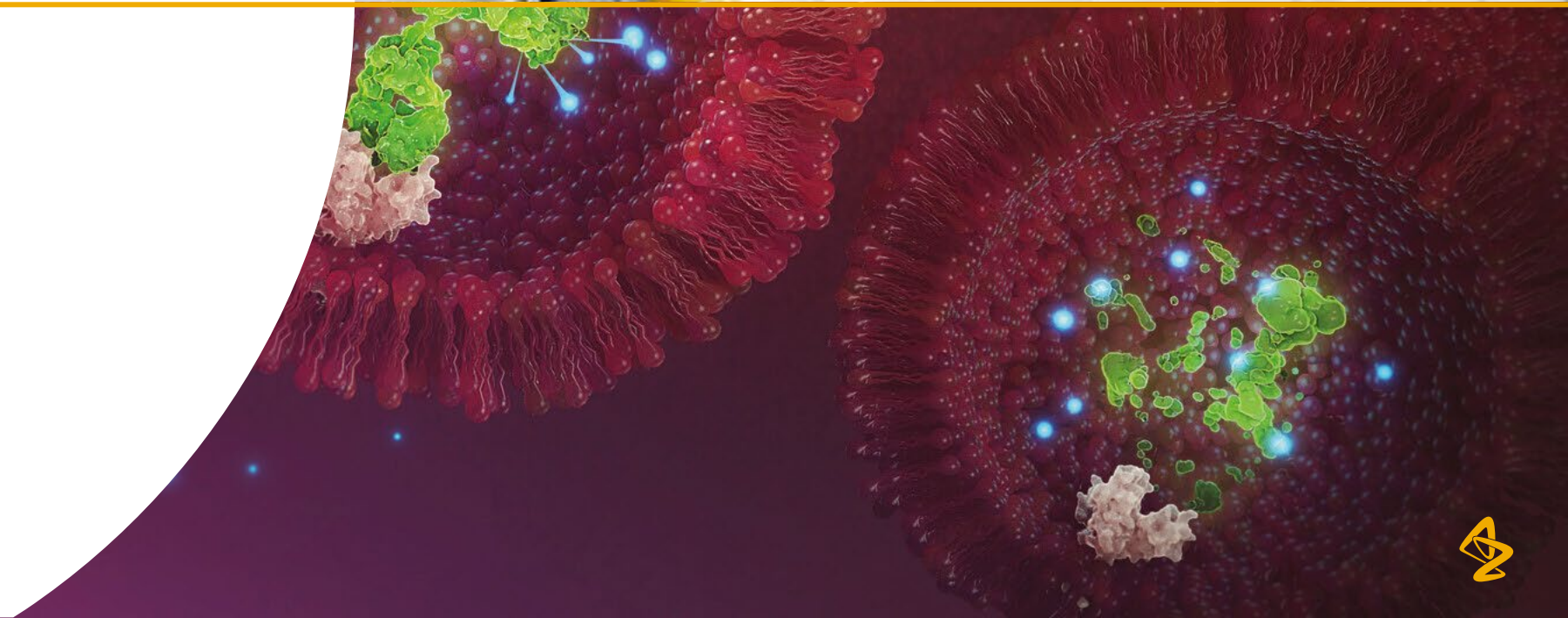
Camizestrant ngSERD, capivasertib extending ET in ER-driven disease



HR = hormone receptor; ET = endocrine therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitors; HRD = homologous recombination deficiency; gBRCAm = breast cancer gene mutation; ER = oestrogen receptor; AI = aromatase inhibitors; HER2 = human epidermal growth receptor 2; Dato-DXd = datopotomab deruxtecan.

capivasertib **CAPItello-291** Phase III trial

Dr Nicholas Turner
The Institute of Cancer Research, London, and Principal Investigator



CAPItello-291: trial overview

Patients with HR+/HER2– aBC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumours (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumours

Objective response rate
- Overall
- AKT pathway-altered tumours

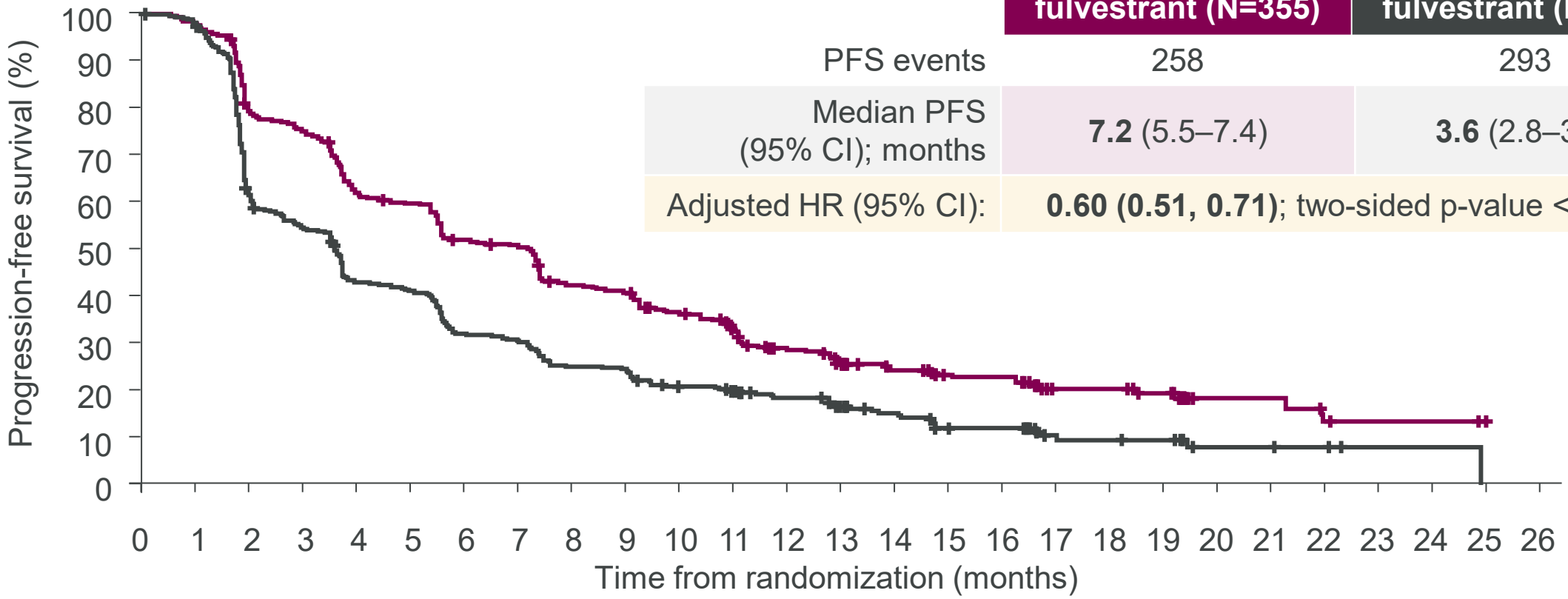
HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

CAPItello-291: dual-primary endpoint

Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



Number of patients at risk

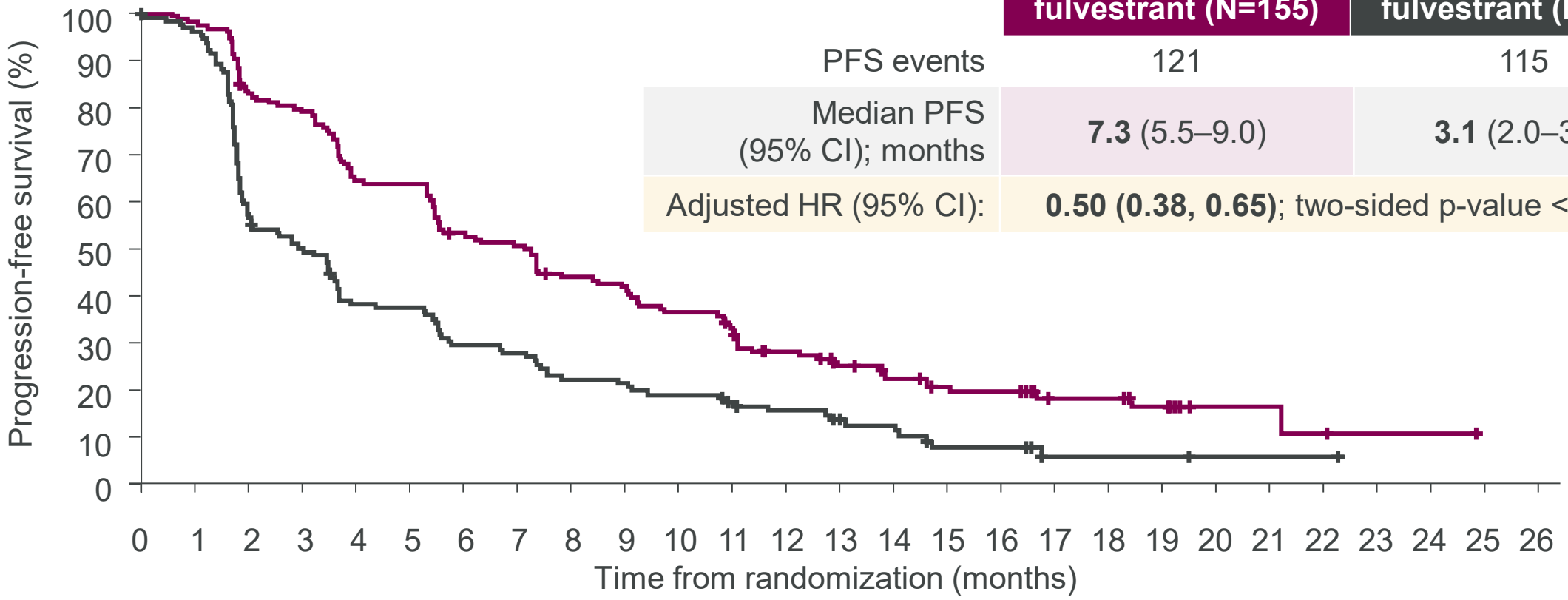
Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

