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SAN ANTONIO BREAST CANCER SYMPOSIUM®

Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center

AACR American Association for Cancer Research

Metastatic Breast Cancer

Donatienne TAYLOR

Clinique Sainte-Elisabeth - CHU UCL Namur

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®

Brussels / Belgium / 27/01/2023

LICENSED BY ENCORE MEDICAL EDUCATION

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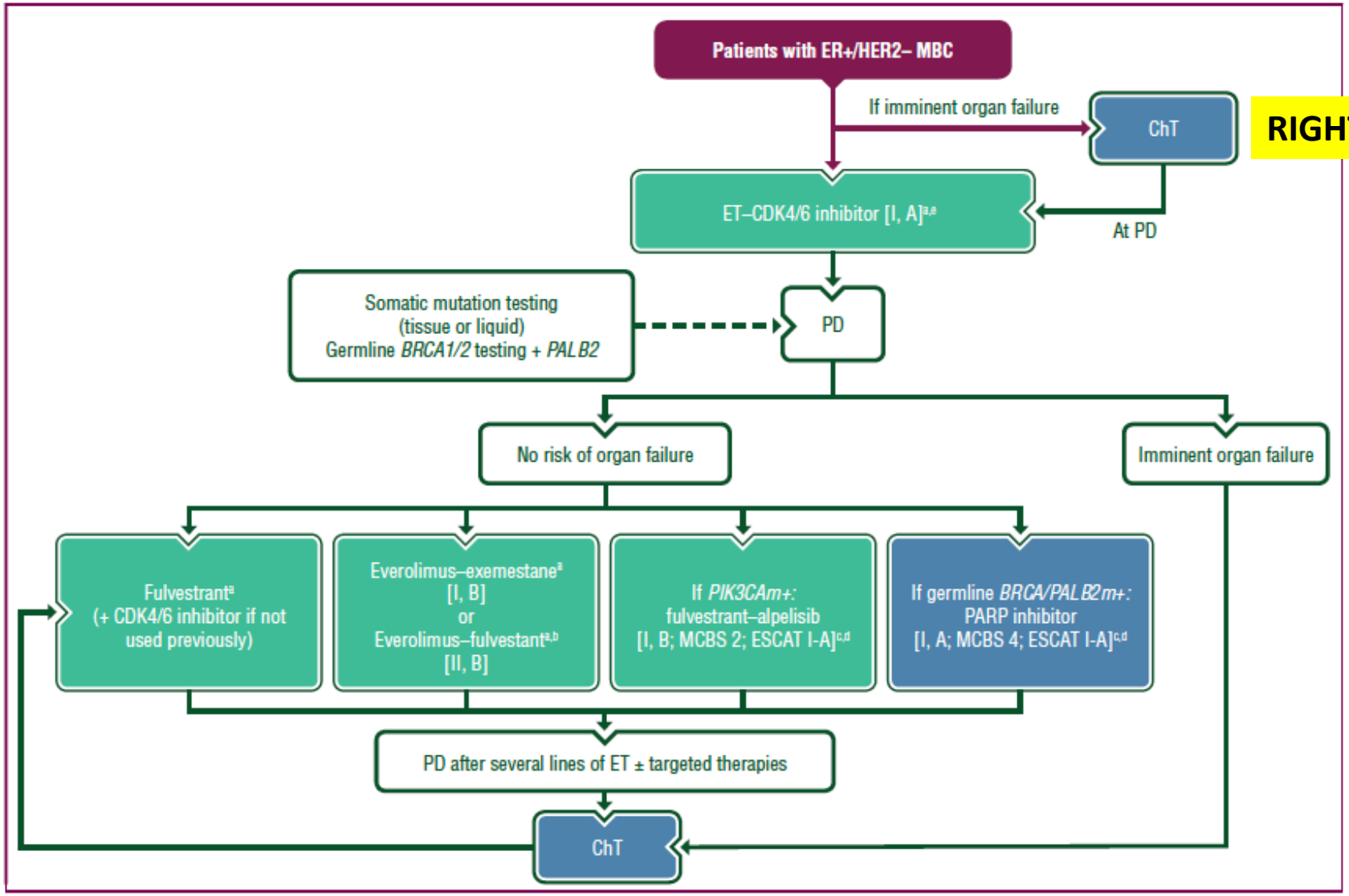
Disclosures

- Consultancy (Honoraria) in the last 24 months: Novartis, Lilly, Daiichi Sankyo, AstraZeneca, MSD.
- Travel/congresses grants: Pfizer, Roche, AstraZeneca, MSD, Lilly.

Focus

- ER+ HER2 – metastatic breast cancer
- HER2+ metastatic breast cancer

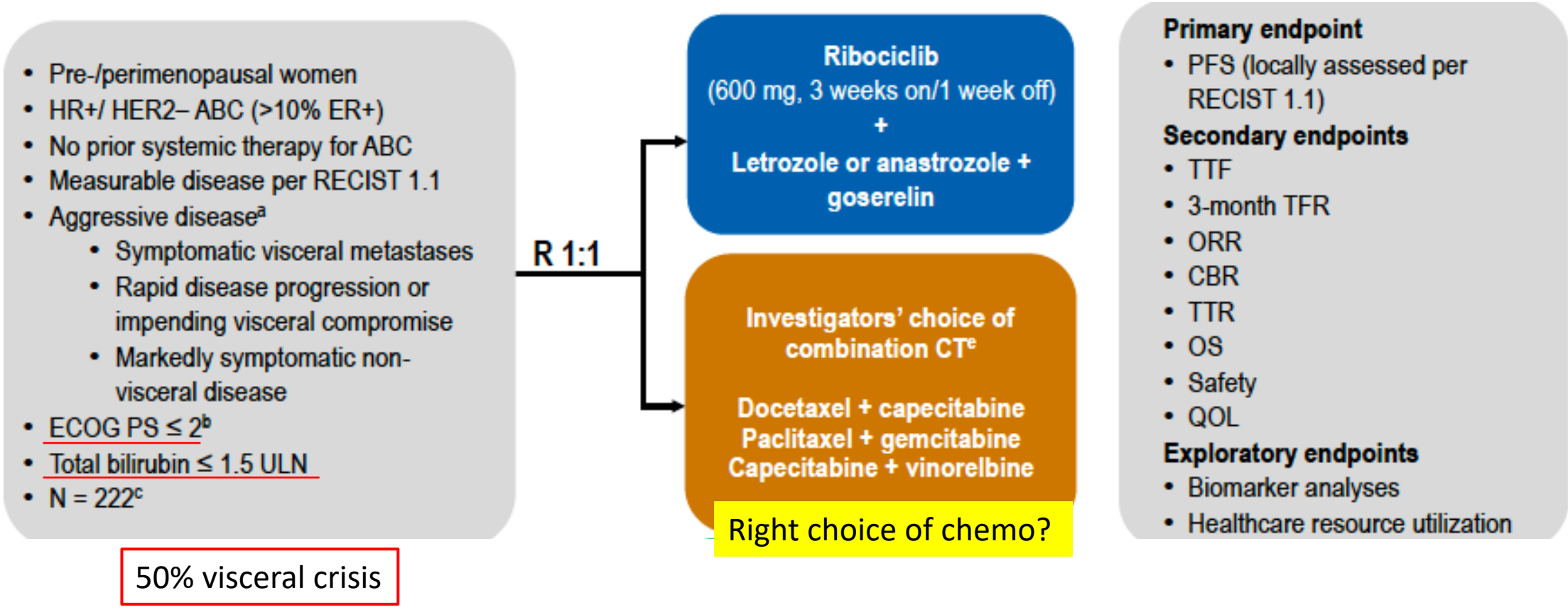
ER+ HER2 “negative” disease



RIGHT Choice Trial

Gennari A et al
ESMO guidelines 2021

RIGHT Choice Trial: Premenopausal women, untreated 'aggressive' disease

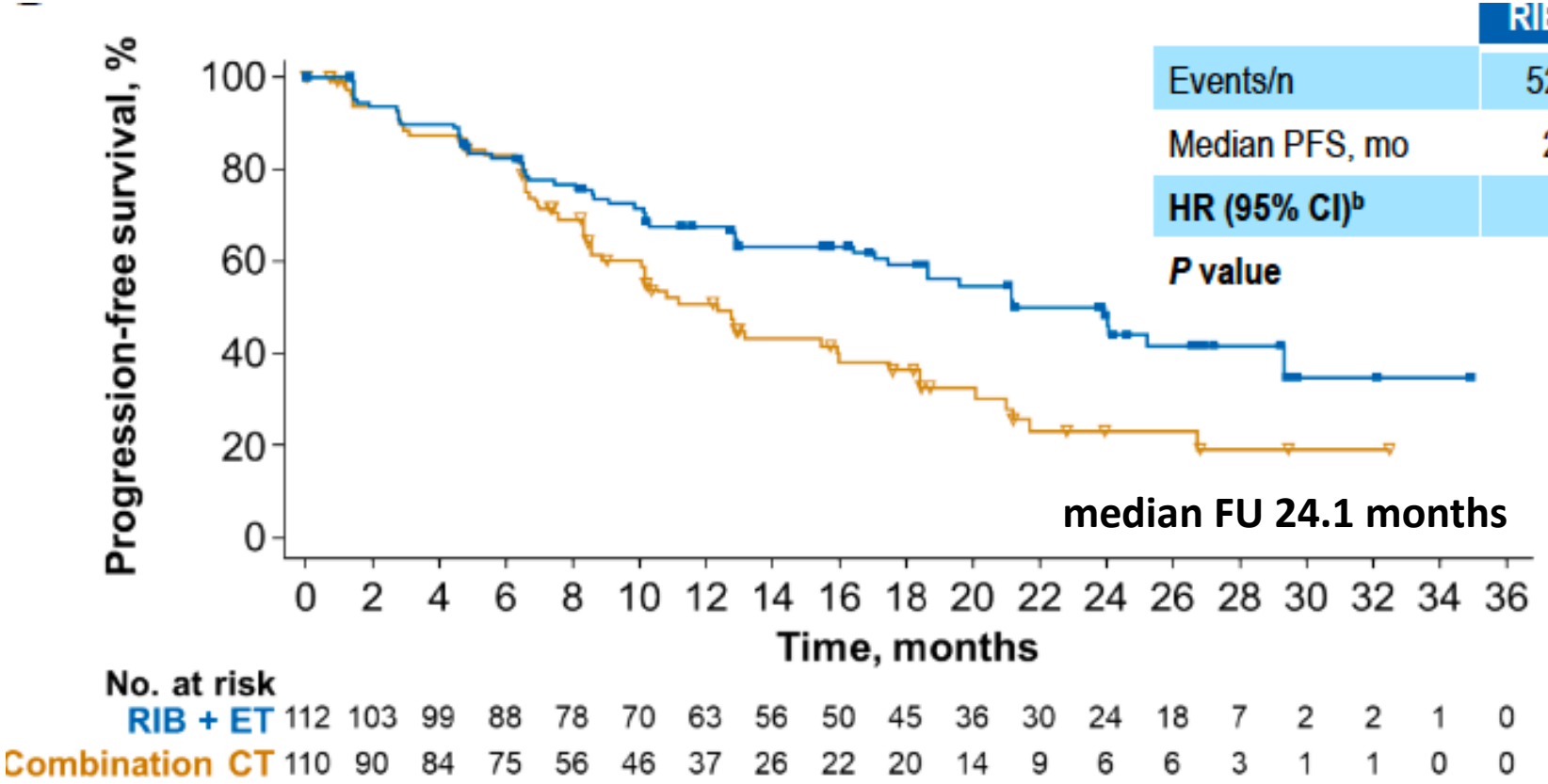


50% visceral crisis

Background: CT vs CDK4/6 inh trial (PEARL) included pretreated patients and no visceral crisis

YS Lu SABCS 22

RIGHT Choice trial: Primary Endpoint - PFS



	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

Gain of 12 months

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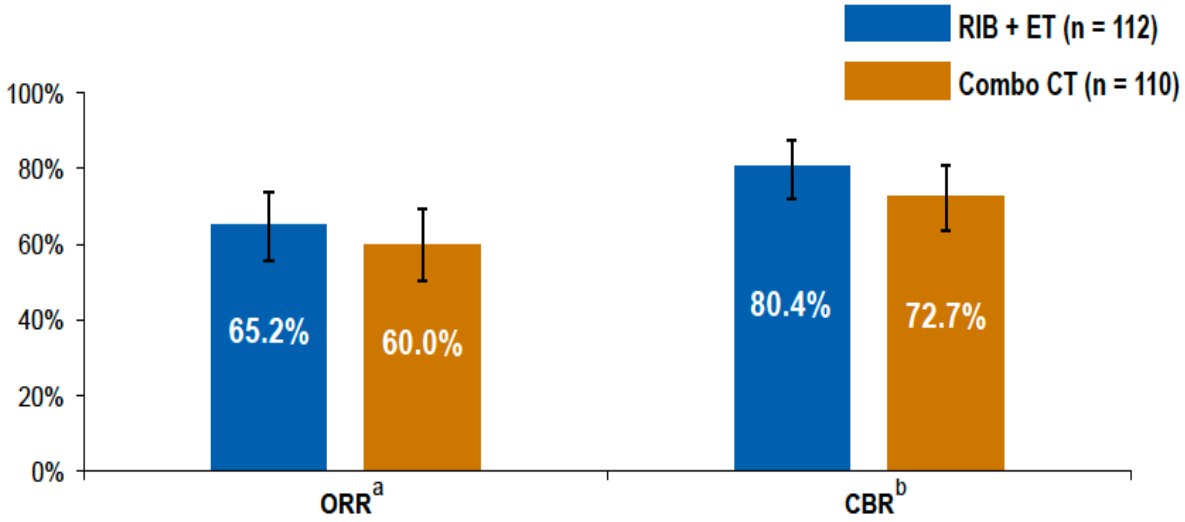
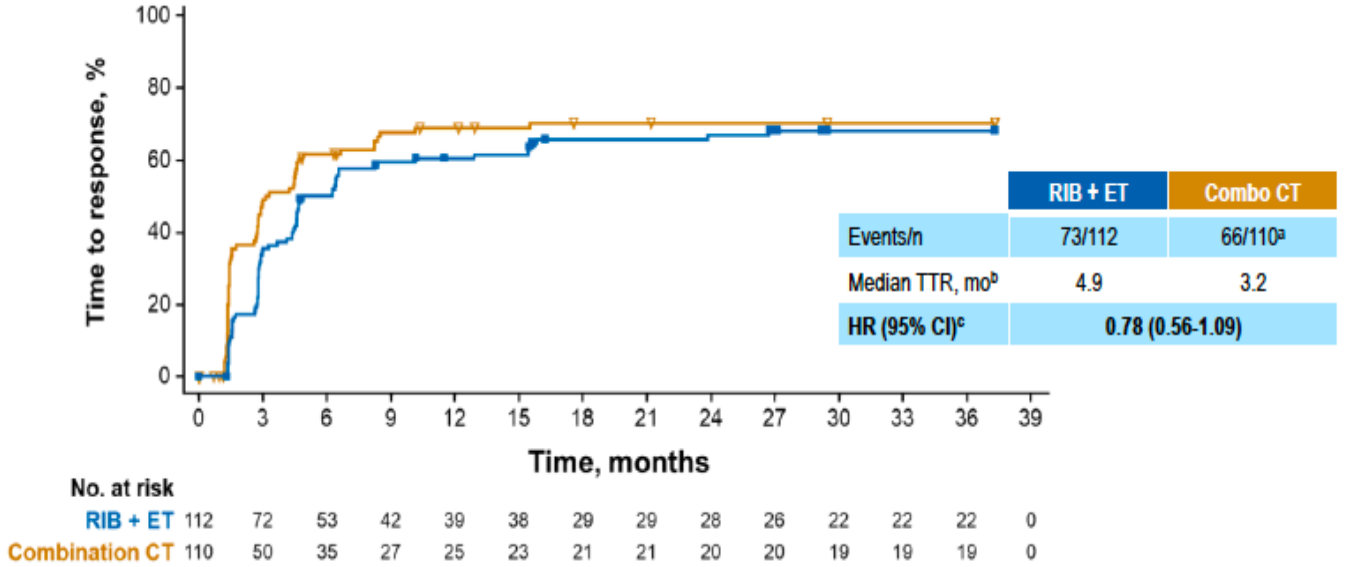
RIGHT Choice trial: Secondary Endpoints ORR, CBR and TTR

Response rates

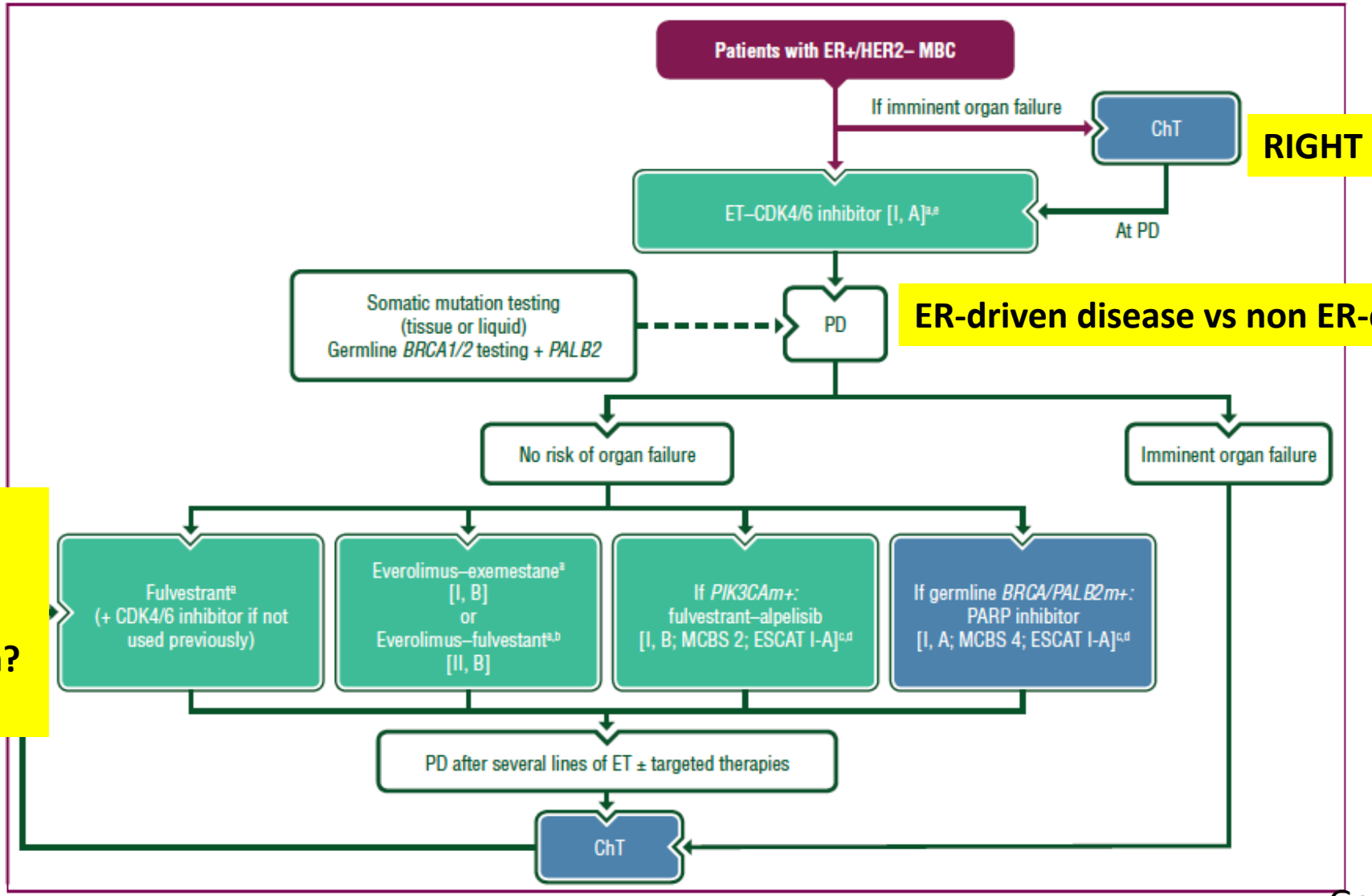


Time to onset of response



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	0.78 (0.56-1.09)	

ER+ HER2 “negative” disease



RIGHT Choice Trial

ER-driven disease vs non ER-driven disease?