CAPItello-291: dual-primary endpoint

Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

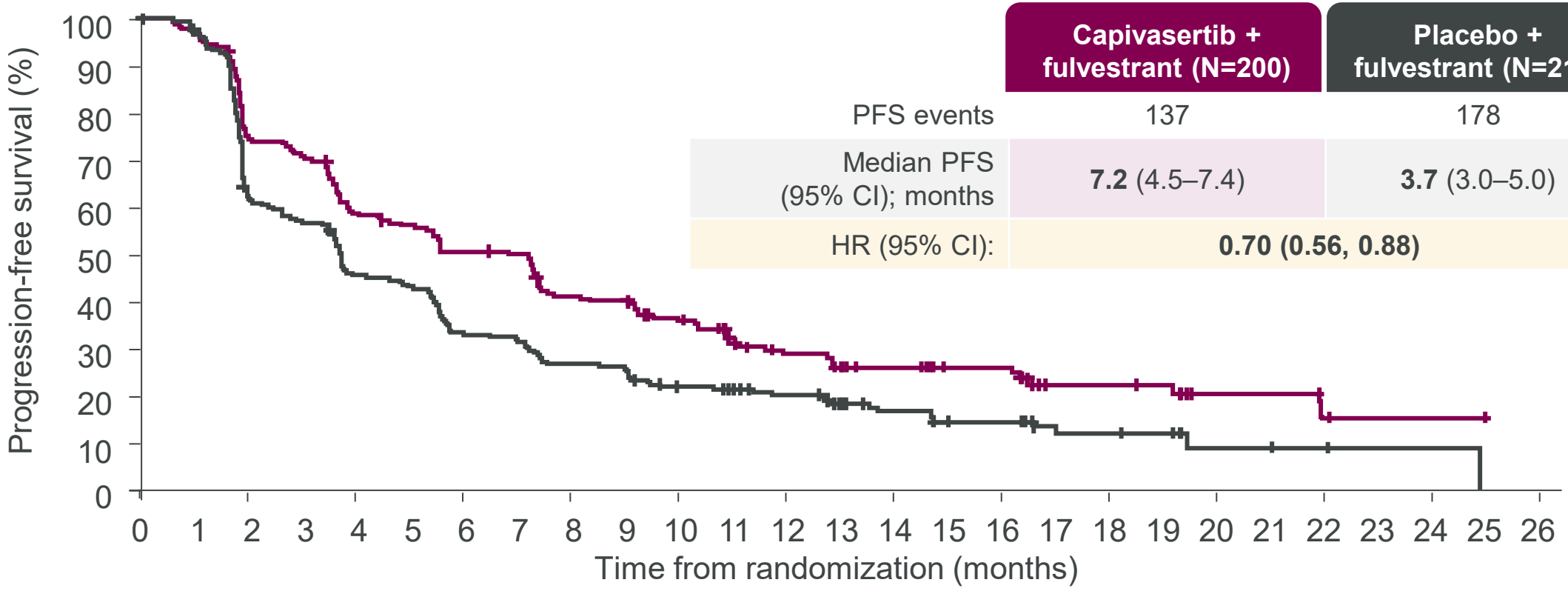


Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

CAPItello-291: investigator-assessed PFS in the non-altered population (including unknown[1])



	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Number of patients at risk

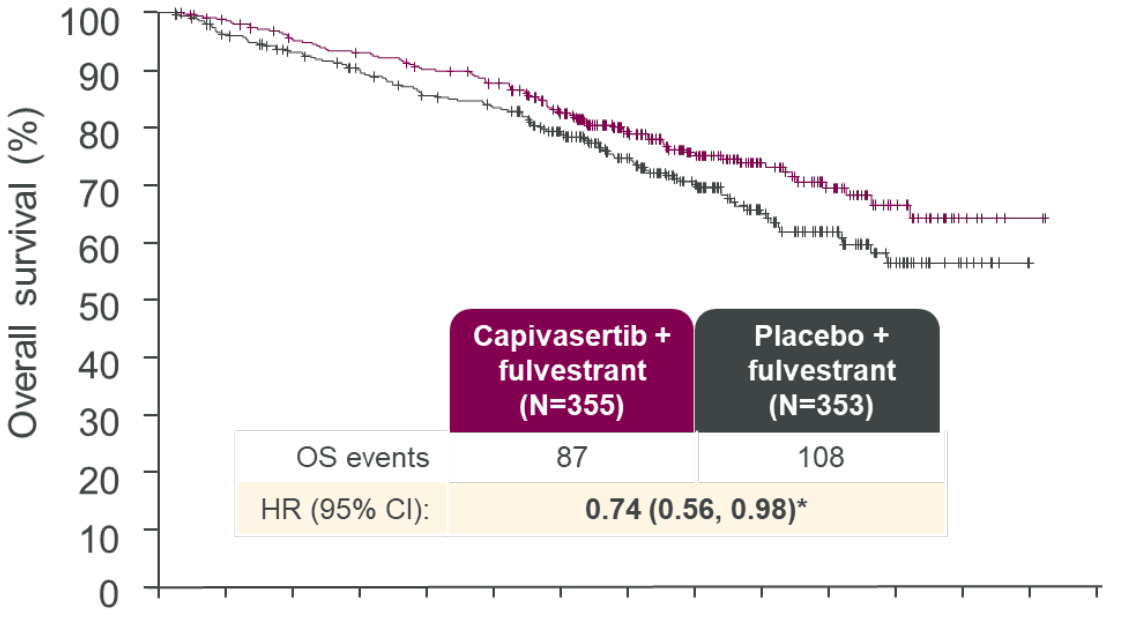
Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)

+ indicates a censored observation. 1.Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

CAPItello-291: overall survival data at 28% maturity

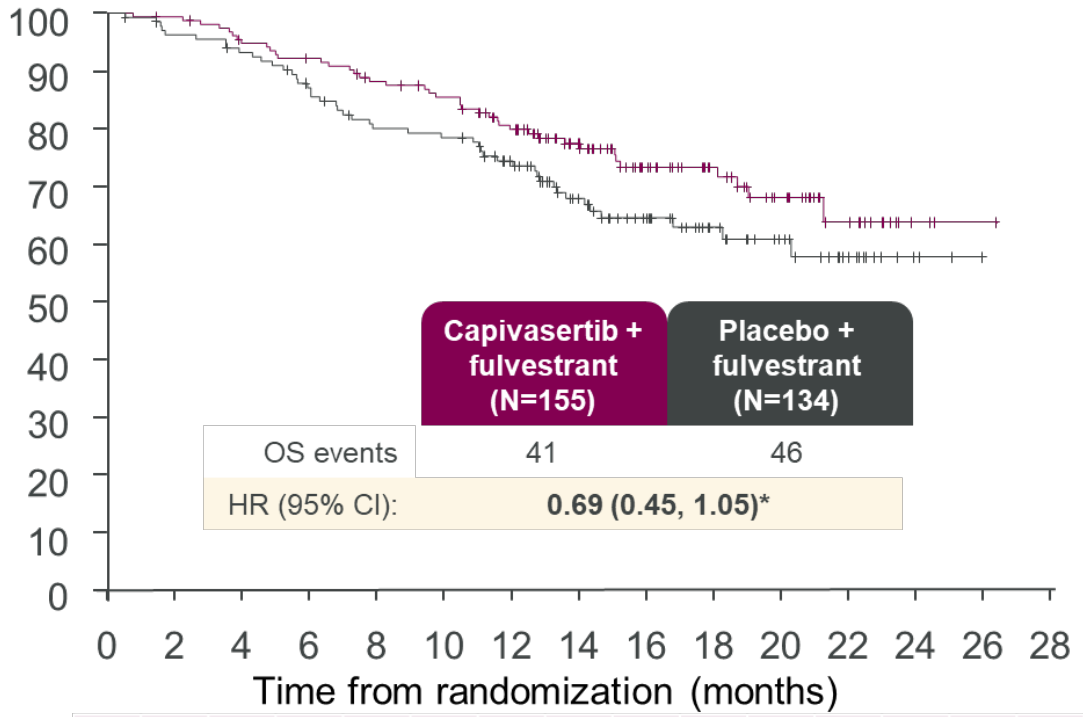
Overall population



Number of patients at risk

Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

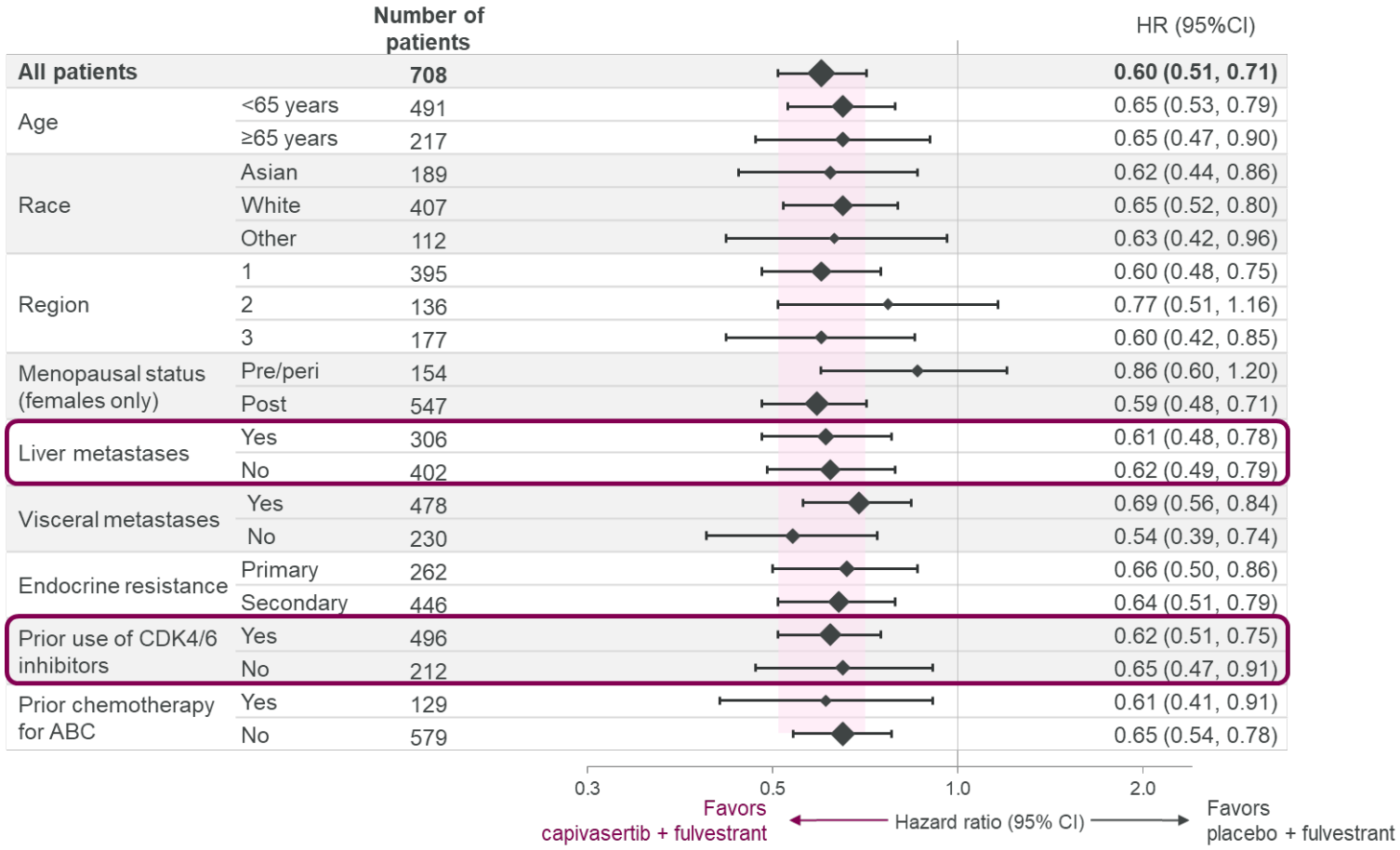
AKT pathway-altered population



	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

CAPItello-291: investigator-assessed PFS by subgroup (overall population)



Prior treatments – overall population

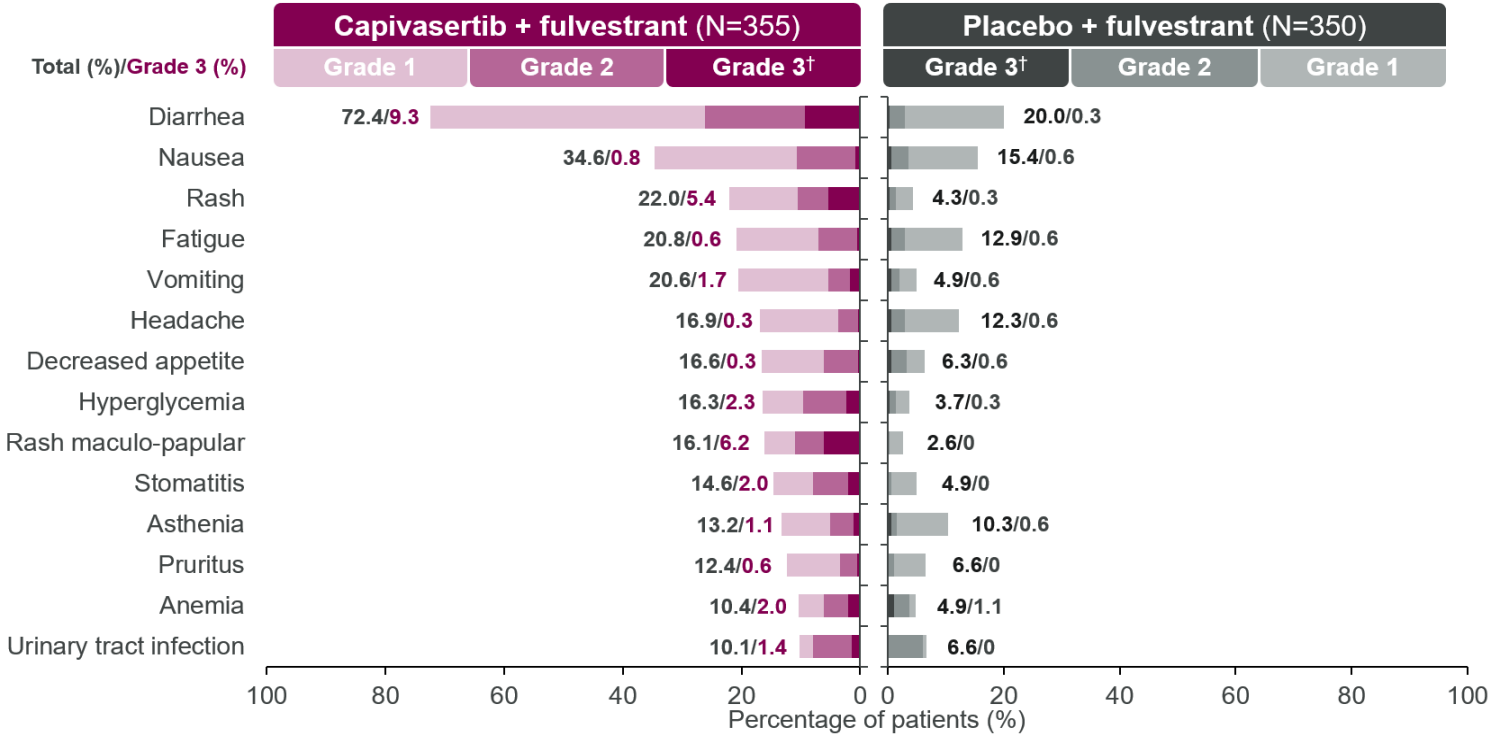
Characteristic		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Prior endocrine therapy for ABC; n (%)	0 1 2	40 (11.3) 286 (80.6) 29 (8.2)	54 (15.3) 252 (71.4) 47 (13.3)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)
Previous chemotherapy; n (%)	Adjuvant/ neoadjuvant ABC	180 (50.7) 65 (18.3)	170 (48.2) 64 (18.1)

Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia; Region 3: Asia. Primary and secondary resistance as per ESMO definition.

CAPItello-291: safety summary

Adverse event and safety profile comparable in AKT pathway-altered population

Adverse events (>10% of patients) – overall population



Safety summary – overall population

n (%)	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (n=350)
Any adverse event	343 (96.6)	288 (82.3)
Any serious adverse event	57 (16.1)	28 (8.0)
Any adverse event leading to death*	4 (1.1)	1 (0.3)
Any adverse event leading to dose discontinuation	46 (13.0)	8 (2.3)
Discontinuation of capivasertib/placebo only	33 (9.3)	2 (0.6)
Discontinuation of both capivasertib/placebo and fulvestrant	13 (3.7)	6 (1.7)
Any adverse event leading to dose interruption of capivasertib/placebo only	124 (34.9)	36 (10.3)
Any adverse event leading to dose reduction of capivasertib/placebo only	70 (19.7)	6 (1.7)

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

CAPItello-291: key takeaways and conclusions

- Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered population (dual primary)
- Benefit from capivasertib was consistent across key clinically relevant subgroups, including in:
  - Patients previously treated with CDK4/6 inhibitor
  - Patients with liver metastases
- Overall survival follow-up is ongoing
- Capivasertib plus fulvestrant safety profile appears consistent with that previously reported, with relatively low discontinuation rate due to adverse events

Capivasertib plus fulvestrant has the potential to be a future treatment option for patients with HR+ ABC who have progressed on an endocrine-based regimen

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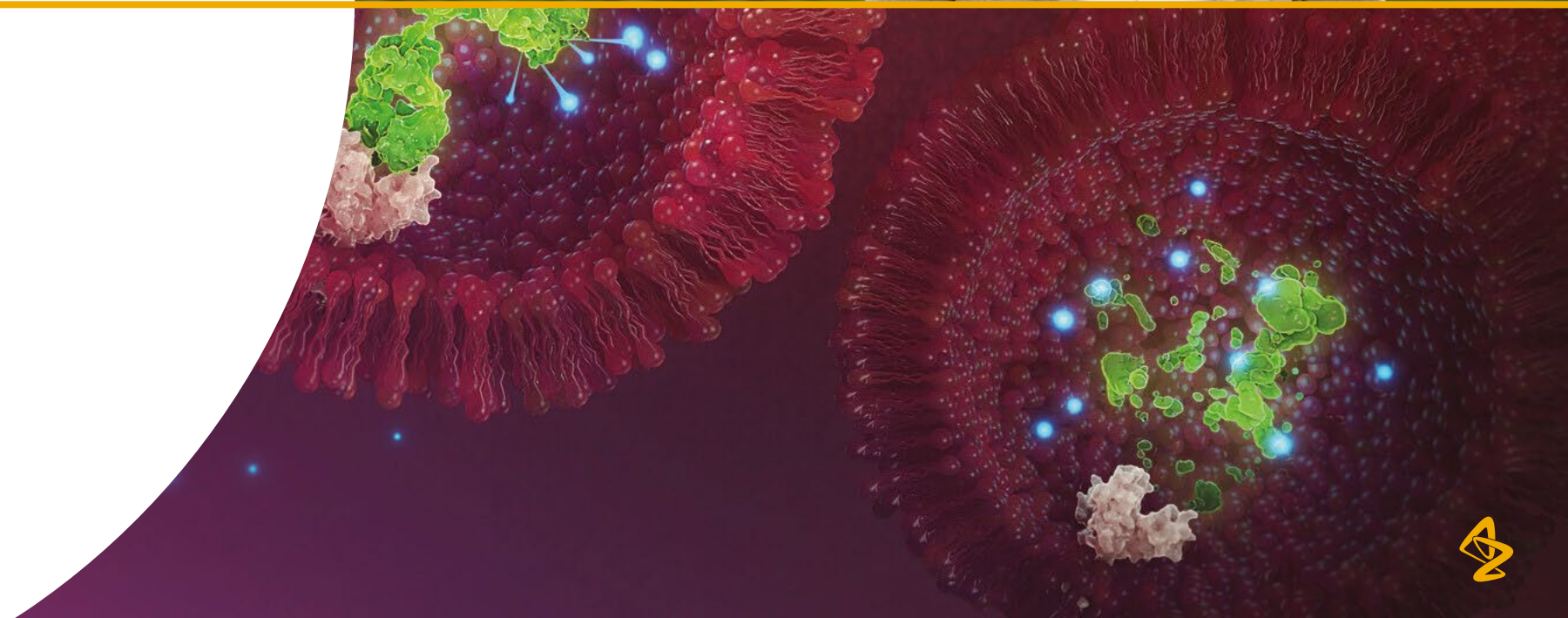
camizestrant **SERENA-2**
Phase II trial