Optimal 2nd line
Single agent?
Combi?
AKT path inhibition?
more CDK4/6 inh?

Gennari A et al
ESMO guidelines 2021

Optimal 2nd line in ER+ HER2- mBC?

- Targeting acquired resistance in ER-driven disease:

(1L endocrine therapy > 6months adapted to >12 months CDK4/6i + ET)[1]

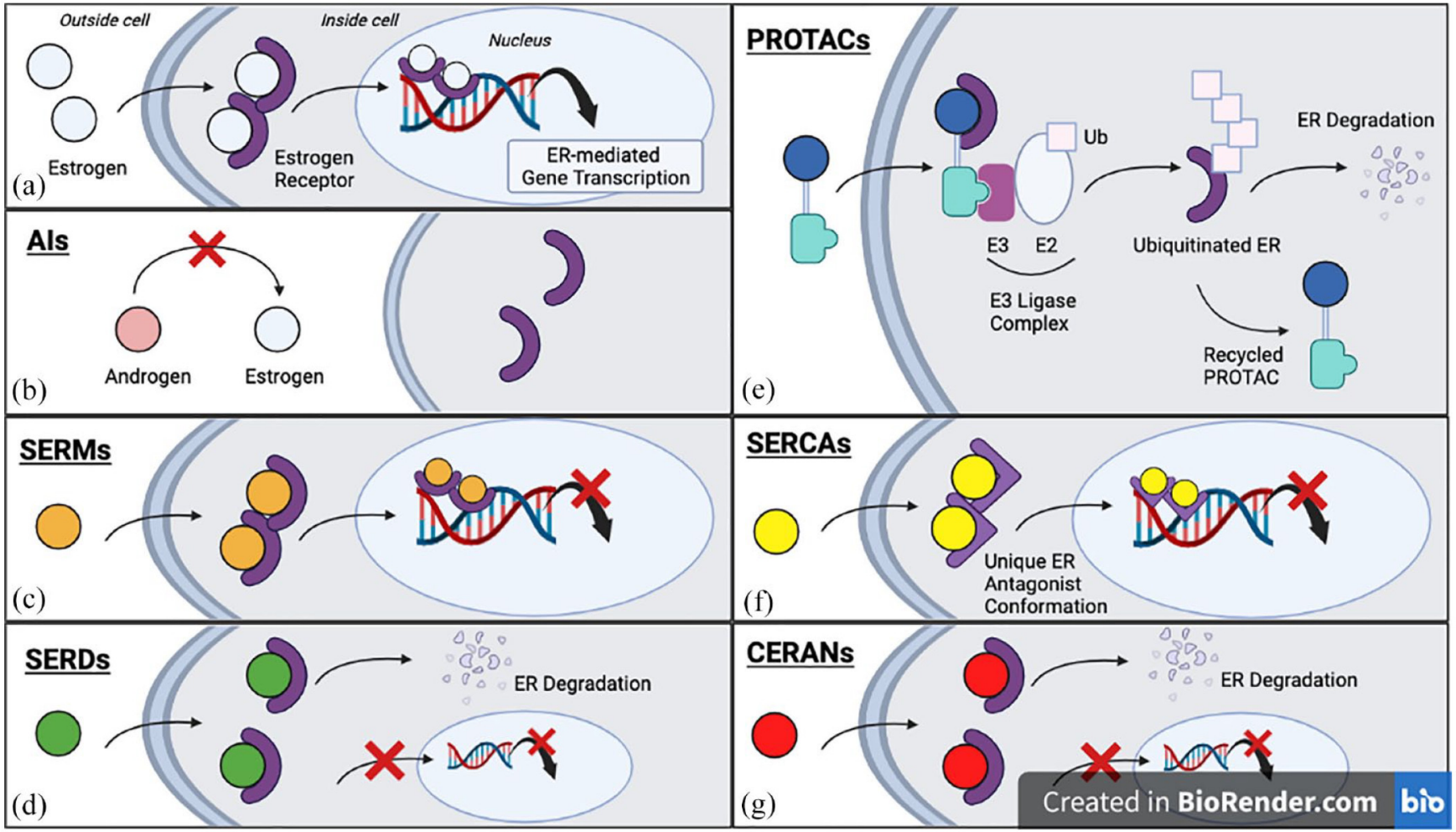
  - Overcoming ESR1 mutations with SERDS
    - **EMERALD** (update)
    - **SERENA-2**
  - New agents PROTACS: **VERITAC**
  - CDK4/6 inhibition after CDK 4/6 inhibition**: PACE**
- Tackling the AKT pathway beyond CDK4/6 inhibition: **CAPItello-291**

[1]ABC5 ESO-ESMO guidelines F.Cardoso

SERD Selective Estrogen Receptor Degraders and novel therapies

Tamoxifen

Fulvestrant
Elacestrant
Camizetrant



ARV-471

Lloyd et al Therapeutic Advances in Med. Oncol 2022

EMERALD phase 3 Trial: Elacestrant vs standard ET

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

R

1:1[b]

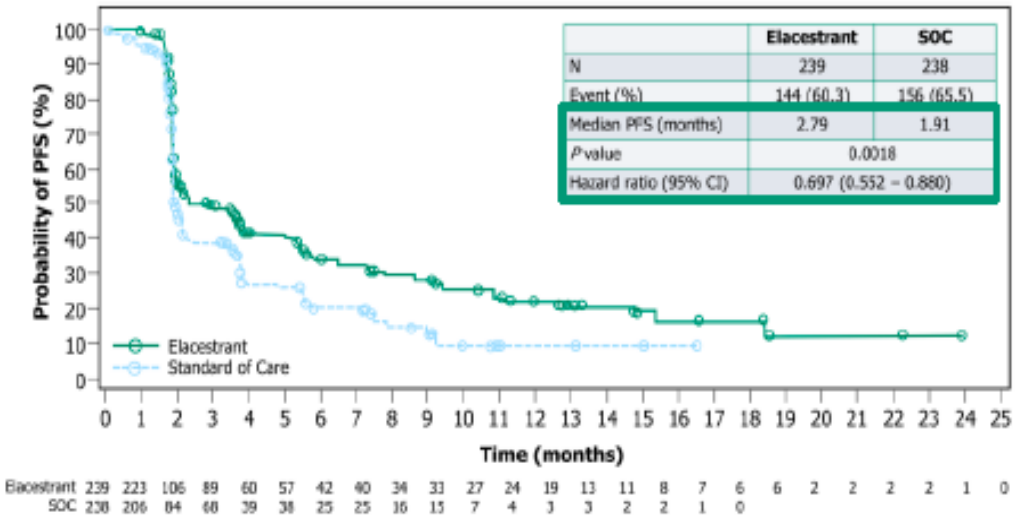
Elacestrant 400 mg daily[c]

Investigator's choice (SOC):
Fulvestrant
Anastrozole
Letrozole
Exemestane

PD or withdrawal criterion[d]

Follow Up

Two Primary Endpoints:[e]
- PFS in all pts
- PFS in *ESR1*-mut

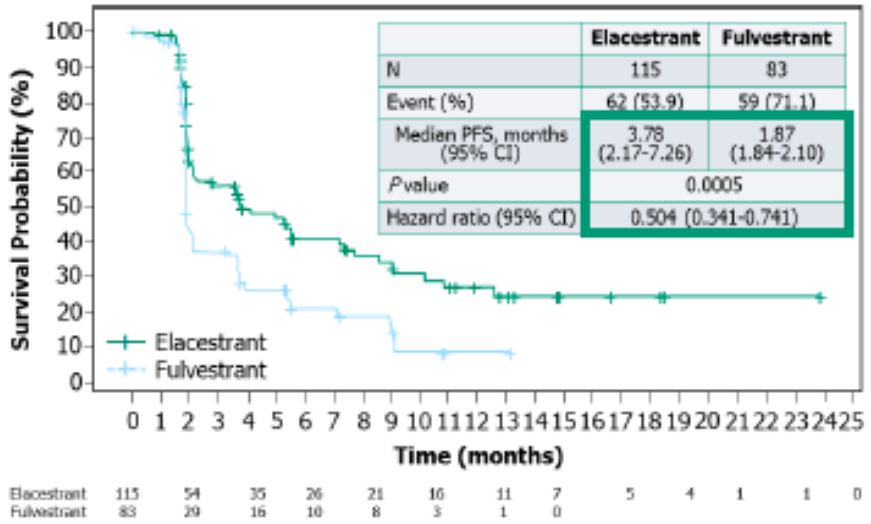


	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

ITT
Δ 0.88 m

ESR1m
Δ 1.91 m

Fulvestrant arm
PFS <2m

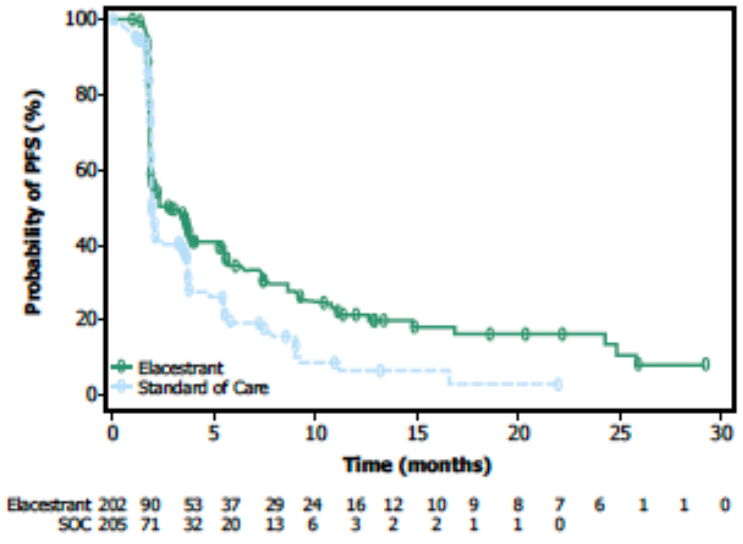


	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Bidard FC JCO 2022
Kaklamani V. SABCS 2022

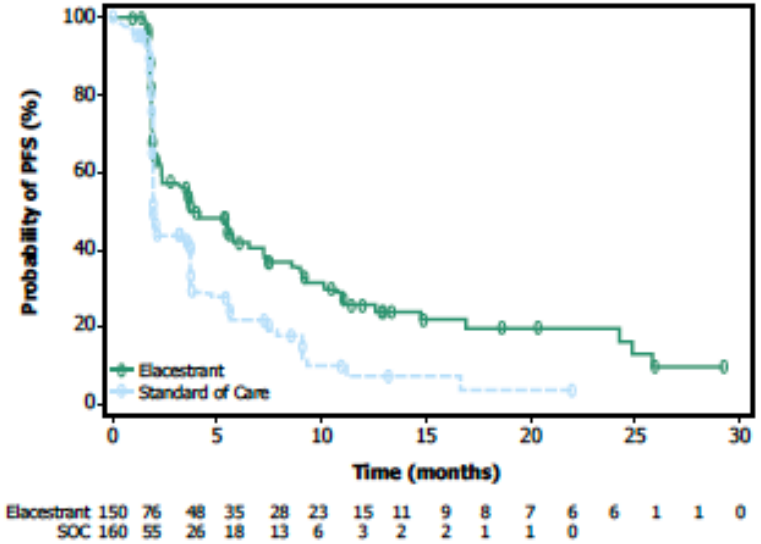
EMERALD Trial: Updated PFS results by duration of previous CDK4/6i

At least 6 mo CDK4/6i



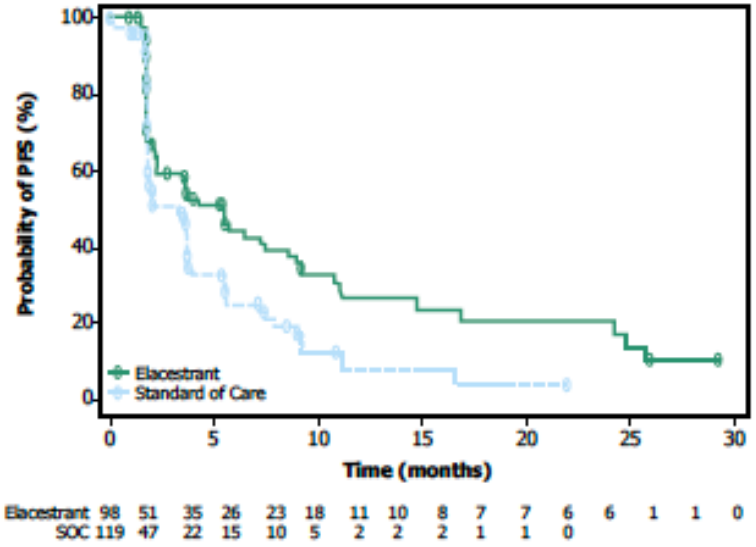
2.79m vs 1.91m
HR 0.69 (0.53-0.88)

At least 12 mo CDK4/6i



3.78m vs 1.91m
HR 0.613 (0.45-0.83)

At least 18 mo CDK4/6i



5.45m vs 3.29m
HR 0.70 (0.48-1.02)

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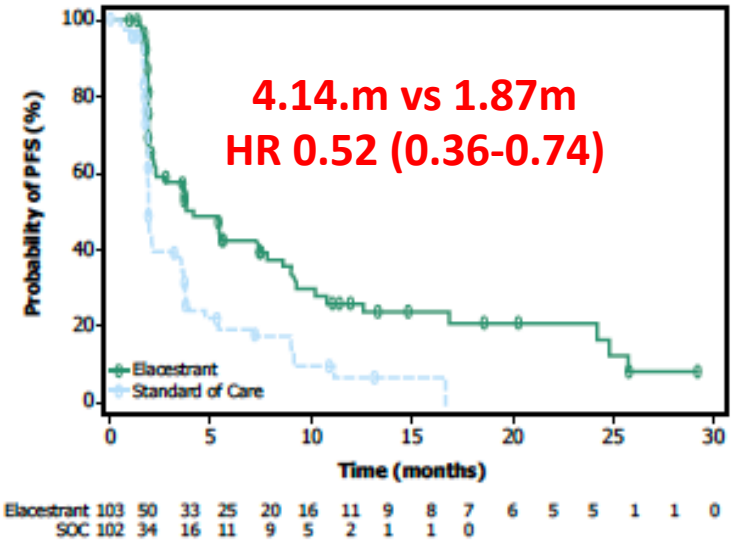
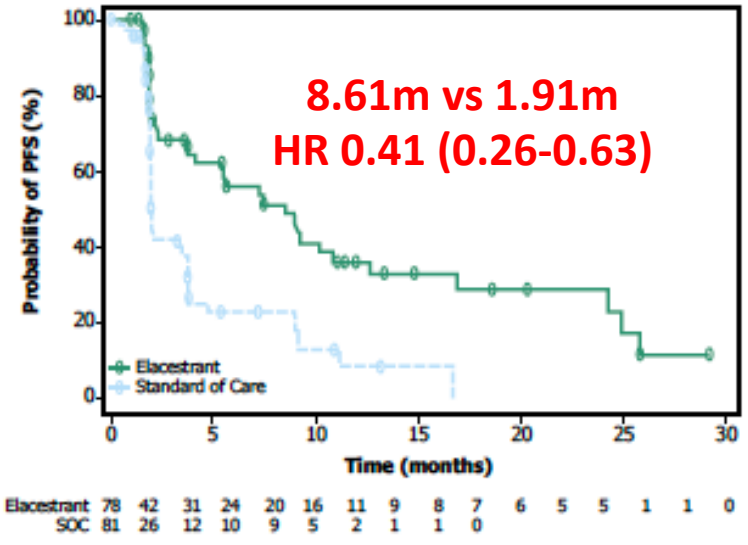
EMERALD Trial: Updated PFS results by duration of previous CDK4/6i – ESR1 mutated tumours

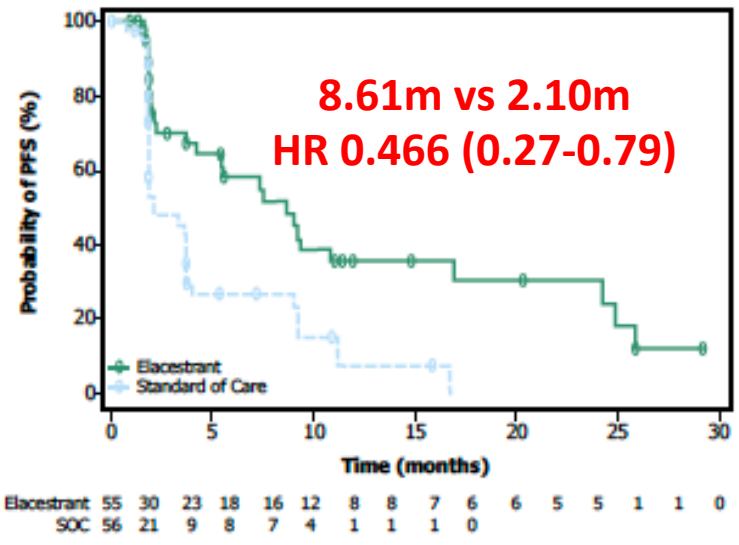
At least 6 mo CDK4/6i



At least 12 mo CDK4/6i



At least 18 mo CDK4/6i



Duration on CDK4/6i in the metastatic setting	<6 months		6- 12 months	
ESR1-mut	Elacestrant (n=9)	SoC (n=8)	Elacestrant (n=25)	SoC (n=21)
Median PFS (months)	1.87 (1.64 - .)	1.87 (1.68 - 5.55)	1.91 (1.87 - 2.79)	1.84 (1.68 - 3.45)
Hazard ratio	1.565 (0.424 - 5.769)		1.122 (0.547 - 2.347)	