Cristian Massacesi
CDO Oncology and CMO

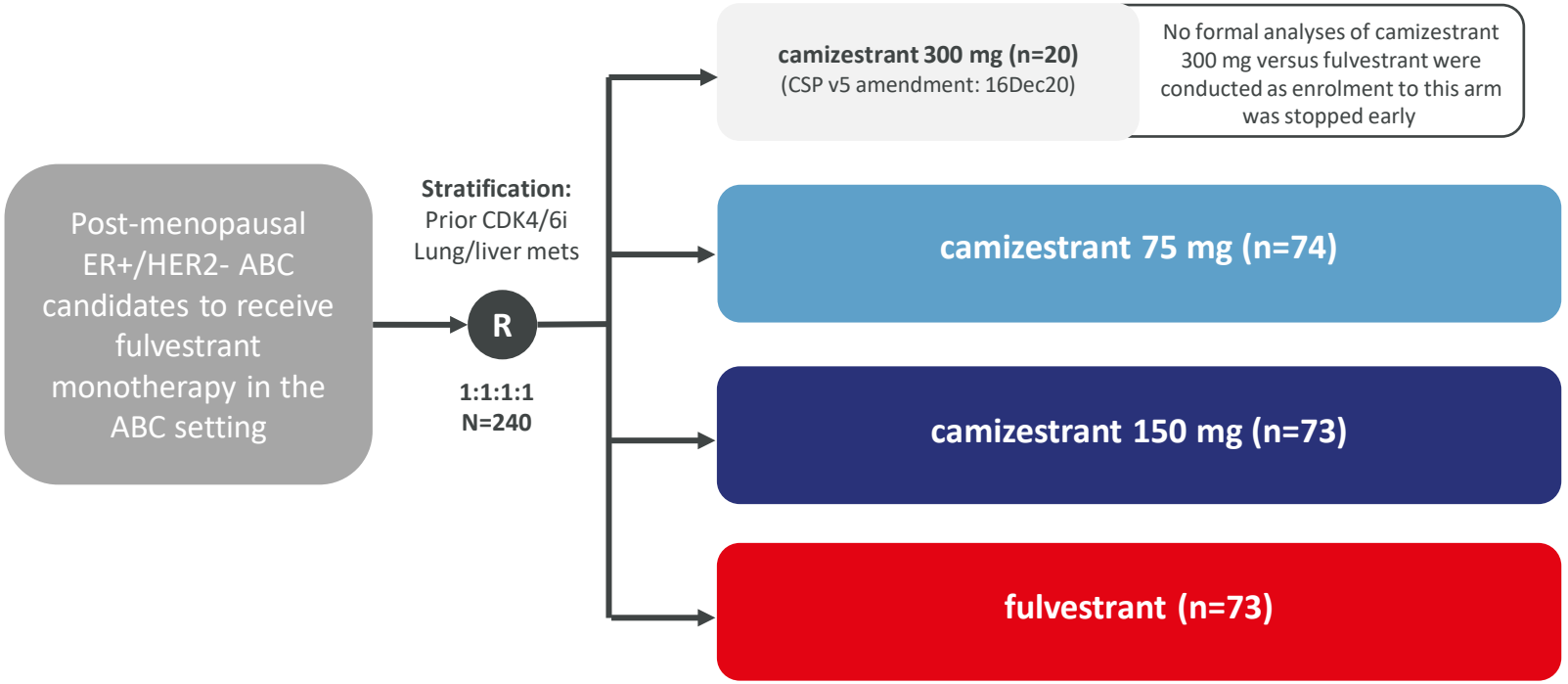


SERENA-2: trial design and inclusion criteria

A randomised, multi-dose Phase II trial of camizestrant (75mg, 150mg) vs. fulvestrant

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease



- **Primary endpoint**: PFS (investigator assessment[1])
- **Secondary endpoints**: CBR24, ORR, OS, Safety
- **Translational endpoints**: serial ctDNA analysis including ESR1m, serial CTCs analysis
- SERENA-2 was not powered to compare between camizestrant doses

1. disease progression assessed by the Investigator and defined using RECIST, version 1.1. ABC = advanced breast cancer; CBR24 = clinical benefit rate at 24 weeks; CDK4/6i = CDK4/6 inhibitor; CT = chemotherapy; CTC: circulating tumour cells; ctDNA = circulating tumour DNA; ER = estrogen receptor; *ESR1*m = mutation in estrogen receptor 1 gene; ET = endocrine therapy; HER2 = human epidermal growth factor; PFS: progression-free survival; R: randomization; RECIST: Response Evaluation Criteria for Solid Tumors; SERD: selective estrogen receptor degrader.

SERENA-2: key baseline characteristics

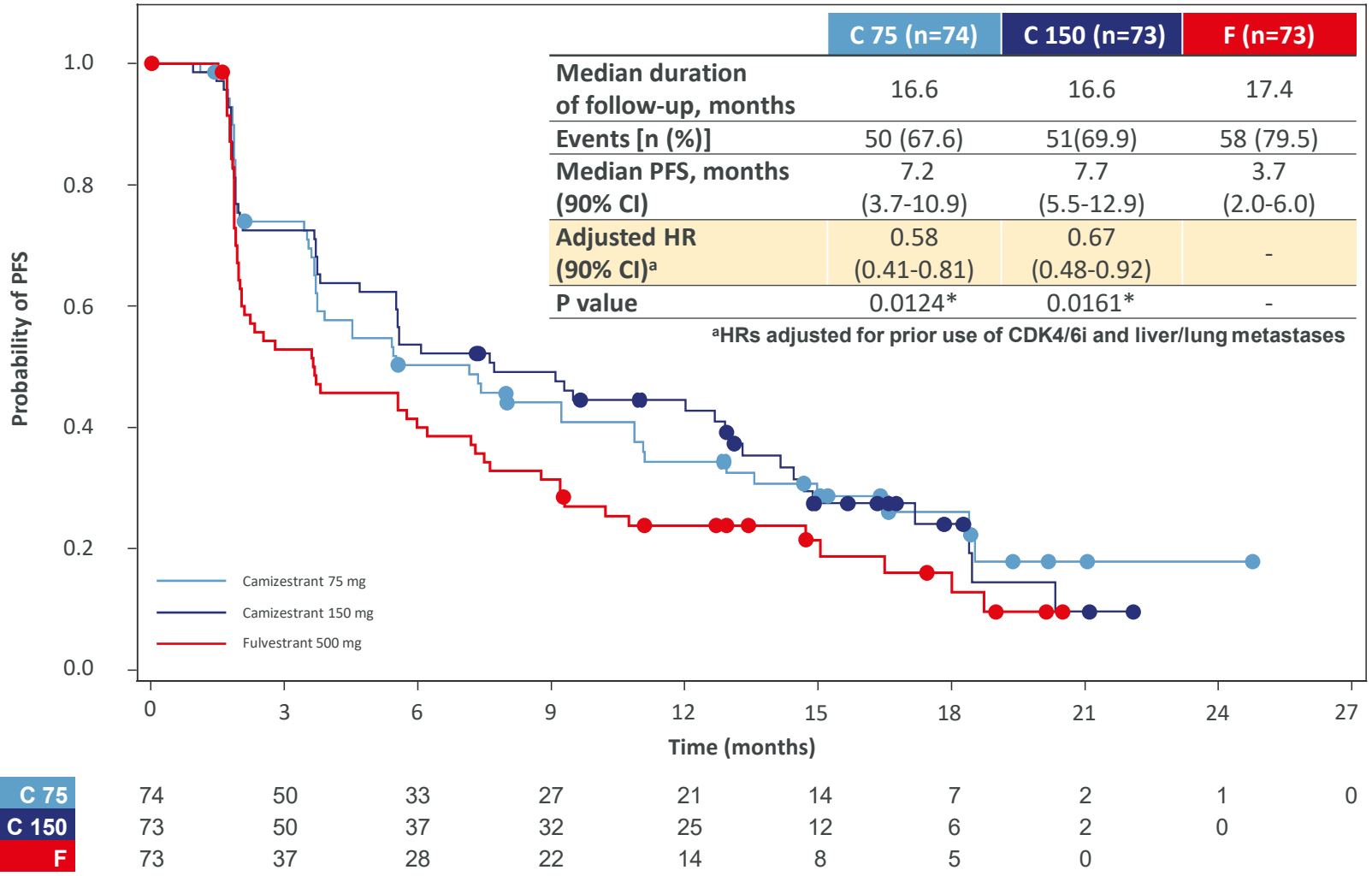
	C 75 (n=74)	C 150 (n=73)	F (n=73)	Total (n=240)
Age (median, range)	61.0 (37-89)	60.0 (42-84)	60.0 (35-84)	60.0 (35-89)
Gender, F (%)[a]	100	100	100	100
Race, White (%)	95.9	95.9	89.0	94.2
ER+ (%)	100	100	100	100
PgR+ (%)	81.1	84.9	79.5	79.6
ECOG 0 (%)	62.2	57.5	58.9	58.8
Lung/liver metastasis Y (%)	58.1	58.9	58.9	58.3
Liver metastasis (%)	31.1	41.1	47.9	40.8
Bone only disease (%)	14.9	19.4	17.8	17.6
***ESR1*m detectable (%)[b]**	29.7	35.6	47.9	36.7

	C 75 (n=74)	C 150 (n=73)	F (n=73)	Total (n=240)
CT adjuvant, Y (%)	54.1	53.4	52.1	52.1
CT in ABC, Y (%)	21.6	12.3	26.0	19.2
ET overall, lines (%)				
0	1.4	1.4	0	0.8
1	81.1	72.6	76.7	77.1
2	16.2	24.7	19.2	20.0
3	1.4	1.4	4.1	2.1
ET adjuvant, Y (%)	66.2	71.2	60.3	66.7
ET in ABC, lines (%)				
0	37.8	28.8	26.0	31.3
1	62.2	71.2	74.0	68.8
AI	55.4	67.1	67.1	63.3
SERM	6.8	2.7	6.8	5.0
Prior CDK4/6i Y (%)[c]	51.4	50.7	50.7	49.6

[a]All post-menopausal women; [b]*ESR1*m assessed in plasma samples at screening (GuardantOMNI™) and Cycle 1 Day 1 (Guardant360®), *ESR1*m defined as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G, individual mutations present in >2% total cases reported; [c]Missing or not specified in 3 patients ABC: advanced breast cancer; AI: aromatase inhibitor; C: camizestrant; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; F: female; PgR: progesterone receptor; SERM: selective estrogen receptor modulator (tamoxifen or toremifene) .

SERENA-2: primary endpoint

Progression free survival by investigator assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

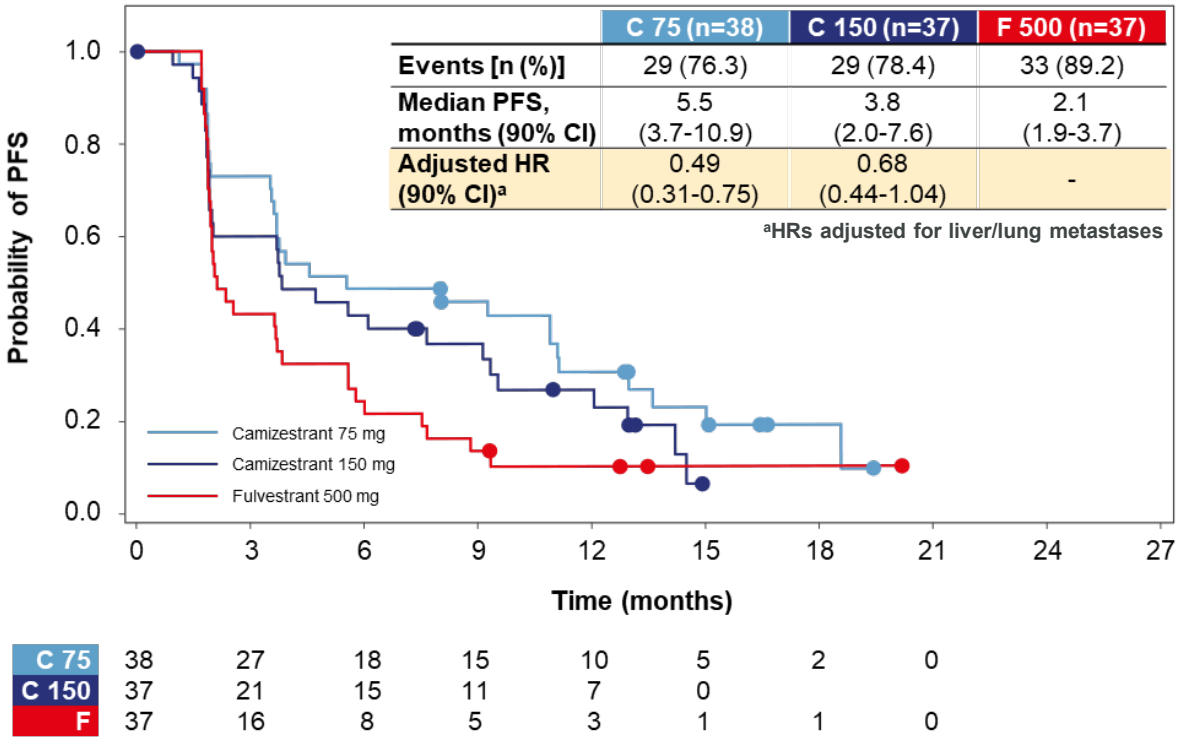
In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

*Statistically significant; CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

SERENA-2:

PFS in patients by prior use of CDK4/6 inhibitors

Prior CDK4/6i

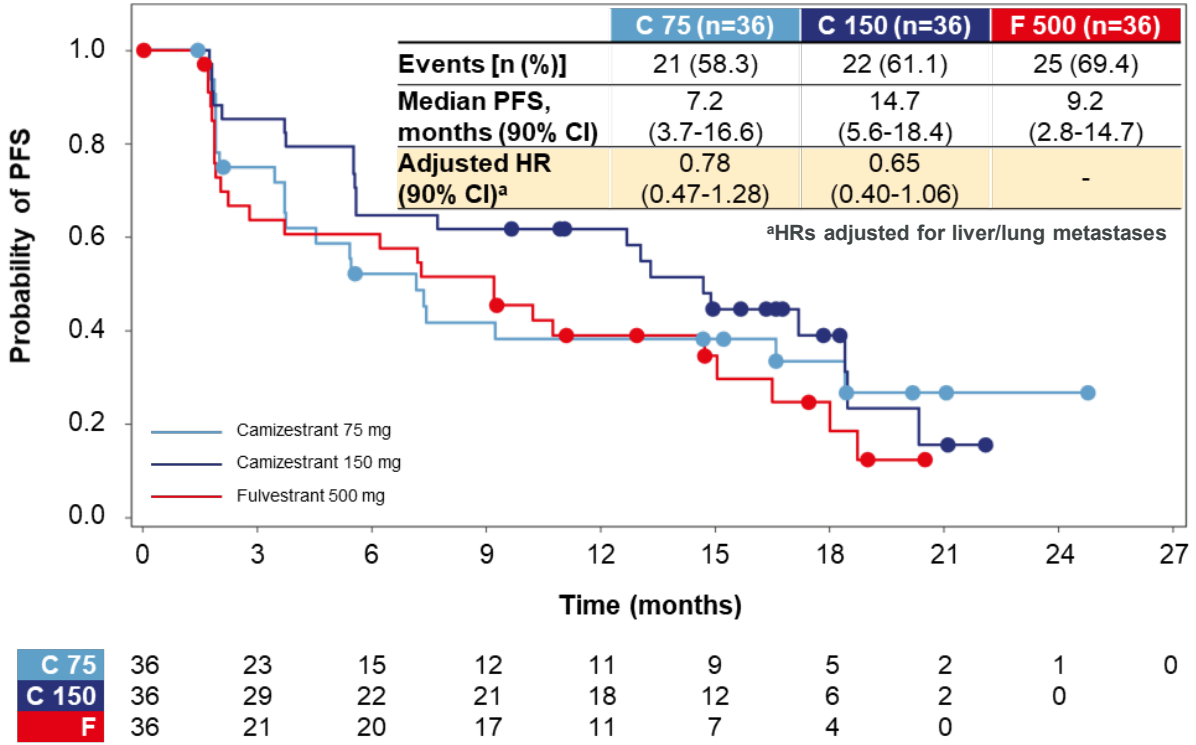


	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

[a]HRs adjusted for liver/lung metastases

C 75	38	27	18	15	10	5	2	0
C 150	37	21	15	11	7	0		
F	37	16	8	5	3	1	1	0

No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

[a]HRs adjusted for liver/lung metastases

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

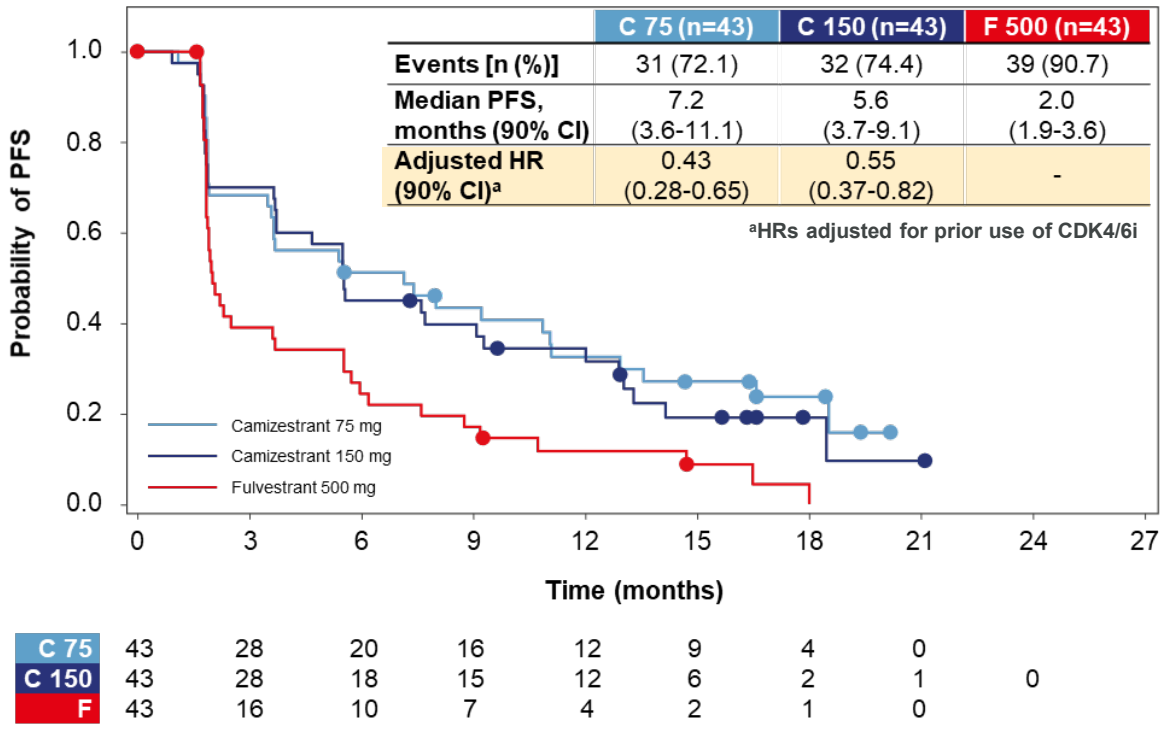
In the sub-population of patients previously treated with CDK4/6i + endocrine therapy, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; HR: hazard ratio; PFS: progression-free survival; [a]HRs adjusted for liver/lung metastases

SERENA-2:

PFS in patients by lung and/or liver metastases

Presence of lung and/or liver metastases

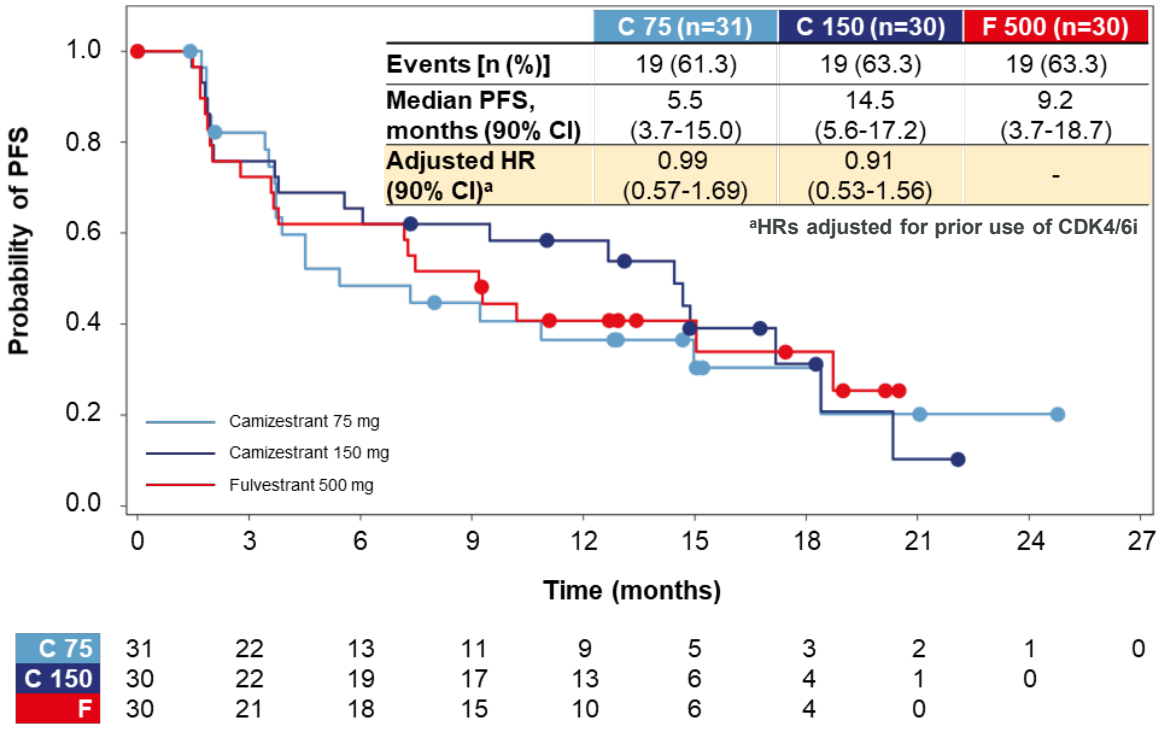


	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-

[a]HRs adjusted for prior use of CDK4/6i

C 75	43	28	20	16	12	9	4	0		
C 150	43	28	18	15	12	6	2	1	0	
F	43	16	10	7	4	2	1	0		

No lung or liver metastases



	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

[a]HRs adjusted for prior use of CDK4/6i

C 75	31	22	13	11	9	5	3	2	1	0
C 150	30	22	19	17	13	6	4	1	0	
F	30	21	18	15	10	6	4	0		

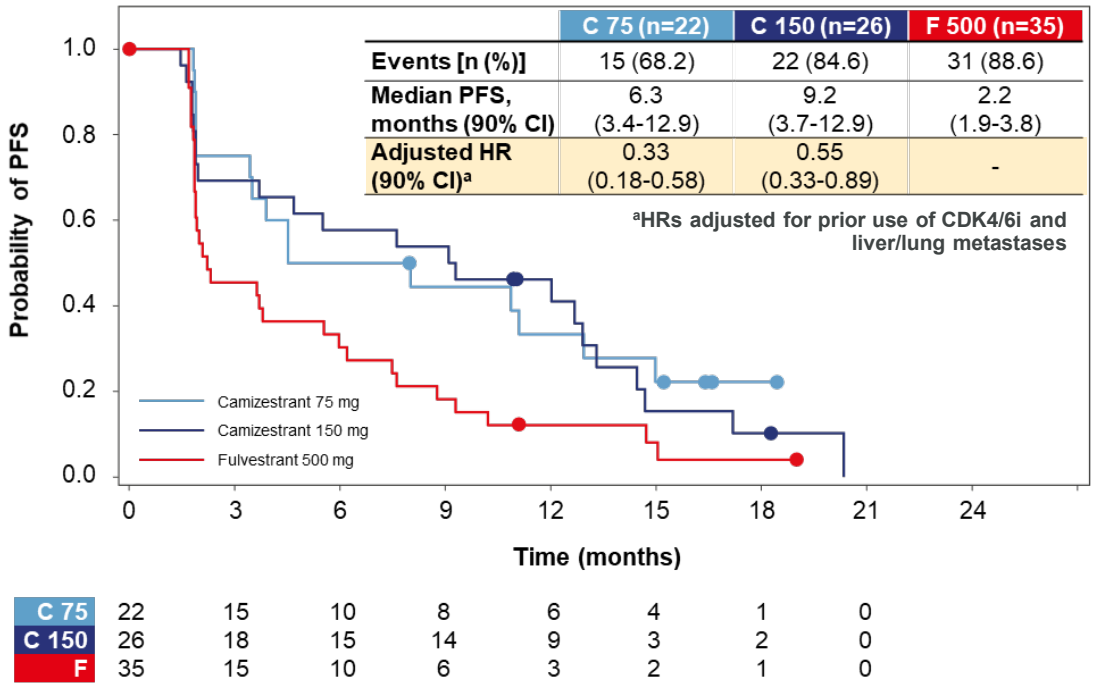
In the sub-population of patients with lung and/or liver metastases, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; HR: hazard ratio; PFS: progression-free survival This presentation is the intellectual property of the author/presenter; [a]HRs adjusted for prior use of CDK4/6i

SERENA-2:

PFS in patients by detectable *ESR1*m at baseline

*ESR1*m detectable at baseline

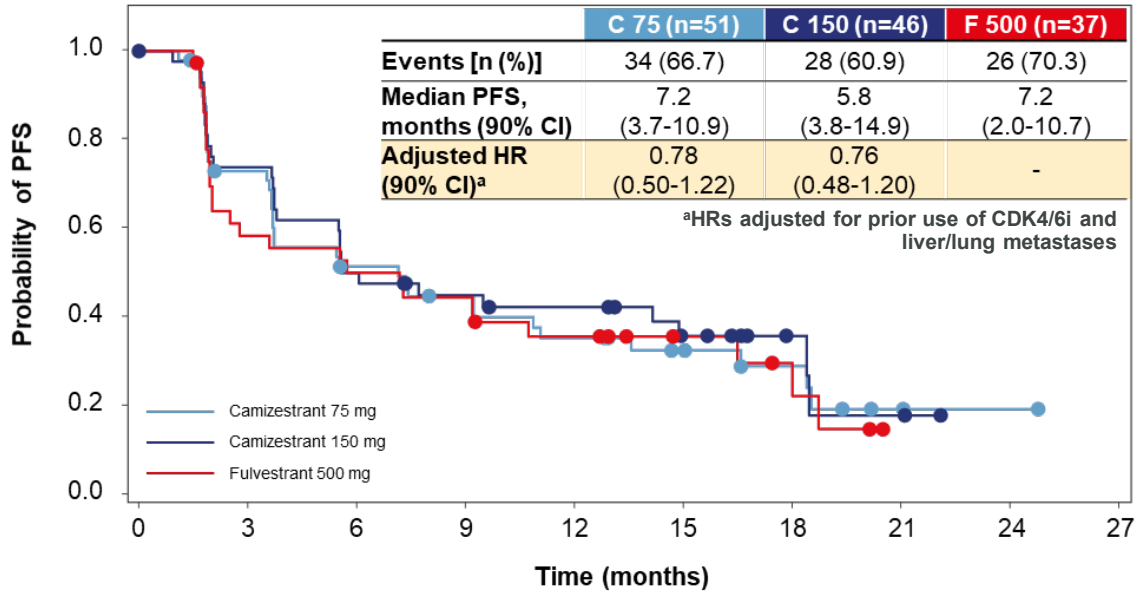


	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

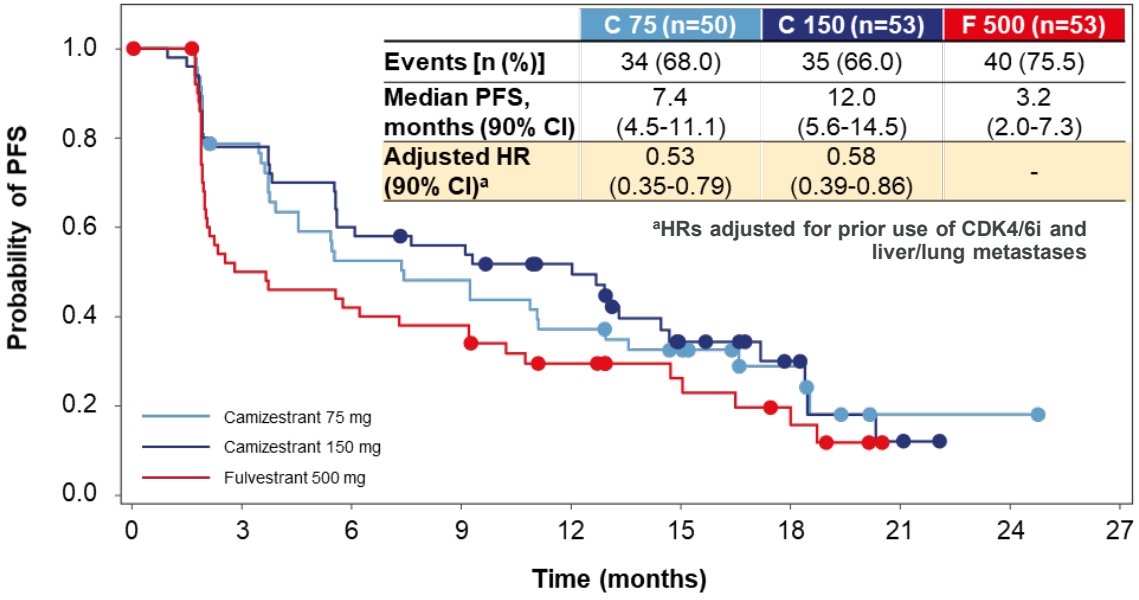
In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; ESR1m: mutation in estrogen receptor 1 gene; HR: hazard ratio; PFS: progression-free survival

SERENA-2:

PFS in patients by ER-driven disease[1]

Patients with evidence of ER-driven disease*

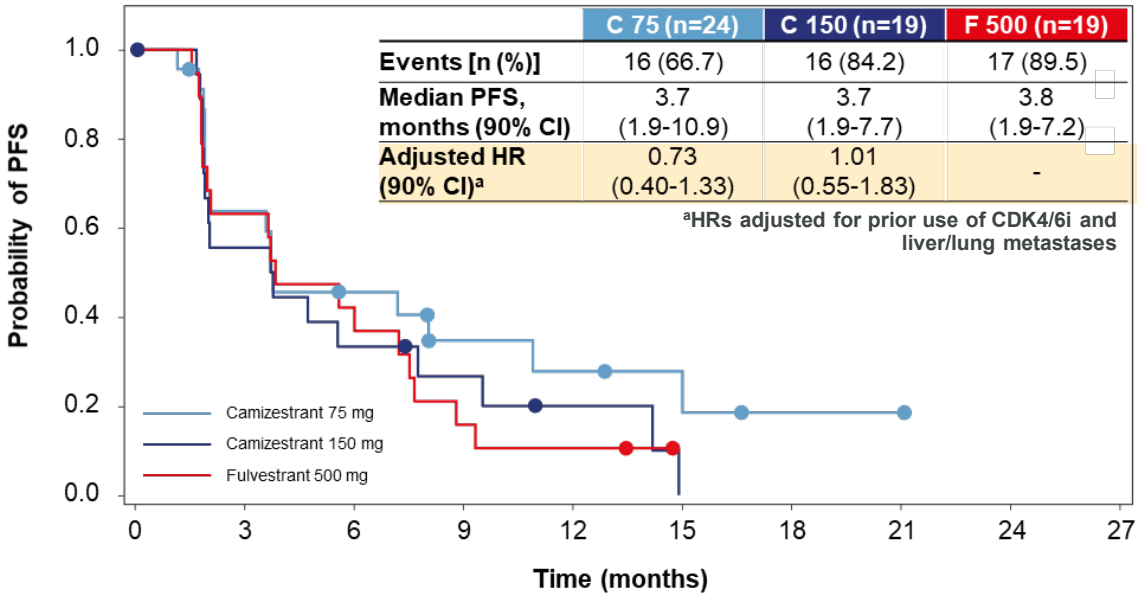


	C 75 (n=50)	C 150 (n=53)	F 500 (n=53)
Events [n (%)]	34 (68.0)	35 (66.0)	40 (75.5)
Median PFS, months (90% CI)	7.4 (4.5-11.1)	12.0 (5.6-14.5)	3.2 (2.0-7.3)
Adjusted HR (90% CI)[a]	0.53 (0.35-0.79)	0.58 (0.39-0.86)	-

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

C 75	50	36	24	22	17	12	6	1	1	0
C 150	53	39	30	27	22	11	6	2	0	
F	53	25	21	19	12	8	5	0		

Patients without evidence of ER-driven disease*



	C 75 (n=24)	C 150 (n=19)	F 500 (n=19)
Events [n (%)]	16 (66.7)	16 (84.2)	17 (89.5)
Median PFS, months (90% CI)	3.7 (1.9-10.9)	3.7 (1.9-7.7)	3.8 (1.9-7.2)
Adjusted HR (90% CI)[a]	0.73 (0.40-1.33)	1.01 (0.55-1.83)	-