Patient with a short duration of 1rst line should probably not receive a single agent SERD in 2nd line

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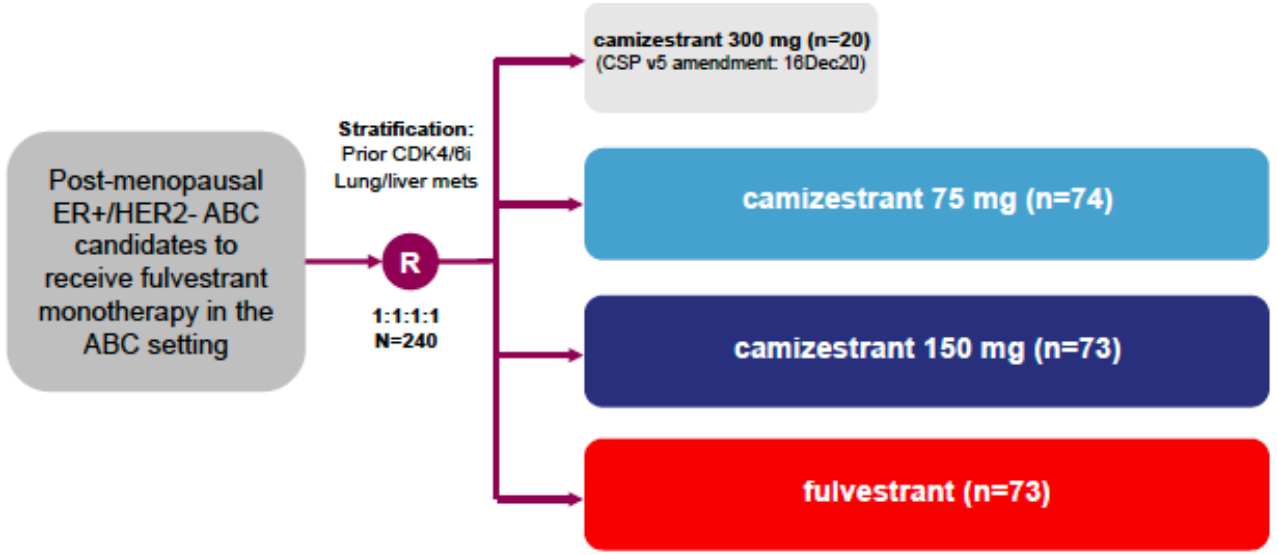
SERENA-2 phase 2 Trial: Camizestrant vs Fulvestrant in post-menopausal women ER+HER2-

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*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

50% Prior CDK4/6 inh
58% Visceral M+
36% ESR1 mutations (pl)

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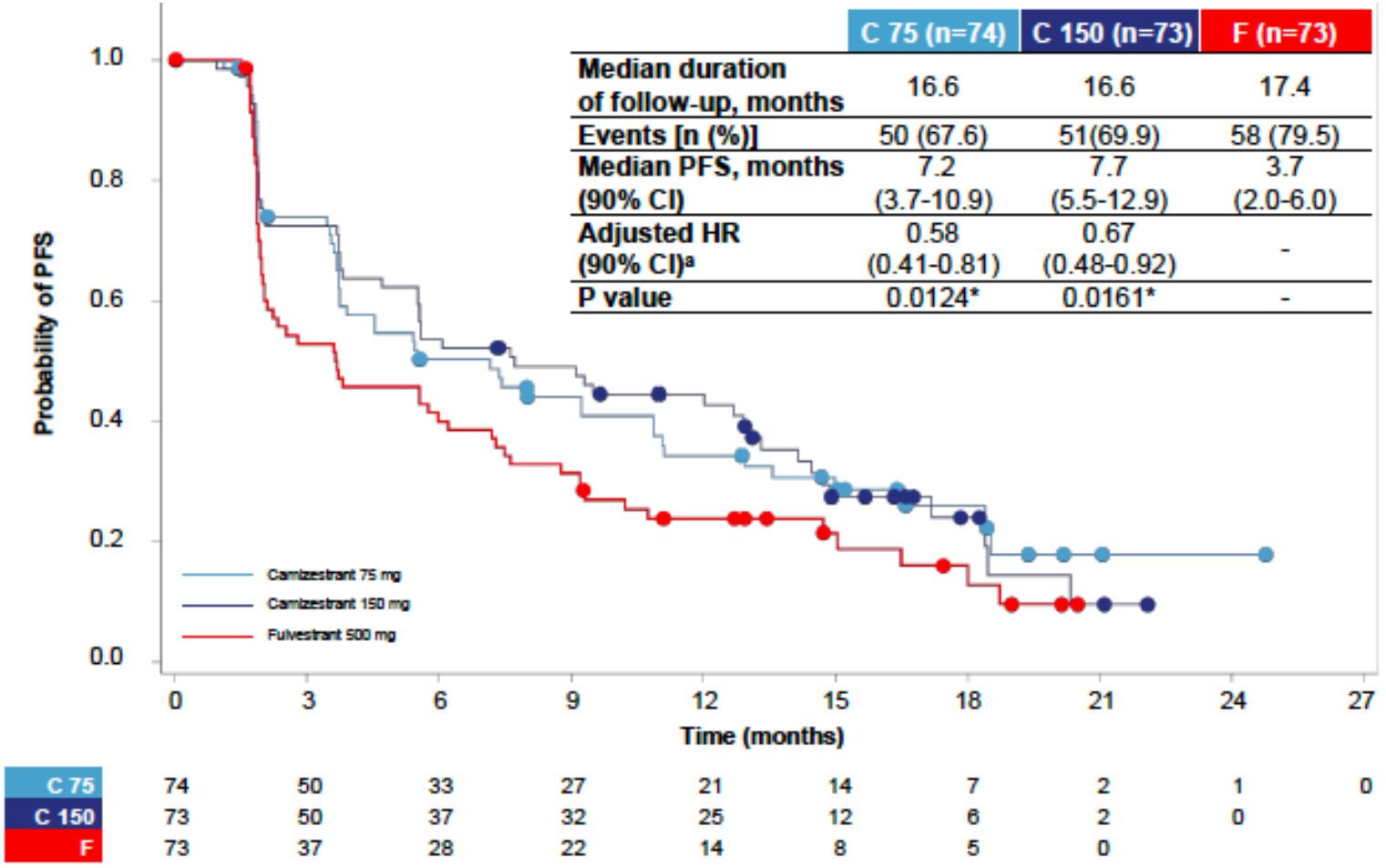
SERENA-2 phase 2 Trial: Primary Endoint: PFS by investigator assessment



	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*	-

75mg: PFS Δ 3.5m

100mg: PFS Δ 4m in favour of camizestrant

Safety in camizestrant arms (75-150mg):

CTCAE gr 3 was low (1.4-2.7% vs 1.4%)

Discontinuation due to tox in 2.7% (n=2)

Dose interruption in 15-20% vs 4%

Most frequently and mostly gr1:

photopsia (12%)and

bradycardia (5%)

fatigue (5%)

anemia (10%)

asthenia (8%)

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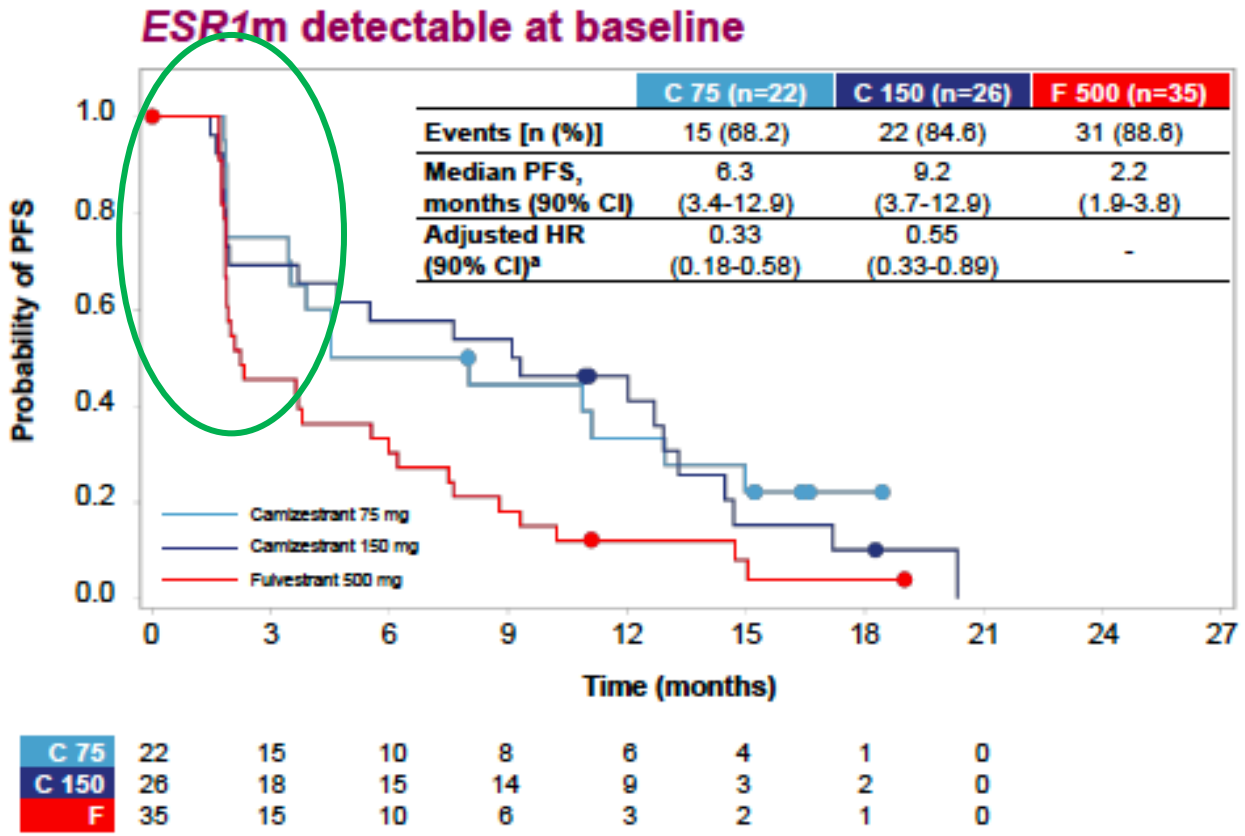
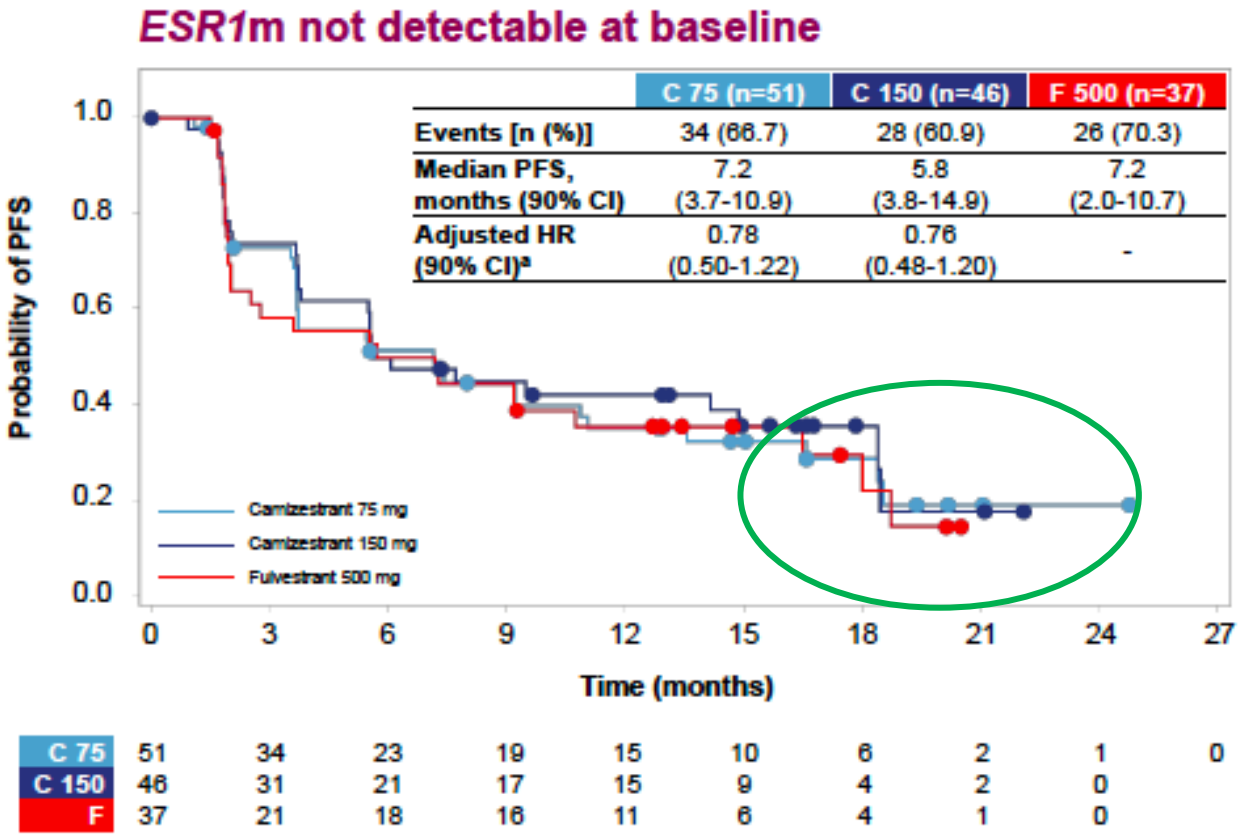
SERENA-2 phase 2 Trial: PFS by ESR1m





Some ESR1 mutant derive no benefit from SERDs

Camizestrant and Fulvestrant have similar benefit in ESR1 wt group

Some ESR1 wt patients will benefit from SERDs

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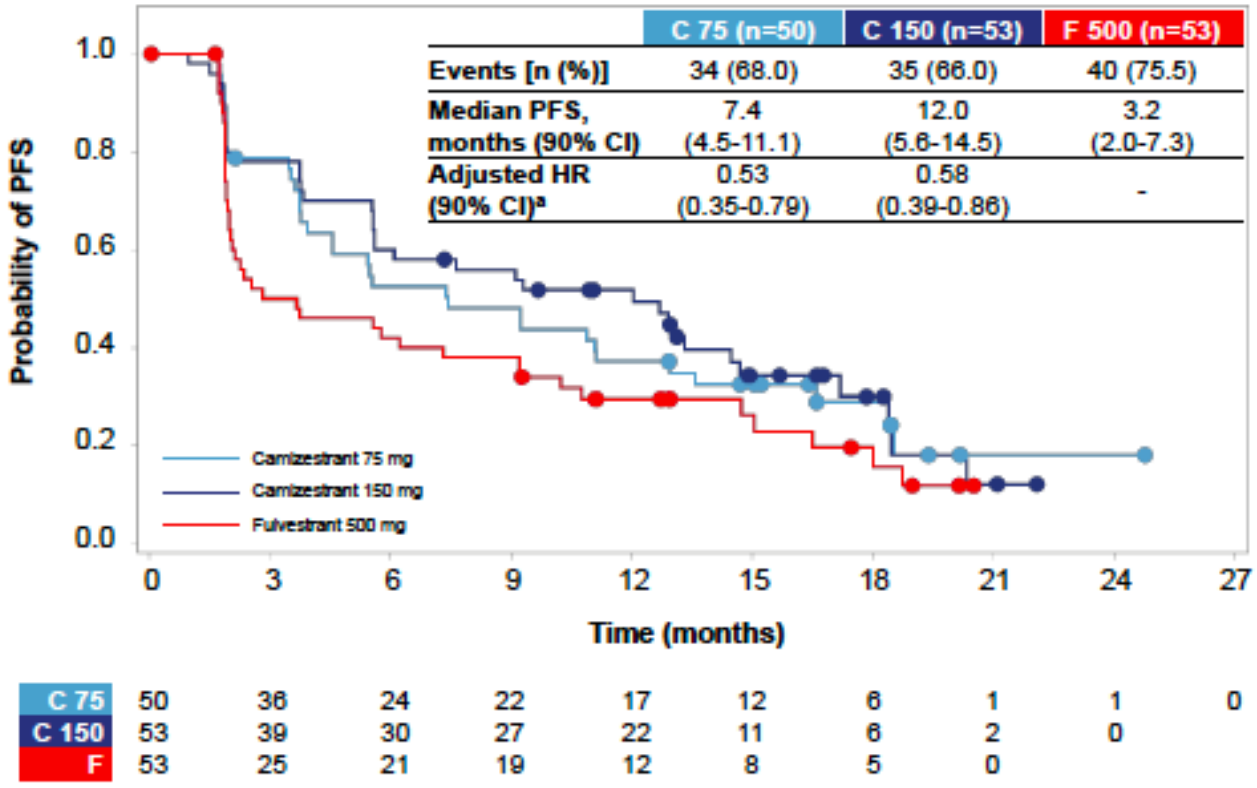
SERENA-2 phase 2 Trial: PFS by ER-driven disease

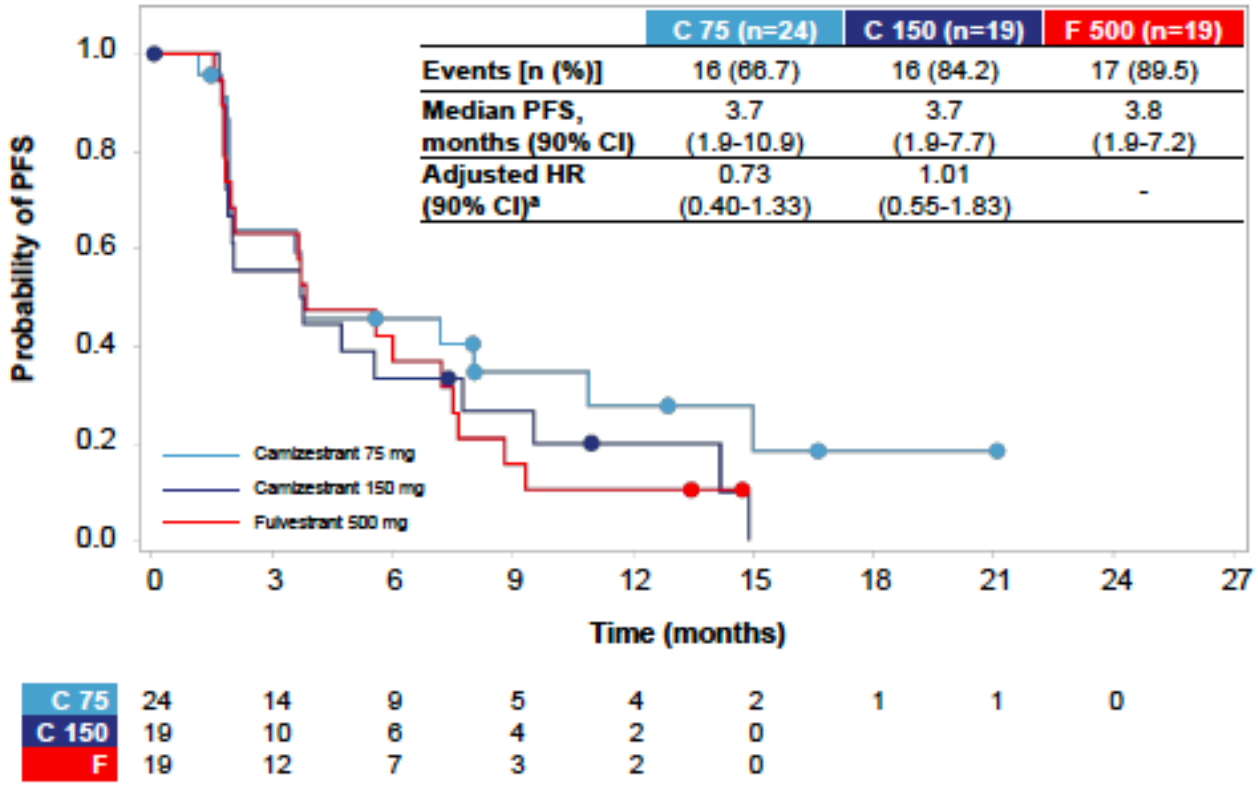
Patients with evidence of ER-driven disease*