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

C 75	24	14	9	5	4	2	1	1	0	
C 150	19	10	6	4	2	0				
F	19	12	7	3	2	0				

- In the subgroup of patients with evidence of ER-driven disease (71.3% of overall population), both 75 mg (HR 0.53) and 150 mg (HR 0.58) produced a clinically meaningful PFS improvement over fulvestrant
- In the (small, 28.7% of overall population) subgroup patients without evidence of ER-driven disease, 75 mg (HR 0.73) produced a trend to benefit over fulvestrant; the effect for 150 mg (HR 1.01) was less clear

1 Defined in accordance with 5th ESO-ESMO ABC guidelines where the cut-point is increased to 12 months for patients receiving ET+CDK4/6i therapy in the advanced setting [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; ESR1m: mutation in estrogen receptor 1 gene; HR: hazard ratio; PFS: progression-free survival

SERENA-2: patient level safety summary

	C 75 (n=74)	C 150 (n=73)	C 300 (n=20)	F 500 (n=73)
Total duration, months, mean (SD)	8.27 (6.59)	8.91 (6.78)	9.26 (8.19)	7.34 (6.09)
Any treatment-emergent AE (TEAE), n (%)	57 (77.0)	66 (90.4)	19 (95.0)	50 (68.5)
Any treatment-related AE (TRAE), n (%)	39 (52.7)	49 (67.1)	14 (70.0)	13 (17.8)
CTCAE Grade 3 or higher, n (%)	1 (1.4)	2 (2.7)	1 (5.0)	1 (1.4)
serious, n (%)	3 (4.1)	2 (2.7)	1 (5.0)	0
fatal	0	0	0	0
leading to discontinuation of treatment, n (%)	2 (2.7)	0	0	0
TEAE leading to dose reduction, n (%)	1 (1.4)	9 (12.3)	4 (20.0)	0
TEAE leading to dose interruption, n (%)	11 (14.9)	16 (21.9)	4 (20.0)	3 (4.1)
TRAE leading to dose interruption, n (%)	7 (9.5)	8 (11.0)	3 (15.0)	0
Median duration of dose interruption (days)	7.0	7.5	7.0	-

- TRAEs of Grade 3 or higher and TRAEs leading to discontinuation were infrequent across all treatment arms
- TRAEs leading to dose interruptions were numerically similar for camizestrant 75 and 150 mg, and of short duration
- All camizestrant doses are well tolerated

AE: adverse event; CTCAE: common terminology criteria for adverse events; SD: standard deviation; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event

SERENA-2: all treatment-emergent adverse events

AE, n (%)	C 75 (n=74)		C 150 (n=73)		C 300 (n=20)		F 500 (n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0
AST increased	2 (2.7)	0	6 (8.2)	0	2 (10.0)	0	5 (6.8)	1 (1.4)
ALT increased	1 (1.4)	0	6 (8.2)	1 (1.4)	3 (15.0)	0	4 (5.5)	1 (1.4)
Covid-19	4 (5.4)	0	4 (5.5)	0	3 (15.0)	0	3 (4.1)	0
Diarrhea	4 (5.4)	0	4 (5.5)	0	3 (15.0)	1 (5.0)	2 (2.7)	1 (1.4)
Pain in extremity	1 (1.4)	0	4 (5.5)	1 (1.4)	2 (10.0)	0	3 (4.1)	0
Dyspepsia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Insomnia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Hyponatremia	0	0	3 (4.1)	1 (1.4)	2 (10.0)	0	1 (1.4)	1 (1.4)
Blood pressure increased	2 (2.7)	1 (1.4)	1 (1.4)	1 (1.4)	2 (10.0)	1 (5.0)	0	0
Cataract	2 (2.7)	0	0	0	2 (10.0)	0	0	0
Vitreous floaters	2 (2.7)	0	0	0	2 (10.0)	0	0	0

Ranked by all grades for the 150mg dose, ≥10% in any arm, irrespective of causality assessment

AE: adverse event; CTCAE: common terminology criteria for adverse events; SD: standard deviation; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event

SERENA-2: conclusions

- SERENA-2 met its primary objective: camizestrant at both 75 and 150 mg doses improves PFS over fulvestrant in post-menopausal women with ER+/HER2- ABC
- Camizestrant delivers statistically significant and clinically meaningful PFS benefit at both 75 and 150 mg doses over fulvestrant in the overall population
- A clinically meaningful PFS benefit was observed across the pre-specified subgroups of unmet medical need (post-CDK4/6i, lung/liver metastases, ESR1m and evidence of ER-driven disease)
- Both camizestrant doses are well tolerated, with infrequent Grade ≥3 TRAEs, dose reductions and discontinuations

SERENA-2 results support the further development of camizestrant in ER+ breast cancer, ongoing enrolment Phase III SERENA-4 and SERENA-6 trials

[a]SERENA-4 NCT04711252; [b]SERENA-6 NCT04964934 ABC: advanced breast cancer; AE: adverse event; CDK4/6i: CDK4/6 inhibitor; *ESR1*m: mutation in estrogen receptor 1 gene; HER2: human epidermal growth factor receptor 2; PFS: progression-free survival; TRAE: treatment-related adverse event.

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Other key data @ SABCS

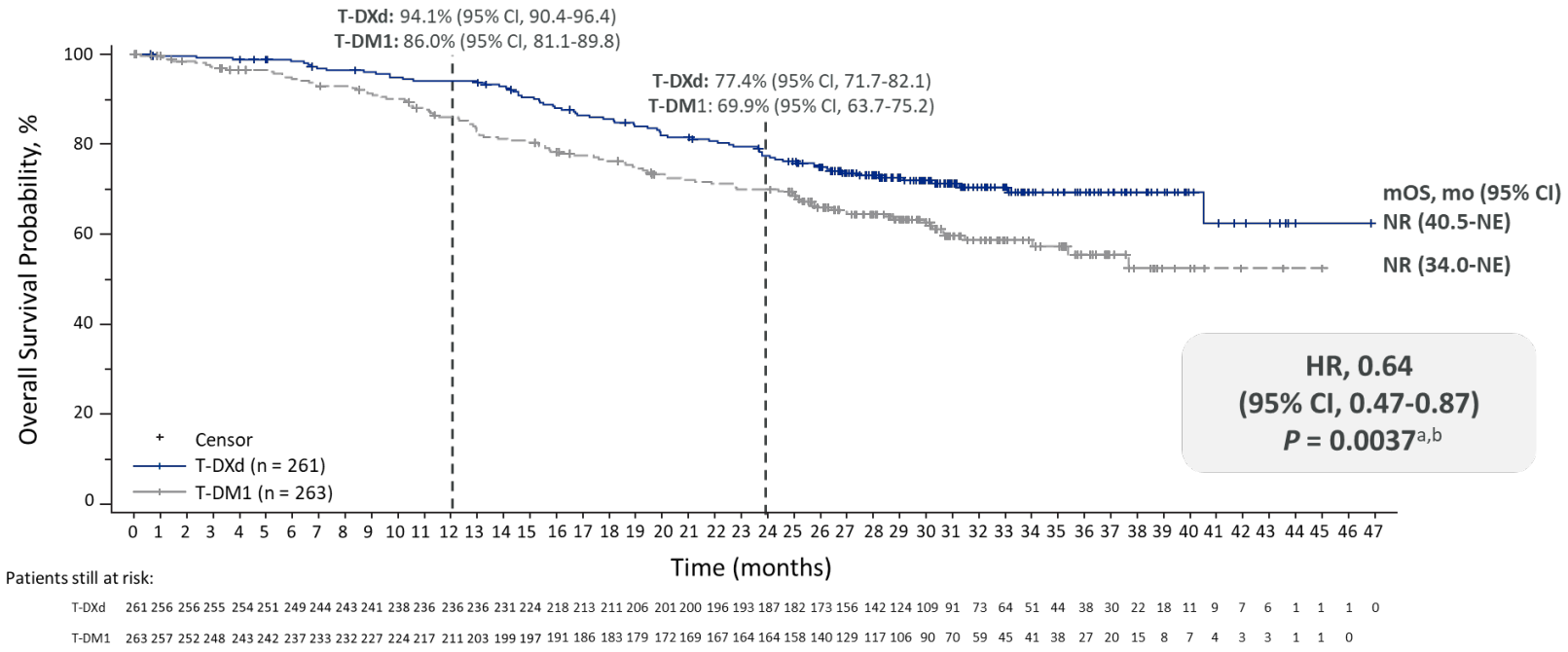
Susan Galbraith
EVP, Oncology R&D

Enhertu DESTINY-Breast03

Reinforces *Enhertu* as established standard of care in 2L HER2-high

Key secondary endpoint: overall survival

Clinically meaningful, statistically significant improvement over T-DM1



- mPFS with *Enhertu* 4x longer than T-DM1 (28.8m vs. 6.8m)
  - CLEOPATRA mPFS 18.7m in 1L[1]
- 78.5% of patients experienced confirmed objective response
- 1 in 5 (21.1%) of patients experienced complete response

***Enhertu* significantly reduced risk of death by 36% (HR, 0.64)**

1 transtuzumab + pertuzumab + taxane (Swain SM et al. *N Engl J Med.* 2015; 372: 724-34) ; HER2 = human epidermal growth receptor 2; T-DM1 = Ado-trastuzumab emtansine; HR = hazard ratio; T-DXd = trastuzumab deruxtecan; mFPS = median progression free survival.

Dato-DXd

Reinforcing potential of next-gen ADCs to replace chemo across HR+ and TNBC

Potential in heavily pre-treated HR+/HER2-

Phase I TROPION-PanTumor01

- Encouraging, durable efficacy in heavily pre-treated patients (95% received prior CDK4/6i)
  - ORR by BICR of 27%, DCR by BICR of 85%
- Durable response with mPFS by BICR of 8.3m (CI 5.5-11.1m)
- Phase III TROPION-Breast01 trial Dato-DXd versus chemotherapy in 2L inoperable or mHR+/HER2- ongoing

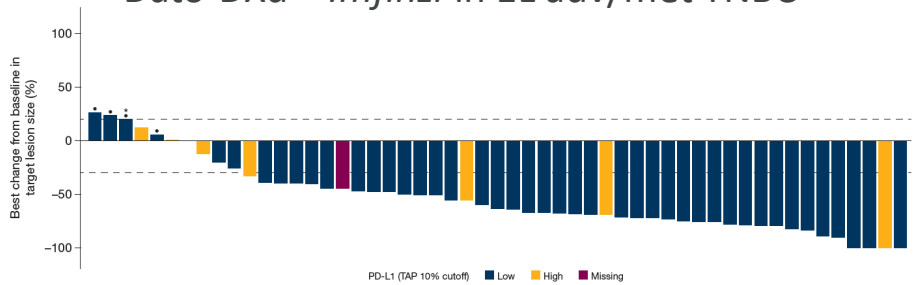
Potential to address advanced TNBC

Phase I TROPION-PanTumor01

- mDOR 16.8 months observed in both overall population and Topo I inhibitor-naïve patients
- ORR by BICR 32% in overall population, 44% in Topo I inhibitor-naïve patients
- Validated 6mg/kg as dose for expansion across development programme; additional trials in TNBC ongoing

Phase Ib/II BEGONIA

Dato-DXd + *Imfinzi* in 1L adv/met TNBC



n = 53.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

- 4 patients observed complete response, with responses observed in PDL1-high and low tumours

Dato-DXd = datopotamab deruxtecan; ADC = antibody drug conjugate; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple negative breast cancer; ORR = overall response rate; mDoR = median duration of response; BICR = blinded independent central review; DCR = disease control rate; mPFS = median progression free survival; PDL-1 = programmed death-ligand 1.