	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)	-

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)	-

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				

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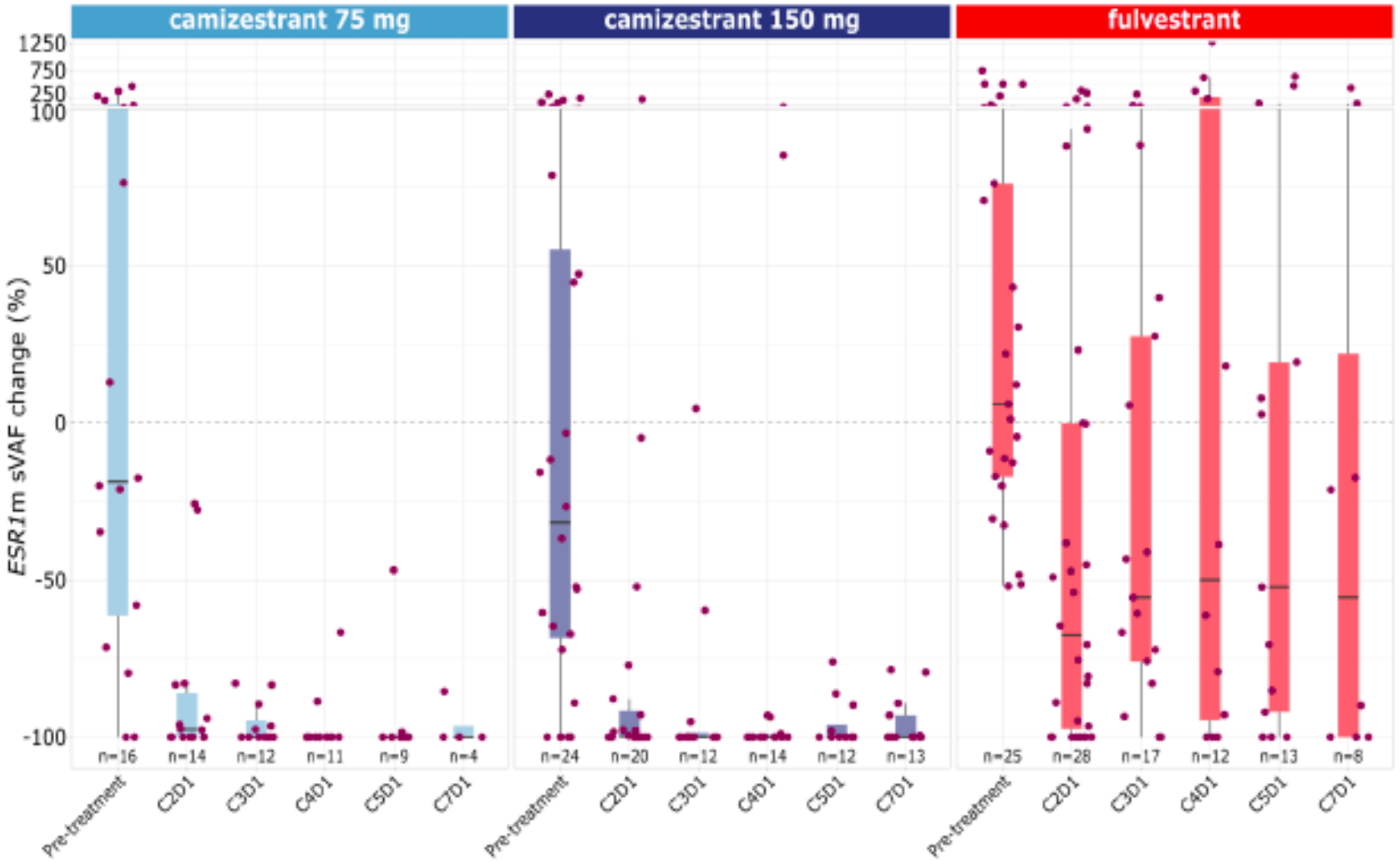
SERENA-2 phase 2 Trial: Changes in ESR1m ctDNA variant allele frequency



- Treatment with camizestrant 75 and 150 mg reduced the level of *ESR1*m ctDNA to undetectable or near undetectable levels by Cycle 2 Day 1 and maintained this to Cycle 7 Day 1
- Fulvestrant also reduced levels of *ESR1*m ctDNA, but not to the same extent as camizestrant

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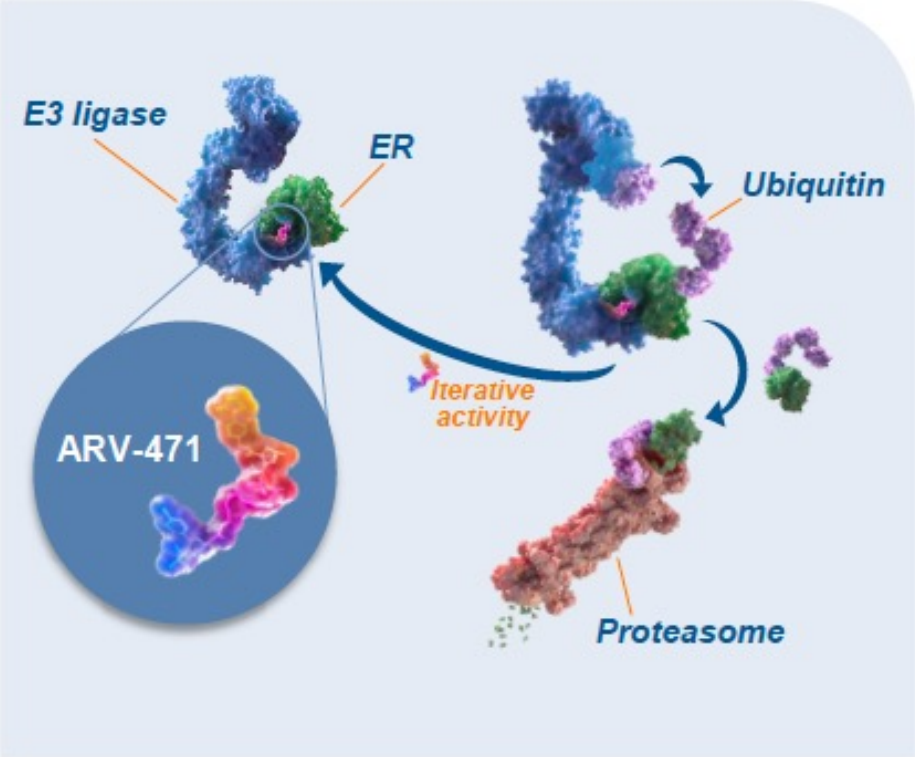
ARV-471, a PROTAC estrogen receptor degrader: phase 2 expansion VERITAC ph1/2



Phase 2 cohort expansion (Part B; VERITAC)

Key eligibility criteria

- Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
- Measurable or nonmeasurable disease per RECIST criteria v1.1
- ≥1 prior endocrine regimen (≥1 regimen for ≥6 months in the locally advanced or metastatic setting)
- ≥1 prior CDK4/6 inhibitor
- ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting

ARV-471 200 mg orally QD[a] (n=35)

ARV-471 500 mg orally QD[a] (n=36)

Primary endpoint

- CBR (rate of confirmed CR or PR or SD ≥24 weeks)[b]

Secondary endpoints

- ORR, DOR, PFS, and OS
- AEs and laboratory abnormalities
- PK parameters

Exploratory endpoints

- *ESR1* mutational status
- ER protein levels

Data cutoff date for this analysis

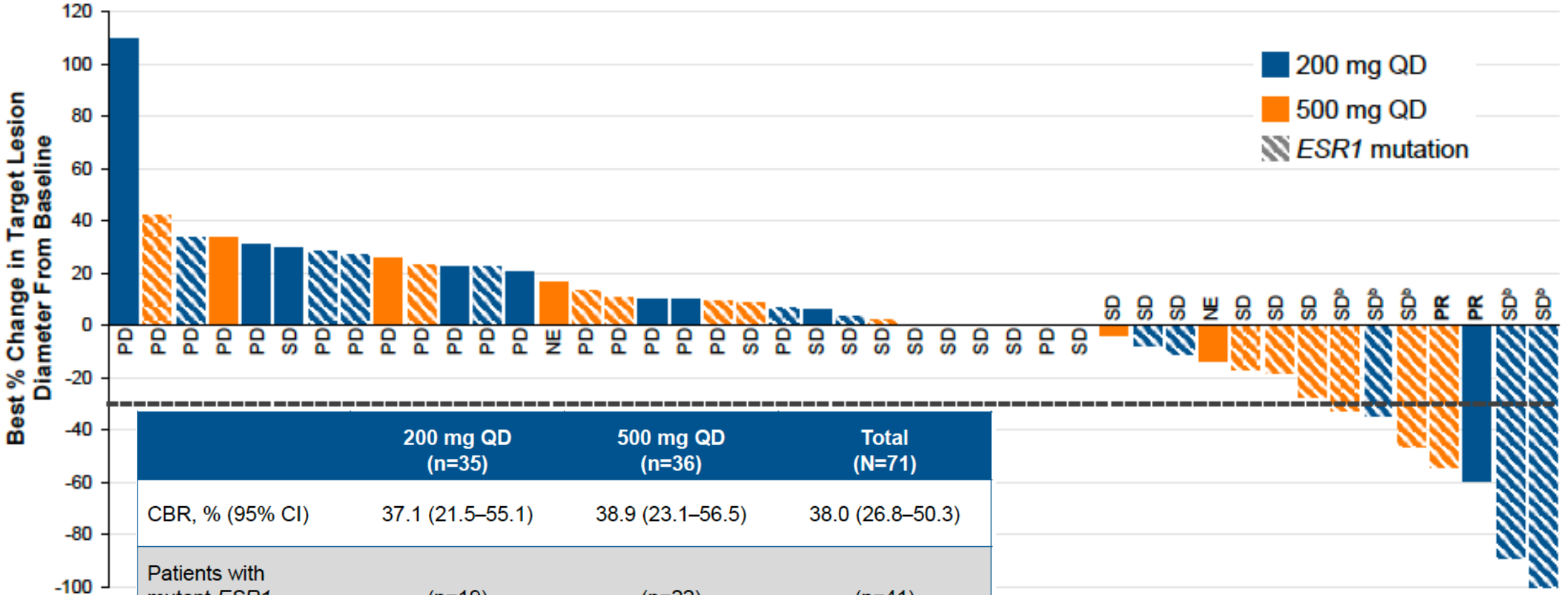
- June 6, 2022

70% prior CDK4/6 inhibitor
60% ESR1 mutant

ARV-71 targets wt and mutant ER
It directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER

Schott A. SABCS 2022

VERITAC: Primary Endpoint: Clinical Benefit Rate



	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

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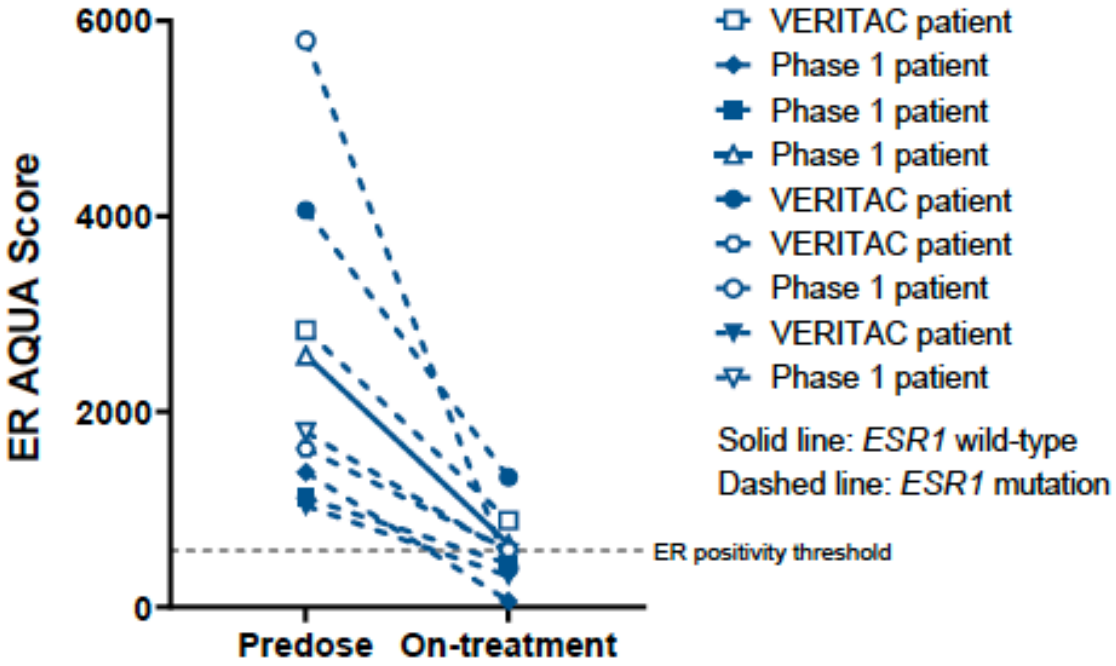
VERITAC: ER degradation with 200mg



- Median ER degradation was 69% (range: 28%–95%)
- Mean ER degradation was 71%

PROOF of CONCEPT

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VERITAC: Safety

n (%)	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
TEAEs			
Any grade	32 (91)	30 (83)	62 (87)
Grade 3/4	9 (26)	6 (17)	15 (21)
Grade 5[a]	1 (3)	0	1 (1)
Leading to discontinuation	1 (3)	2 (6)	3 (4)
Leading to dose reduction	0	3 (8)	3 (4)

- Dose reductions due to TEAEs
  - 500-mg QD cohort (to 400 mg QD)
    - ALT increased (n=1)
    - Neutropenia (n=1)
    - Fatigue (n=1)
- Discontinuations due to TEAEs
  - 200-mg QD cohort
    - QT prolongation (n=1)[b]
  - 500-mg QD cohort
    - ECG T-wave abnormality (n=1)[c]
    - Back pain/spinal cord compression (n=1)

[a]Acute respiratory failure in the setting of disease progression and unrelated to ARV-471 treatment
[b]Patient had QT prolongation at baseline, received a concomitant QT-prolonging drug during ARV-471 treatment, and had hypokalemia
[c]Patient had ECG T-wave abnormality at baseline

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VERITAC: Safety

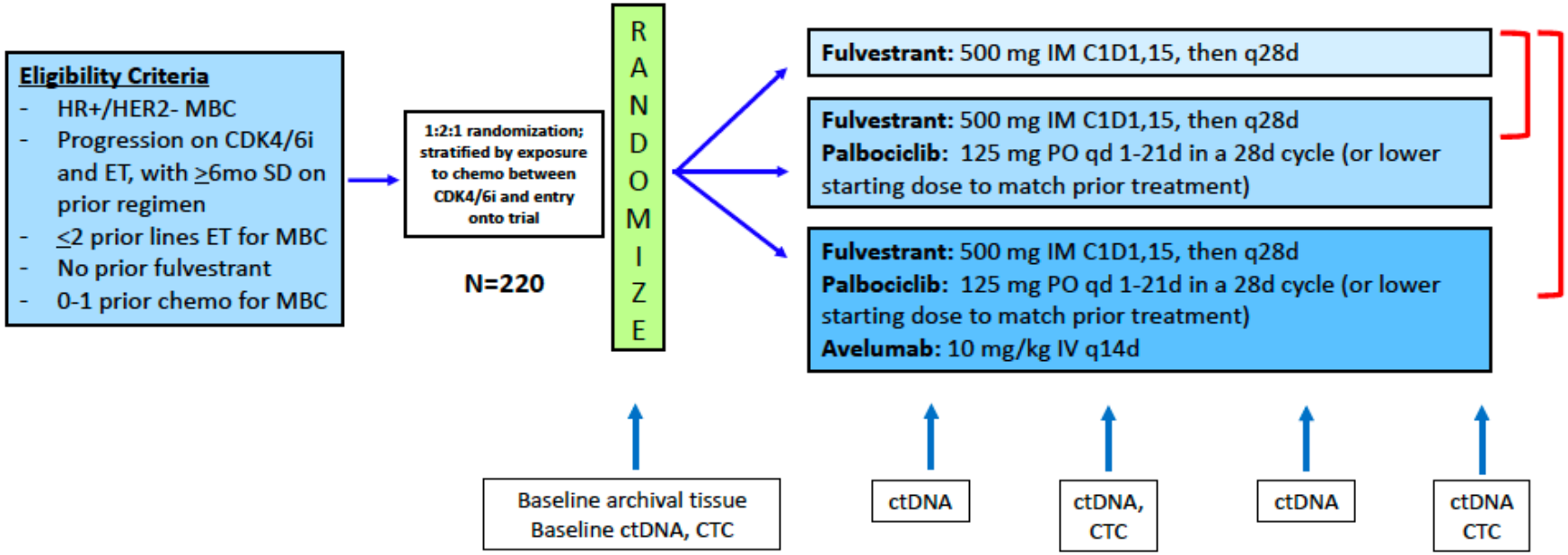
	200 mg QD (n=35)			500 mg QD (n=36)			Total (N=71)		
n (%)	Grade 1	Grade 2	Grade 3/4[a]	Grade 1	Grade 2	Grade 3/4[b]	Grade 1	Grade 2	Grade 3/4
Any TRAE	13 (37)	13 (37)	2 (6)	11 (31)	9 (25)	3 (8)	24 (34)	22 (31)	5 (7)
Fatigue	8 (23)	6 (17)	0	7 (19)	2 (6)	1 (3)	15 (21)	8 (11)	1 (1)
Nausea	2 (6)	3 (9)	0	6 (17)	1 (3)	0	8 (11)	4 (6)	0
Arthralgia	4 (11)	0	0	5 (14)	0	0	9 (13)	0	0
Hot flush	6 (17)	0	0	1 (3)	0	0	7 (10)	0	0
AST increased	3 (9)	1 (3)	0	2 (6)	1 (3)	0	5 (7)	2 (3)	0

[a]Grade 3/4 TRAEs in the 200-mg QD cohort were grade 3 QT prolonged (n=1; same TEAE that led to discontinuation as shown in the prior slide) and grade 3 thrombocytopenia and grade 4 hyperbilirubinemia (n=1)
[b]Grade 3/4 TRAEs in the 500-mg QD cohort were grade 3 fatigue, decreased appetite, and neutropenia (n=1 each)
AST=aspartate aminotransferase; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

Phase 3 VERITAC 2 with 200mg comparing ARV-471 with fulvestrant

Schott A. SABCS 2022

PACE Trial: Palbociclib After CDK and ET



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

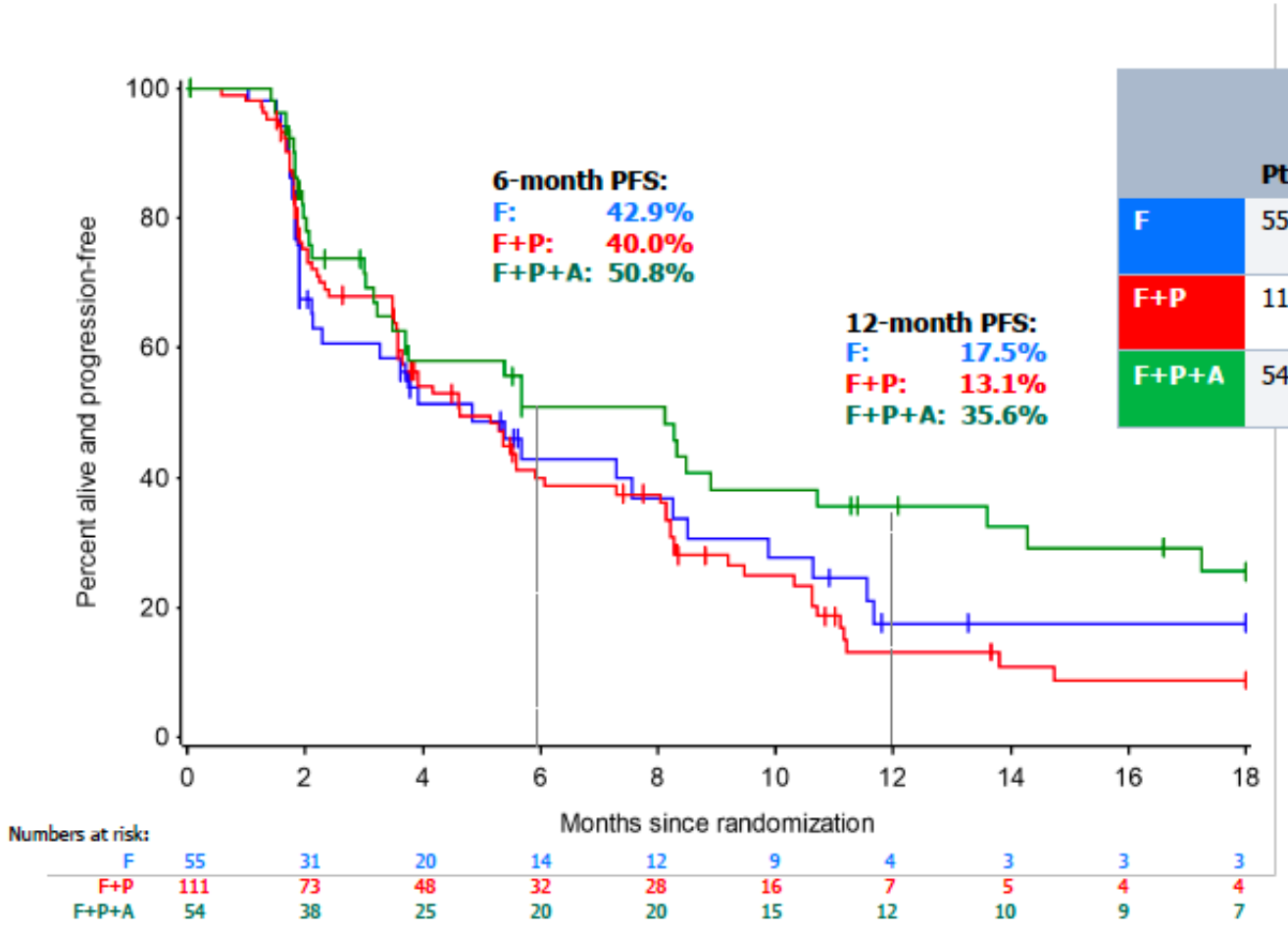
Phase II

Prior CDK4/6i:

90% palbo

>12m 75%

PACE Trial: PFS in the ITT



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

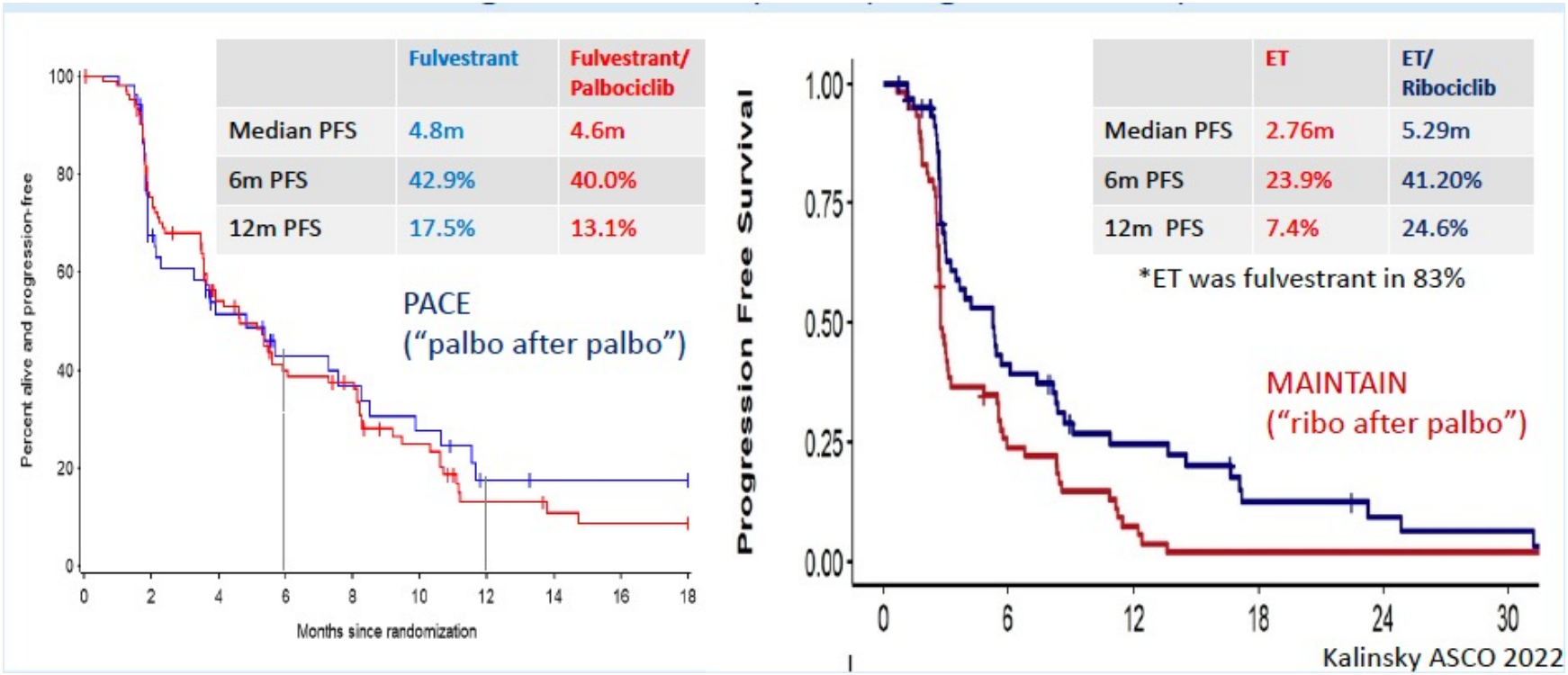
Δ 3.3 m

PFS not significantly improved
Fulvestrant arm did better than in other trials but some imbalance btw the arms

No added TOX with anti PDL1 which differs to what is seen with anti PD1

Erica Mayer SABCS 2022

CDK4/6i after CDK4/6i



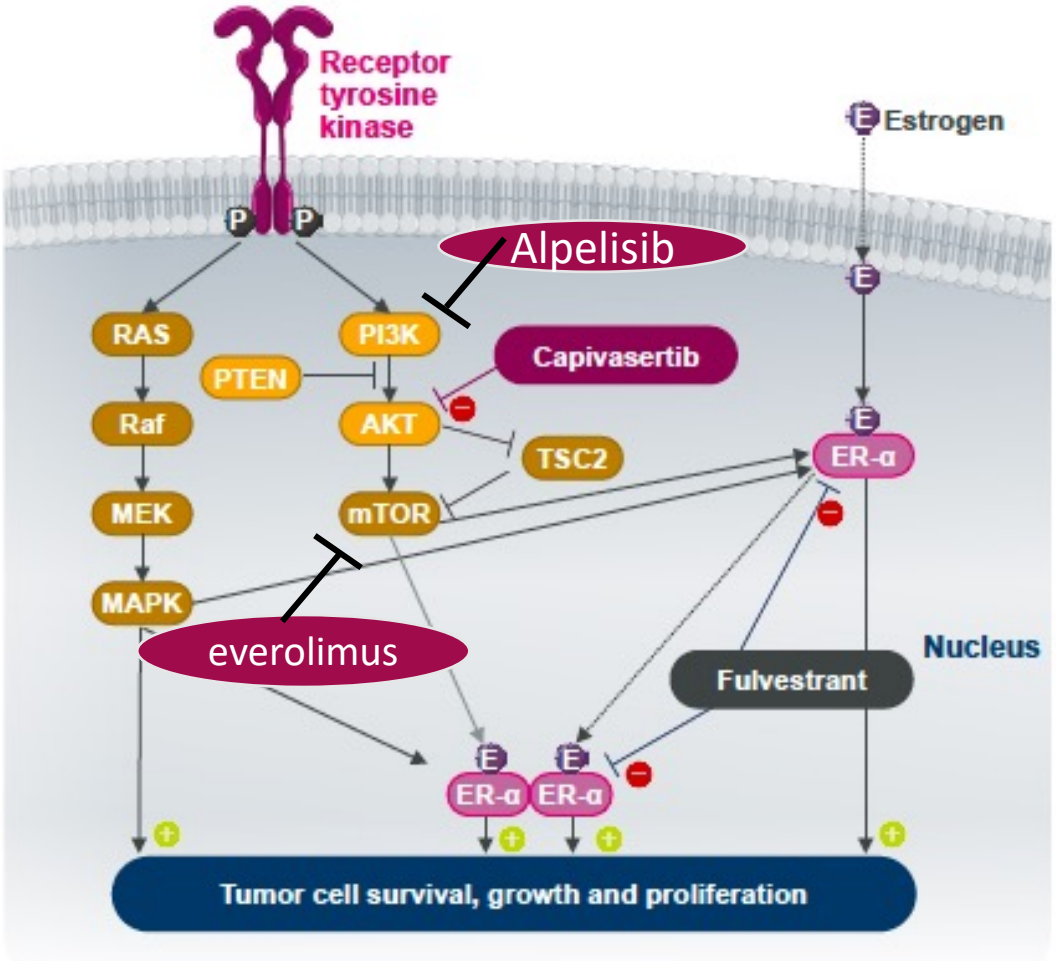
- Small phase 2 trials
- Imbalances btw the arms within the trials
- Ongoing trials: post-monarch, Palmira
- Unclear where this strategy stands in the midst of emerging new combination and drugs

Capivasertib and fulvestrant for patients with AI-resistant ER+/HER2- advanced BC: Results from the Phase III CAPItello-291 Trial

- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- FAKTION phase II showed improved PFS and OS in an AI-resistant population with a more pronounced benefit in pathway-altered tumors

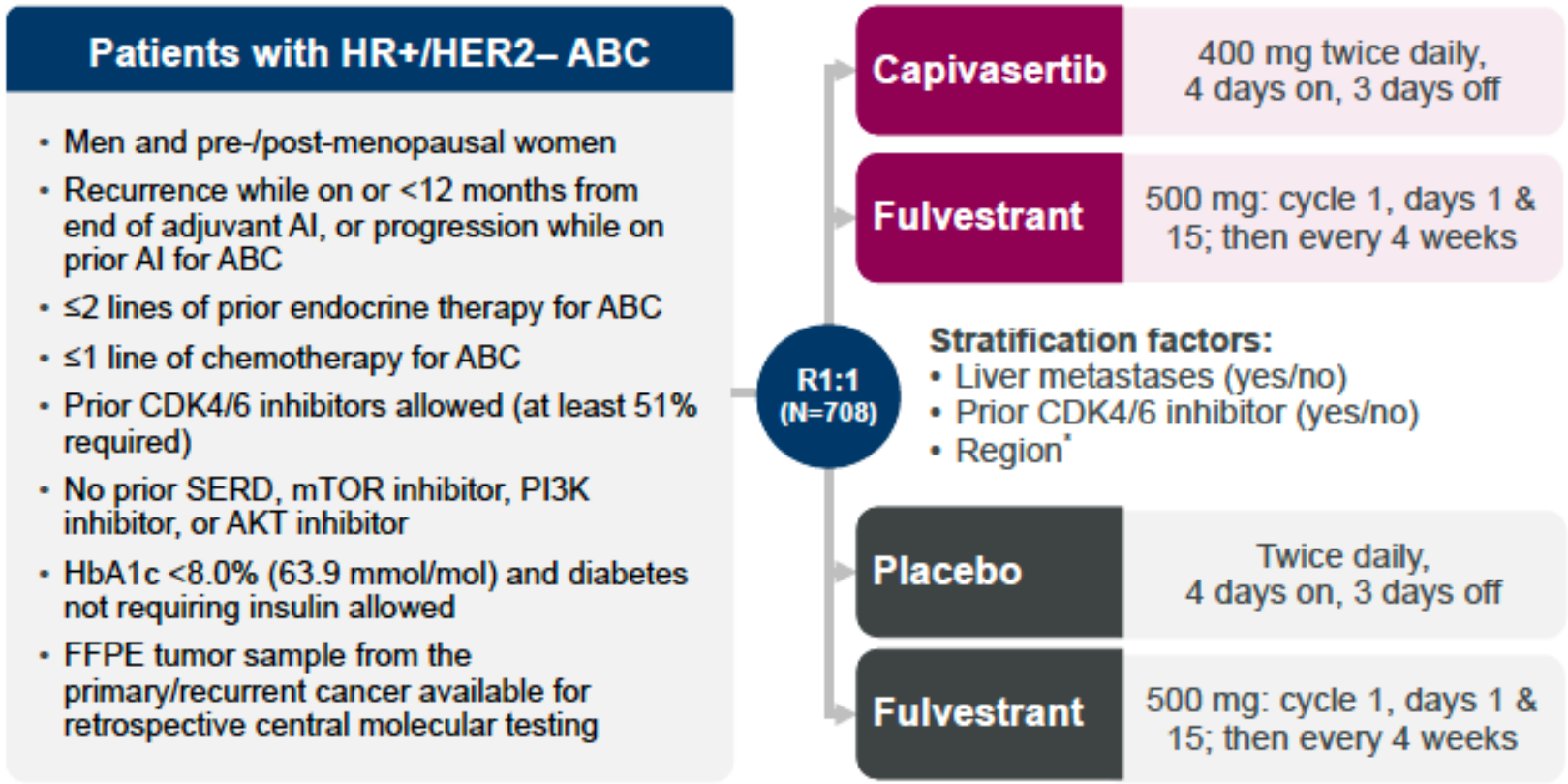
<u>AKT–pathway blockade</u>

- SOLAR-1 showed an improved PFS with alpelisib + Fulv in AI resistant, PIK3CAm, population largely untreated with CDK4/6i
- BYLieve (single arm ph2) showed activity of alpelisib + fulv after CDK4/6i: 50.4% 6-months PFS rate (median 7.3 mo)



Andre F et al NEJM 2019, Rugo H Lancet oncol 21, SABCS 2022

CAPItello-291 phase 3 trial



Dual primary endpoints

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

Key secondary endpoints

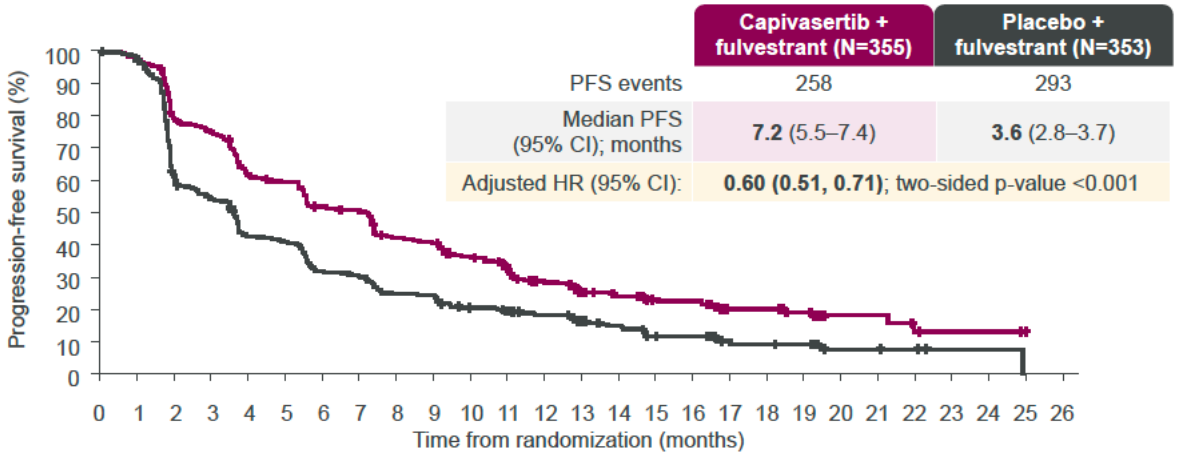
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