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Advancing the treatment paradigm in breast cancer

Dave Fredrickson
EVP, Oncology Business

Addressing the significant unmet need in breast cancer

#1

most diagnosed cancer globally[1]

2.3m

newly identified breast cancer **cases diagnosed** each year globally[2]

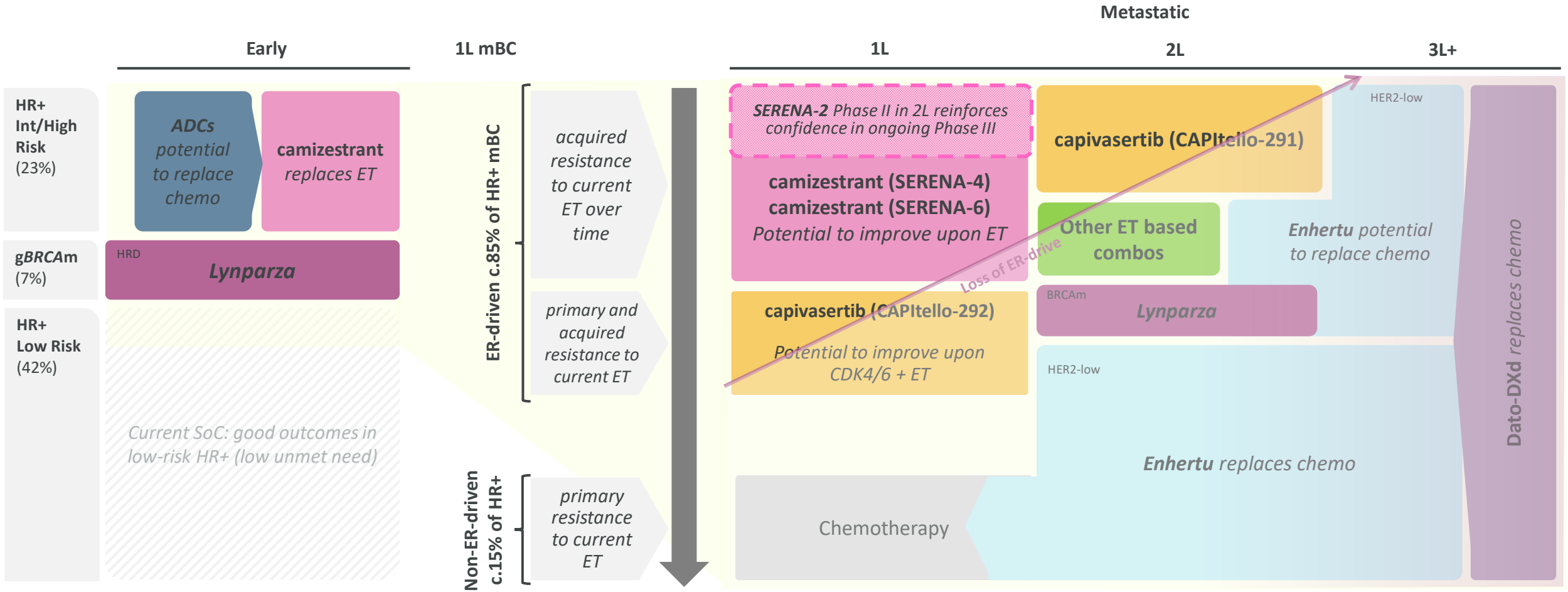
685,000

deaths from breast cancer each year globally[2]

1. breastcancer.org, statistics specific to women in US; 2. GLOBOCAN 2020.

Reshaping HR+ Breast Cancer

Camizestrant ngSERD, capivasertib extending ET in ER-driven disease



HR = hormone receptor; ET = endocrine therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitors; HRD = homologous recombination deficiency; gBRCAm = breast cancer gene mutation; ER = oestrogen receptor; AI = aromatase inhibitors; HER2 = human epidermal growth receptor 2; Dato-DXd = datopotomab deruxtecan.

CAPItello-291: potential new standard of care

Capivasertib first-in-class AKT inhibitor, addresses unmet need in 2L+ mBC

Patient outcomes in 2L+ mBC remain poor

75,000
patients diagnosed each year with metastatic Breast Cancer[1]

Rapid progression
following 1L SoC (CDK4/6i)

65,000
new 2L patients each year, available treatments with underwhelming risk-benefit profile[2]

Lack of clear SoC
in the 2L; 70-80% of patients have ER-driven disease

Capivasertib addresses key unmet need

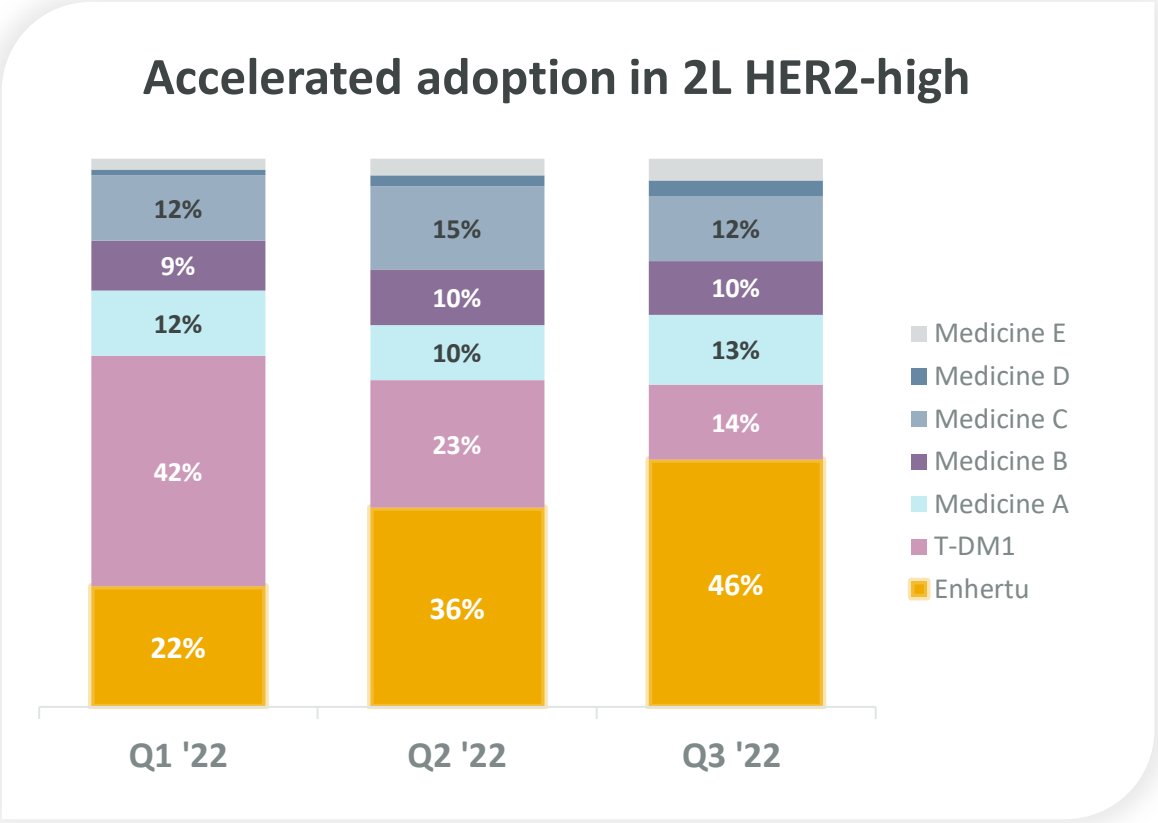
- CAPItello-291 overcomes key mechanism of ET + CDK4/6i resistance, extending ET based therapeutic option in ER-driven disease
- CAPItello-291 reflects clinical practice (post-CDK4/6i)
- Clinically meaningful in the overall population
  - mPFS improvement from 3.6 to 7.2 months (HR 0.6, P<0.001)
- Compelling safety and tolerability profile

CAPItello-291 regulatory submission planned H1 2023

1 US, EU and JP; 2 Across G7 countries; AKT = a serine/threonine protein kinase; mBC = metastatic breast cancer; CDK4/6i = cyclin-dependent kinase 4/6 inhibitors; SoC = standard of care; ER-driven = oestrogen receptor driven; ET = endocrine therapy; mPFS = median progression free survival; HR = hazard ratio.

Enhertu

DESTINY-Breast03 OS data supports *Enhertu* as market leader in 2L HER2-high



DESTINY-Breast03

- OS data shows *Enhertu* significantly reduced risk of death by 36% (HR 0.64)
- Rapid adoption in 2L HER2-high patients following approval May 2022 (US)
- >35% new patient share in Germany and France in first launch quarter

DESTINY-Breast04

- Launch in HER2-low progressing, *Enhertu* used in >1/3 HR+ post-chemo population as of Q3 2022

DESTINY-Breast03 OS data supports ambition to move earlier line with *Enhertu,* potentially curative

Source: Q1'22 data from ZoomRx ENHERTU HER2+ mBC US Quarterly Launch Tracker (PCA); Patient chart sample os c.125-150 patient charts/line/quarter across 125-250 HCPs; Q1 '22 shares are unweighted; Q2-Q3 '22 data from Cerner Enviza ENHERTU HER2+ mBC US Monthly Launch Tracker (PCA) Patient chart sample is c.400-500 patient charts/month across 70-75 HCPs; monthly shares are unweighted; OS = overall survival; 2L = second line; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; T-DM1 = Ado-trastuzumab emtansine; HR+ = hormone receptor positive.

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Q&A session

Q&A Panel

Dr Nicholas Turner

Professor, Institute of Cancer Research, Royal Marsden Hospital, London

Dave Fredrickson

Executive Vice President, Oncology Business

Ingrid Mayer

Global Clinical Strategy Head, Breast Cancer

(for Q&A)

Susan Galbraith

Executive Vice President, Oncology Research and Development

Cristian Massacesi

Chief Oncology Development Officer and Chief Medical Officer

Liz Chatwin

Global Franchise Head, *Enhertu* and Breast Cancer

(for Q&A)


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Appendix

CAPItello-291: prior treatments

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

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