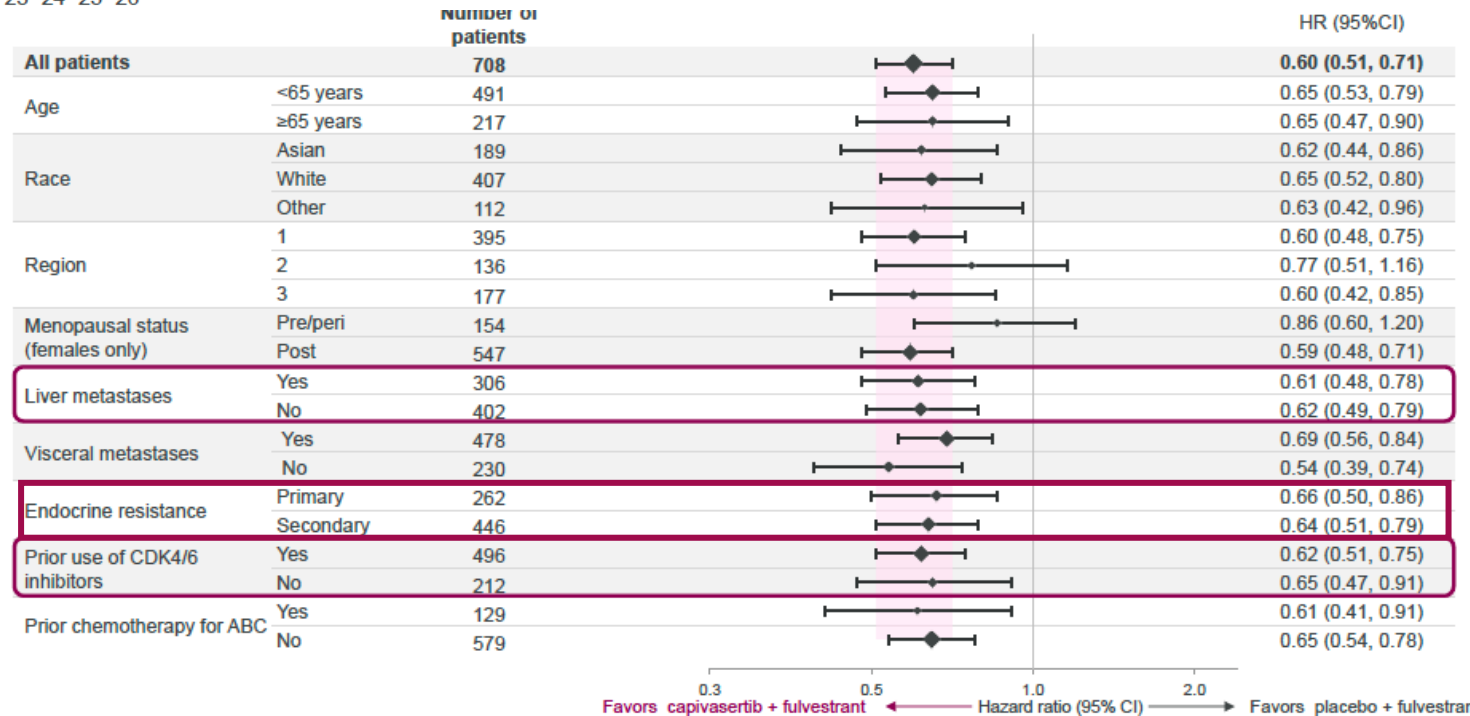
70% received prior CDK4/6 inhibitors
18% received prior CT in the advanced setting

Turner N. SABCS 2022

CAPItello-291: Primary endpoint investigator-assessed PFS in overall population



First Ph 3 results of AKT pathway inhibition in a CDK4/6i pretreated population

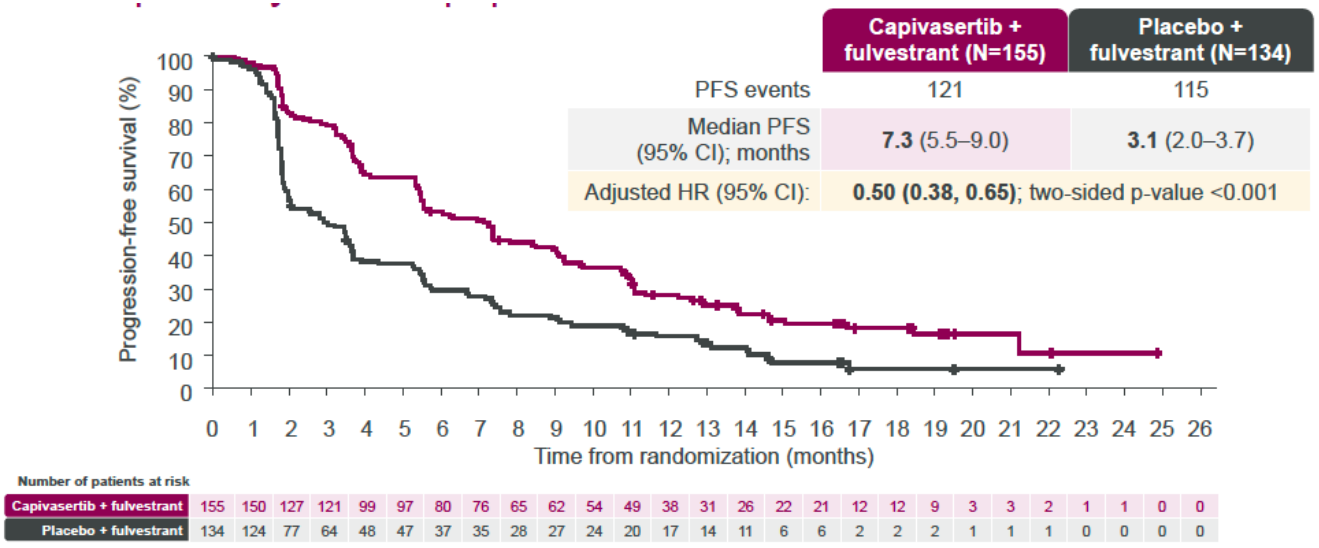


Effective in endocrine R population →

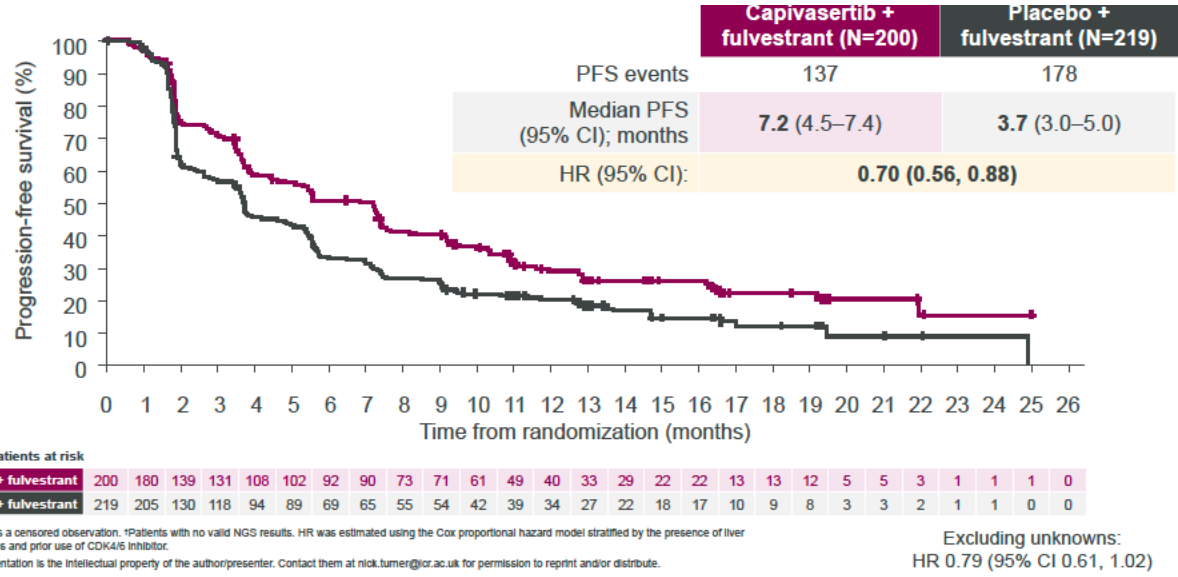
Turner N. SABCS 2022

CAPItello-291: Primary endpoint investigator-assessed PFS in the AKT pathway altered population

AKT pathway altered (Primary endpoint)



AKT pathway non-altered (exploratory)



· Indicates a censored observation. †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.

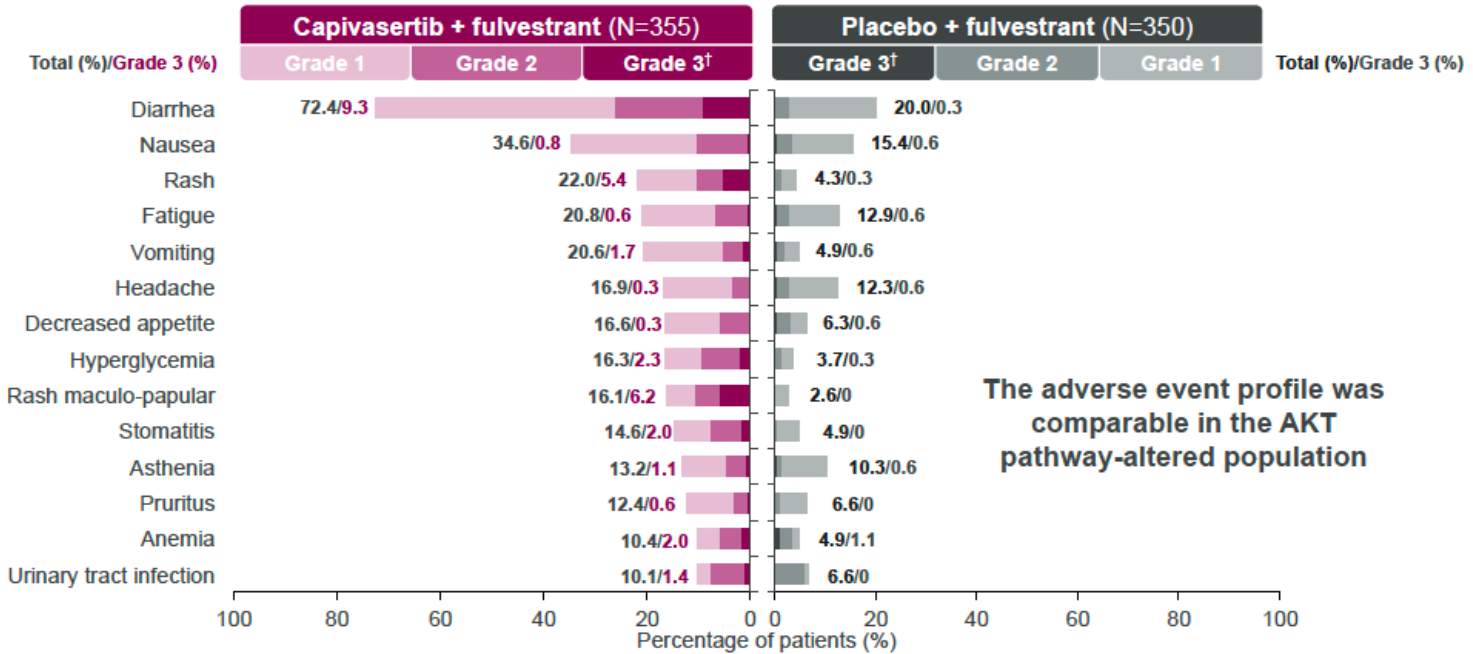
Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)

CAPItello was not a biomarker driven trial with comparison btw AKT pathway altered and unaltered tumours

Turner N. SABCS 2022

CAPItello-291: Safety

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 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)



The adverse event profile was comparable in the AKT pathway-altered population

<u>SOLAR-1- alpelisib AE (all grade/grade3)</u>

Diarrhea 60%, 7%

Nausea 45%,2.5%

Rash 36%,10%

Vomiting 77%,2%

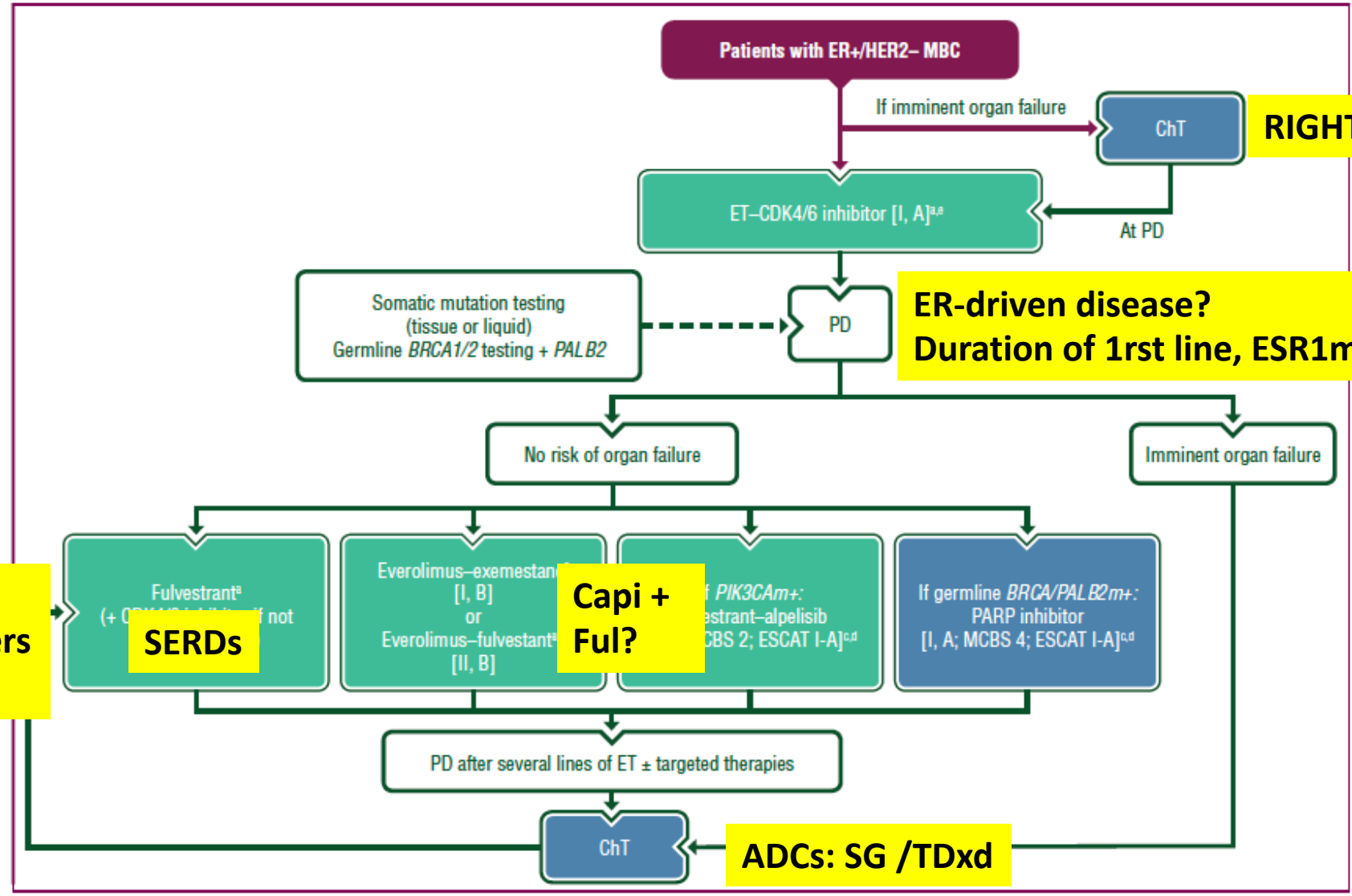
Hyperglycemia 63%,33%

Stomatitis 24%,2.5%

Capivasertib seems to be better tolerated than alpelisib

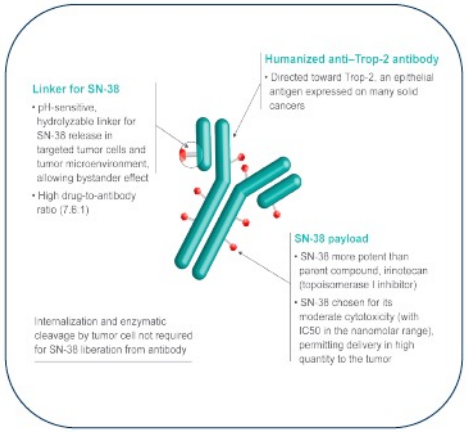
Turner N. SABCS 2022

ER+ HER2 “negative” disease



Gennari A et al
ESMO guidelines 2021

TROPiCS-02 trial: Sacituzumab Govitecan vs TPC Report of outcome by Trop-2 expression (exploratory analysis)



Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

R
1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine, or eribulin)
n=271

Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

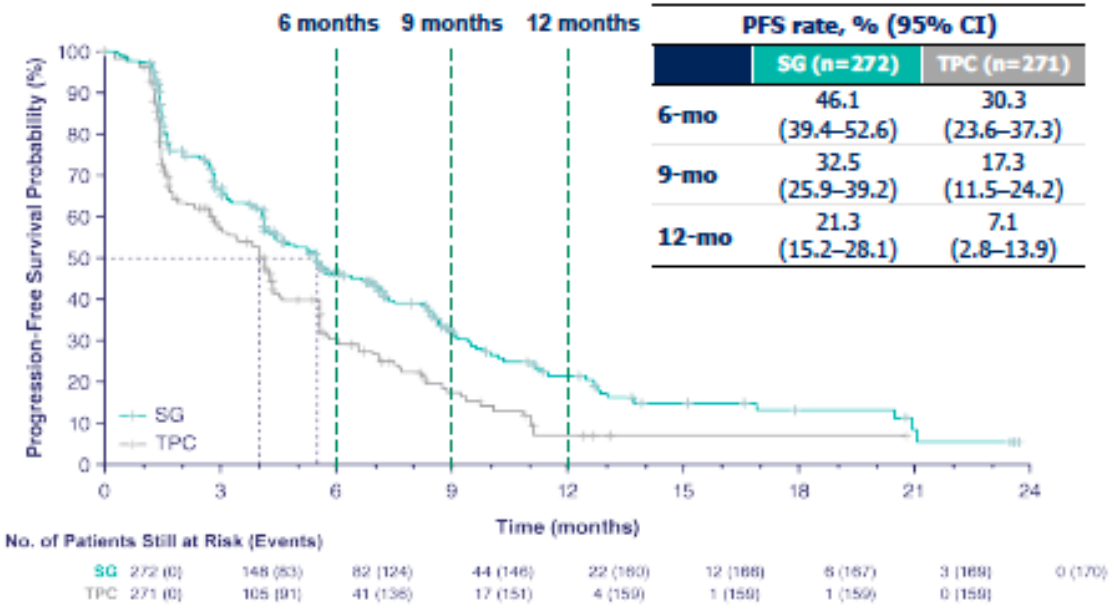
Stratification
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

Trop-2 expression was not an eligibility criteria and was not a stratification factor
Trop-2 membrane expression was determined on primary or M+ biopsy and was scored (H-score)

TROPiCS-02 Trial: Previous Results

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

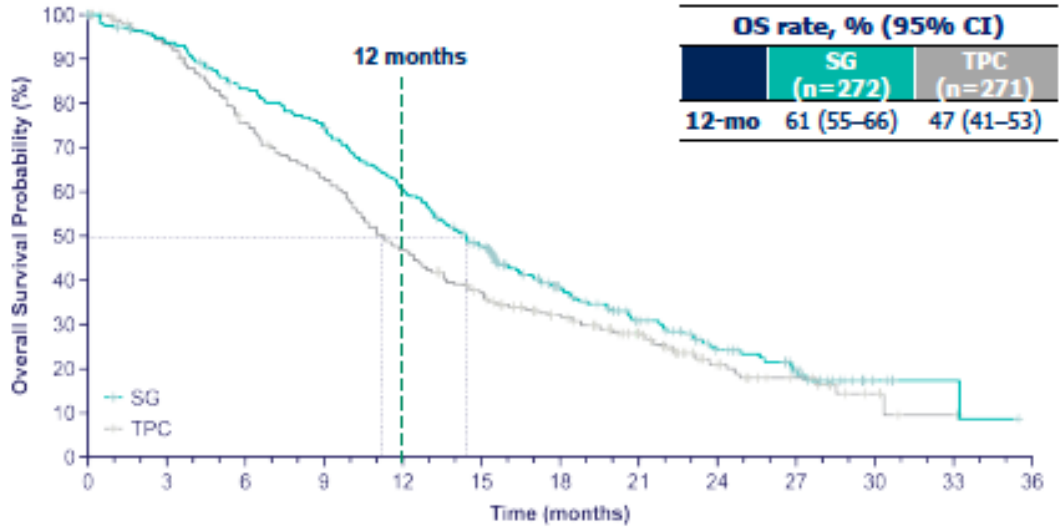
No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

Rugo H. JCO 2022

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



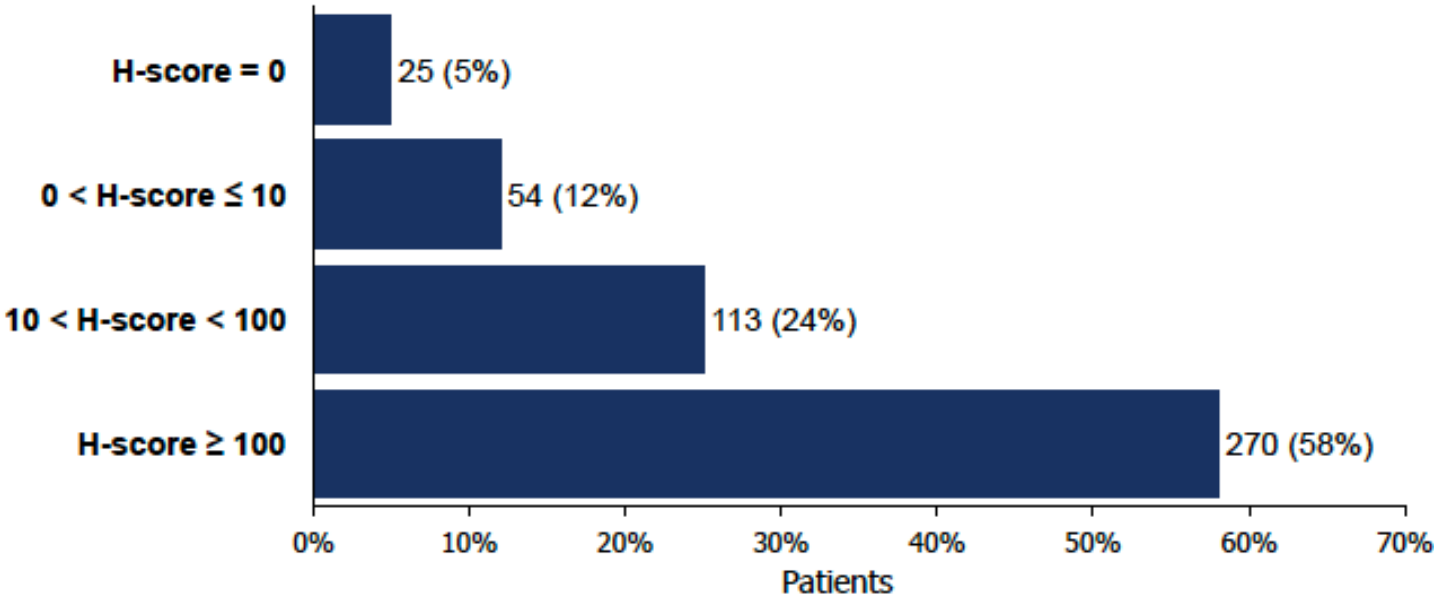
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

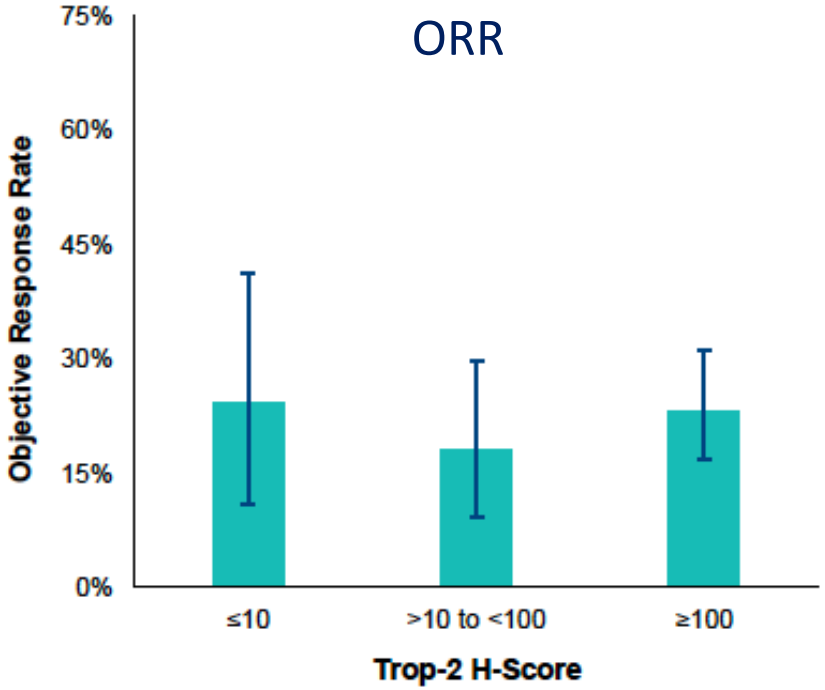
No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (168)	53 (173)	31 (183)	20 (185)	4 (190)	2 (190)	0 (191)		
TPC	271 (0)	246 (16)	196 (64)	184 (96)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)		

Rugo H. ESMO 2022

TROPiCS-02 Trial: Trop-2 expression and ORR

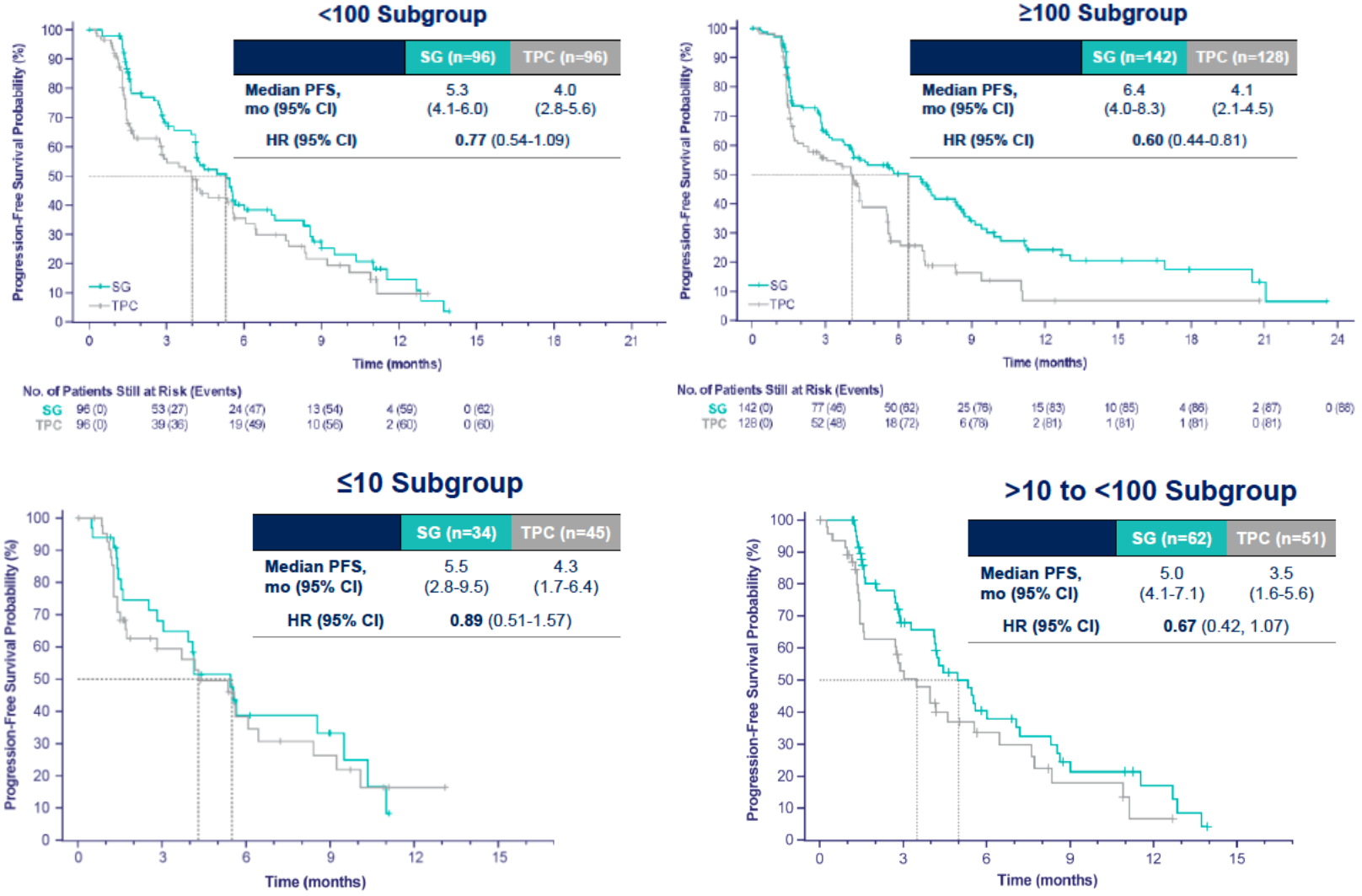




Expression observed in 95% of evaluable samples

Rugo H. SABCS 2022

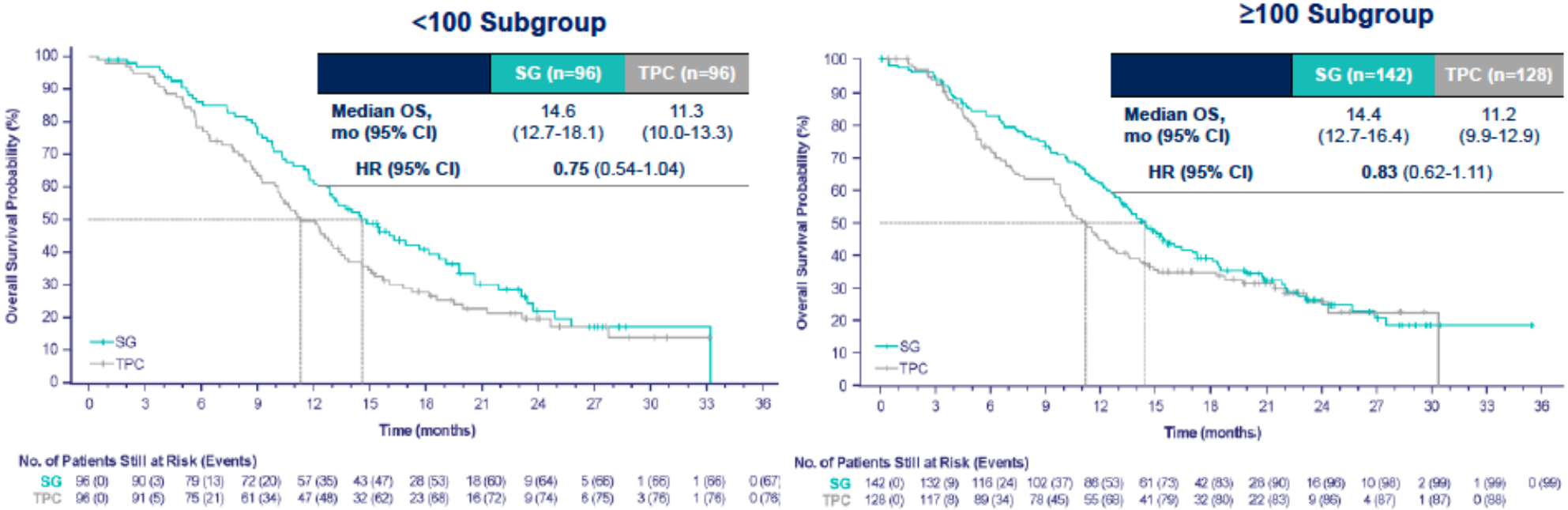
TROPiCS-02 Trial: PFS by Trop-2 H-Score



PFS outcome favoured SG in all subgroups including in very low Trop-2 expression (H-Score≤10)
Trop-2 expression was not demonstrated to be a predictive biomarker for SG efficacy

Rugo H. SABCS 2022

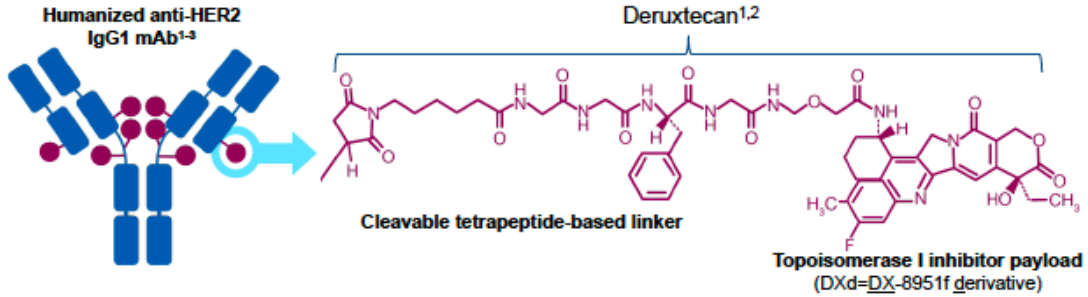
TROPiCS-02 Trial: OS by Trop-2 H-Score



OS outcome favoured SG in both subgroups including in very low Trop-2 expression (H-Score≤10)
Trop-2 expression was not demonstrated to be a predictive biomarker for SG efficacy and should therefore not be tested before treatment

Rugo H. SABCS 2022

HER2+ MBC - Trastuzumab Deruxtecan - Background



1rst line	2nd line	3rd line	>3rd line

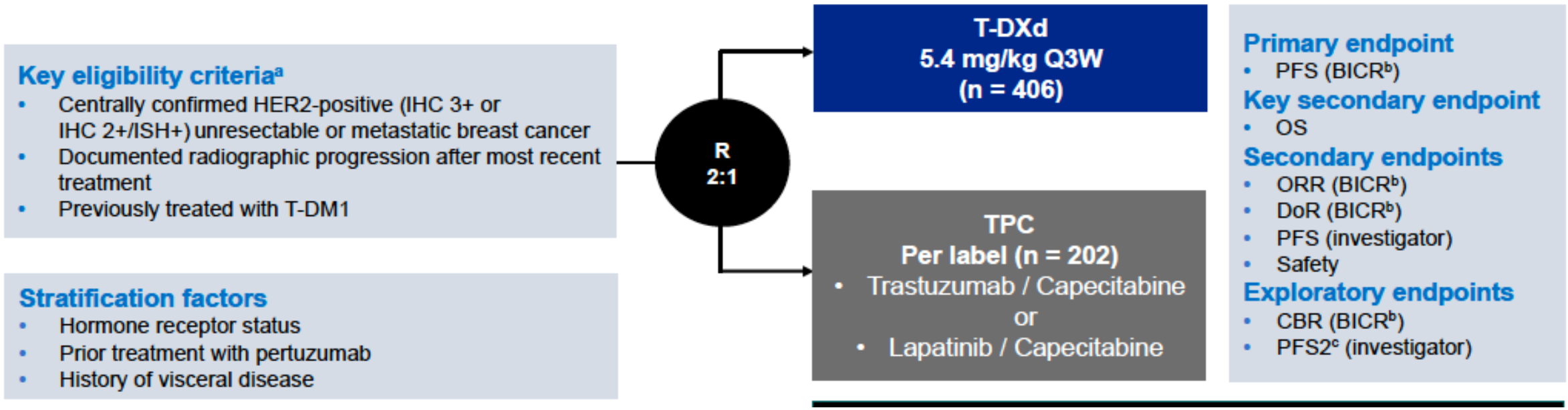
SABCS 2019, 20 — **DESTINY-BR01 phase 2**: ORR 61.4, mPFS 19.4m; nb of lines: 6

ESMO 2021, SABCS 2022 — **DESTINY-BR03 phase 3**: mPFS NR (TDXd) vs 6.8m (TDM1), HR 0.28

SABCS 2022 — **DESTINY-BR02 phase 3**

Trastuzumab Deruxtecan (T-DXd) is a standard for 2nd line HER2+ MBC based on DESTINY-BR03 results presented at ESMO 2021

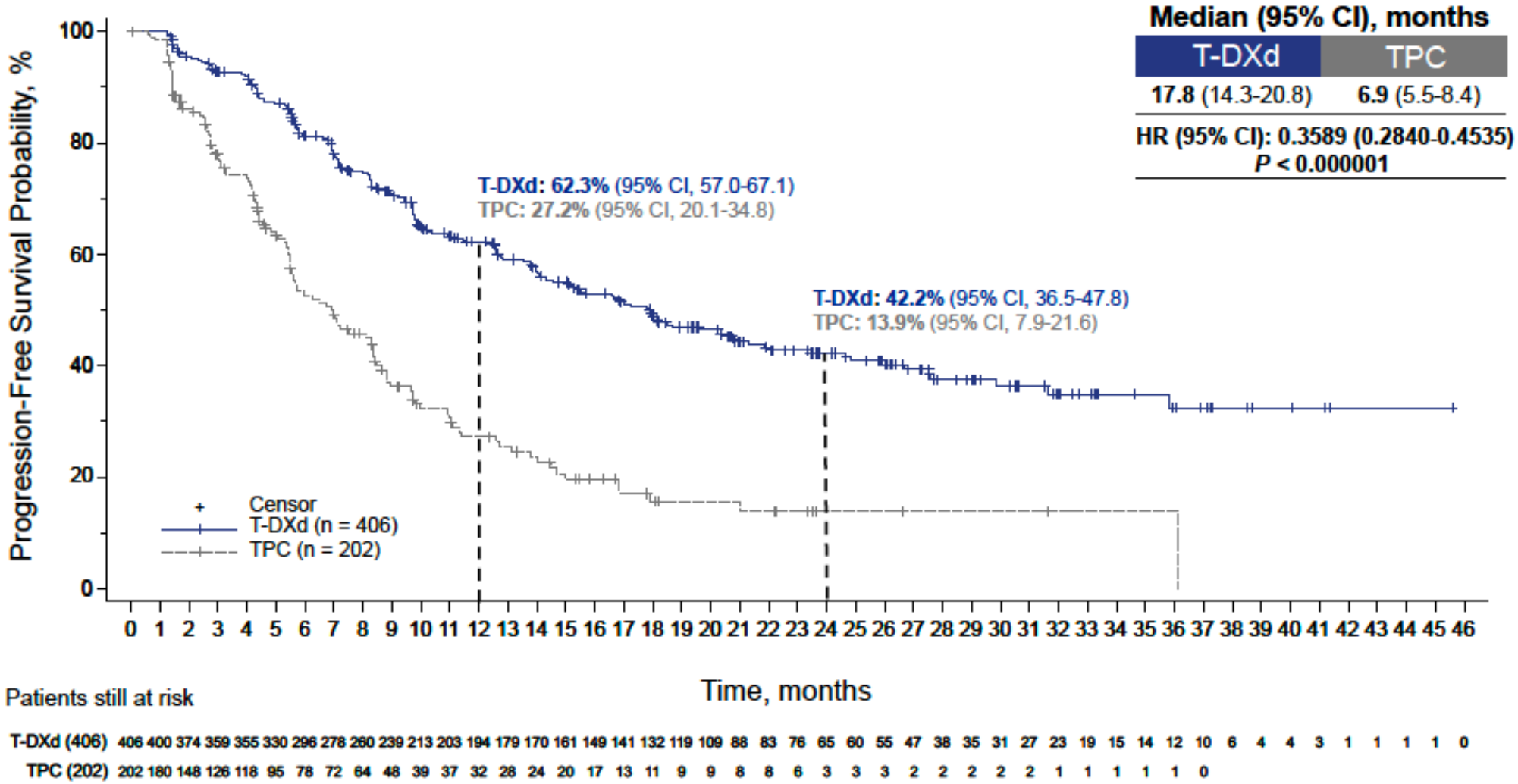
DESTINY-Breast02: phase 3
T-DXd vs TPC in MBC previously treated by T-DM1



Prior therapy for MBC
100% received prior trastuzumab
100% received prior T-DM1
78% received prior pertuzumab
6% received prior TKI
Median lines of prior treatment: 2

Ian Krop SABCS 2022

DESTINY-Breast02: Primary Endpoint – PFS by BICR



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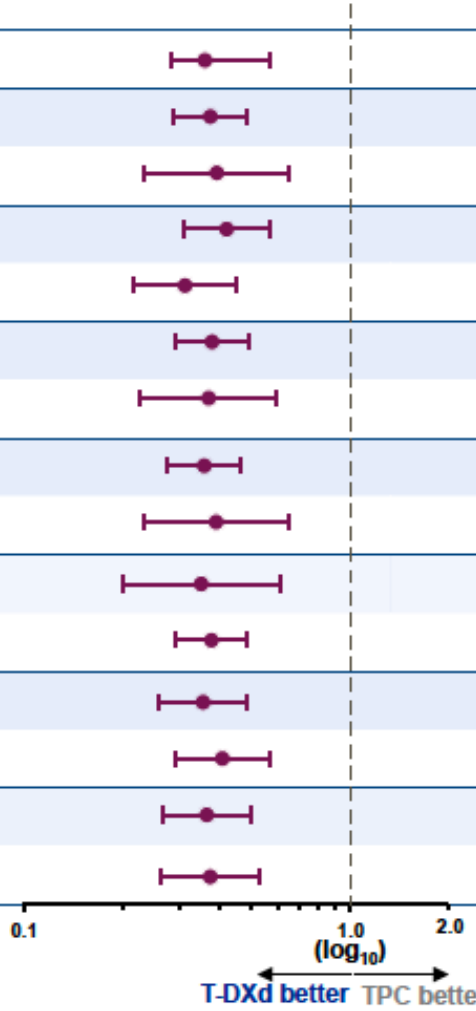
DESTINY-Breast02: PFS by Subgroups

		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	TPC	T-DXd	TPC	
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45)
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor status	Positive	115/238	71/118	18.0 (15.1-21.3)	8.5 (6.5-10.0)	0.42 (0.31-0.57)
	Negative	84/165	53/83	17.0 (12.3-24.6)	5.3 (4.3-6.7)	0.31 (0.22-0.45)
Prior pertuzumab treatment[a]	Yes	155/318	95/156	17.8 (14.0-20.8)	6.2 (5.0-8.4)	0.38 (0.29-0.49)
	No	45/88	30/46	18.0 (13.9-26.7)	8.3 (5.5-12.6)	0.37 (0.23-0.60)
Visceral disease[a]	Yes	164/316	98/160	15.6 (12.8-20.3)	5.7 (5.3-7.2)	0.36 (0.28-0.46)
	No	36/90	27/42	29.8 (16.8-NE)	9.8 (6.2-12.6)	0.39 (0.23-0.64)
Baseline brain metastases	Yes	44/74	20/36	13.9 (11.1-18.0)	5.6 (3.3-8.1)	0.35 (0.20-0.61)
	No	156/332	105/166	18.7 (15.1-24.8)	7.1 (5.5-8.6)	0.38 (0.29-0.48)
Prior lines of therapy[b]	<3	105/212	66/104	16.6 (13.8-24.6)	7.0 (4.6-8.6)	0.35 (0.26-0.49)
	≥3	95/194	59/98	18.2 (14.3-22.0)	6.9 (5.5-8.8)	0.41 (0.29-0.57)
ECOG PS	0	101/228	75/121	24.6 (15.3-31.6)	8.1 (5.7-9.7)	0.36 (0.27-0.50)
	1	98/177	50/81	15.1 (11.5-18.0)	5.4 (4.3-7.5)	0.37 (0.26-0.53)



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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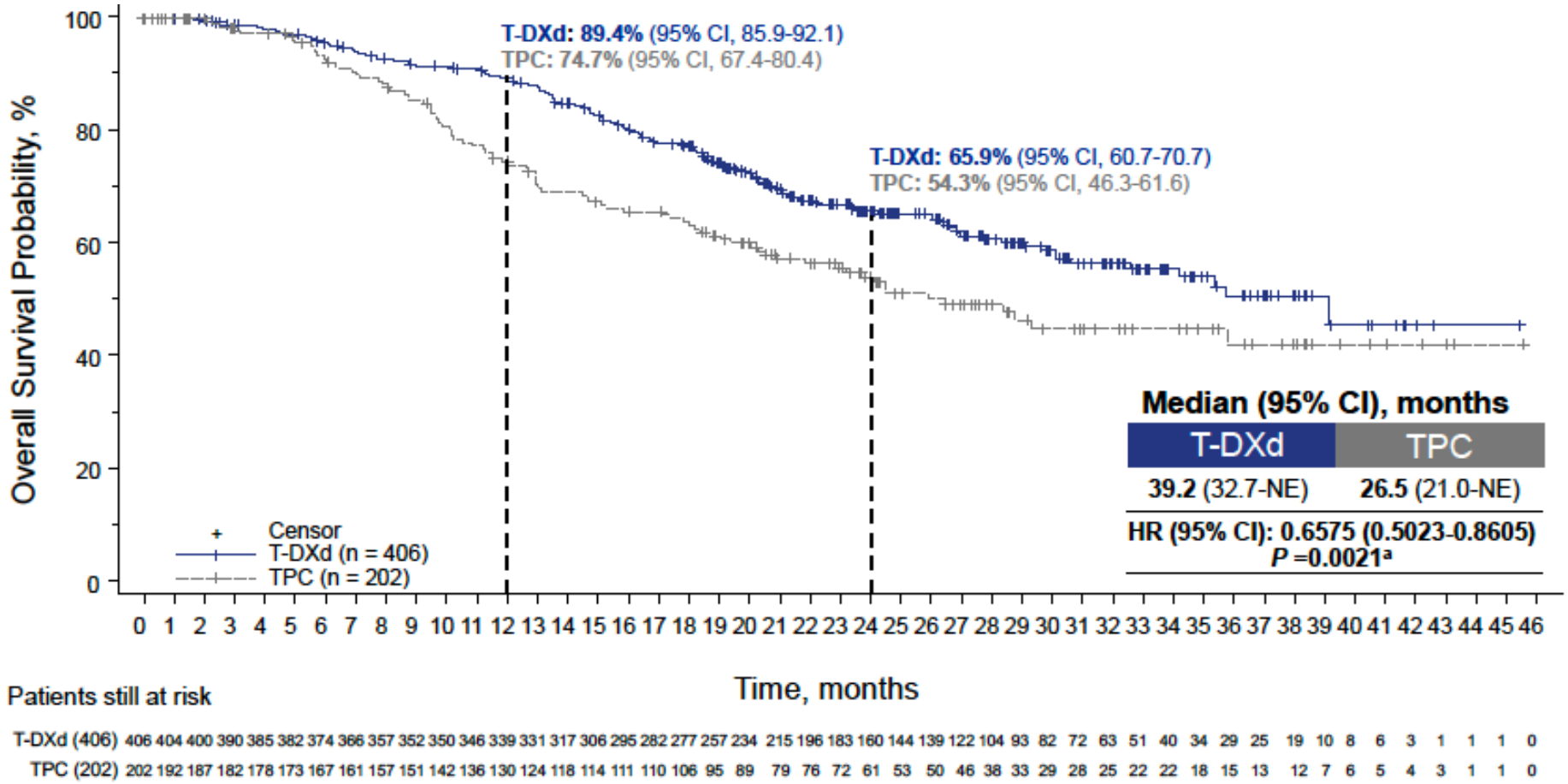
DESTINY-Breast02: Secondary Endpoint - OS



In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

Ian Krop SABCS 2022

DESTINY-Breast02: Safety

Adverse Events of Special Interest: ILD and LV Dysfunction

Adjudicated as Drug-related ILD[a]						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV dysfunction[b]

- In the T-DXd arm, 18 (4.5%) patients experienced an LV dysfunction event[c]
  - 2 (0.5%) patients had a grade ≥3 event
- In the TPC arm, 3 (1.5%) patients experienced an LV dysfunction[d]
  - 1 (0.5%) patient had a grade ≥3 event

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DESTINY-Breast03: ESMO 2021

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 1:1

- T-DXd 5.4 mg/kg Q3W (n = 261)
- T-DM1 3.6 mg/kg Q3W (n = 263)

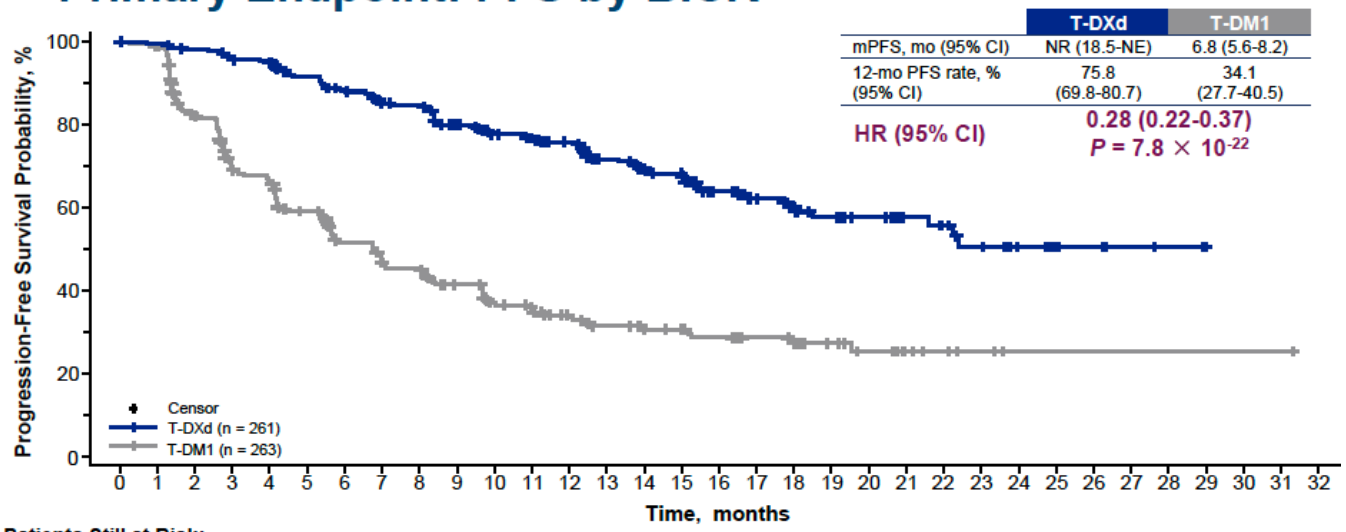
Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Prior therapy for MBC
100% received prior trastuzumab
60% received prior pertuzumab
15% received other HER2 agents
Median lines of prior treatment: 2

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

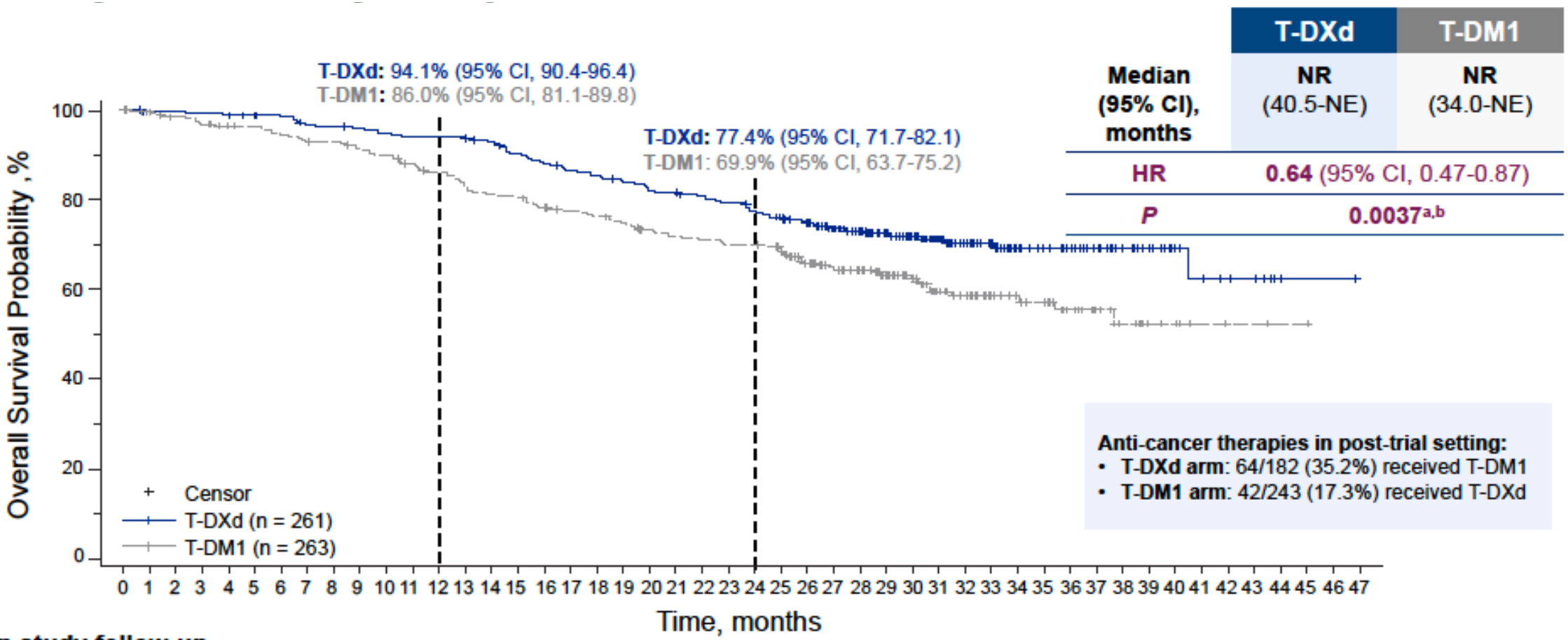
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

First results: median FU 15 months

Javier Cortès ESMO 2021

DESTINY-Breast03: updated results
Key Secondary Endpoint: OS



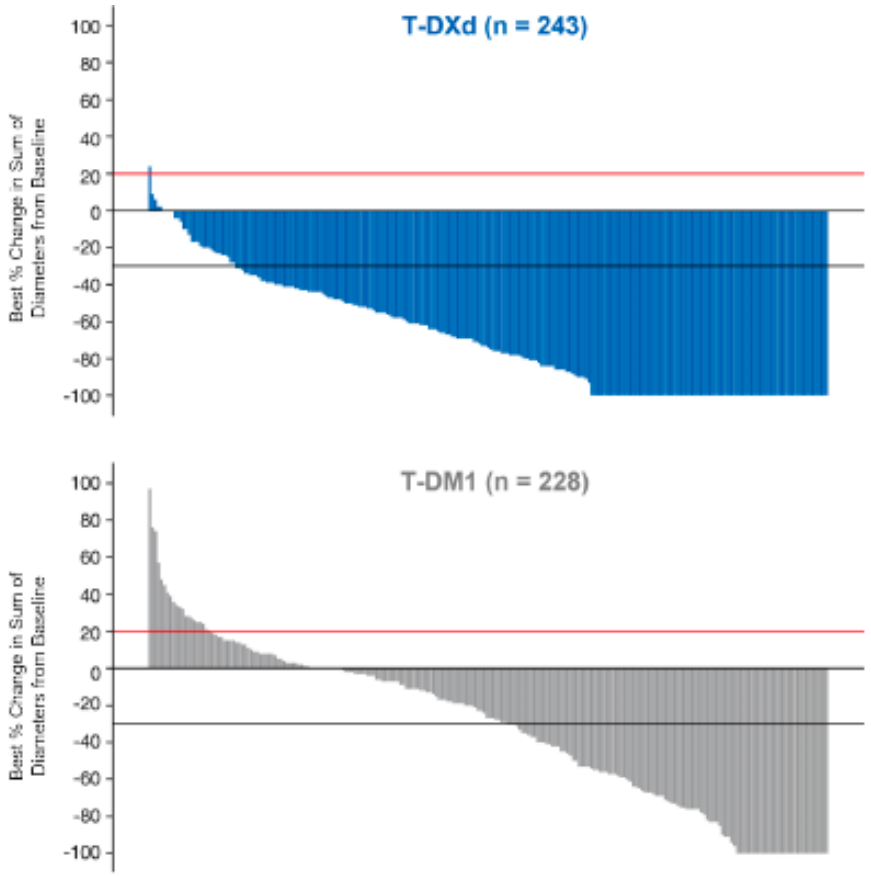
	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	0.64 (95% CI, 0.47-0.87)	
P	0.0037[a,b]	

Anti-cancer therapies in post-trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Median study follow-up
- **T-DXd arm: 28.4 months (range, 0.0-46.9 months)**
- **T-DM1 arm: 26.5 months (range, 0.0-45.0 months)**

Sara Hurvitz SABCS 2022

DESTINY-Breast03: confirmed ORR and other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

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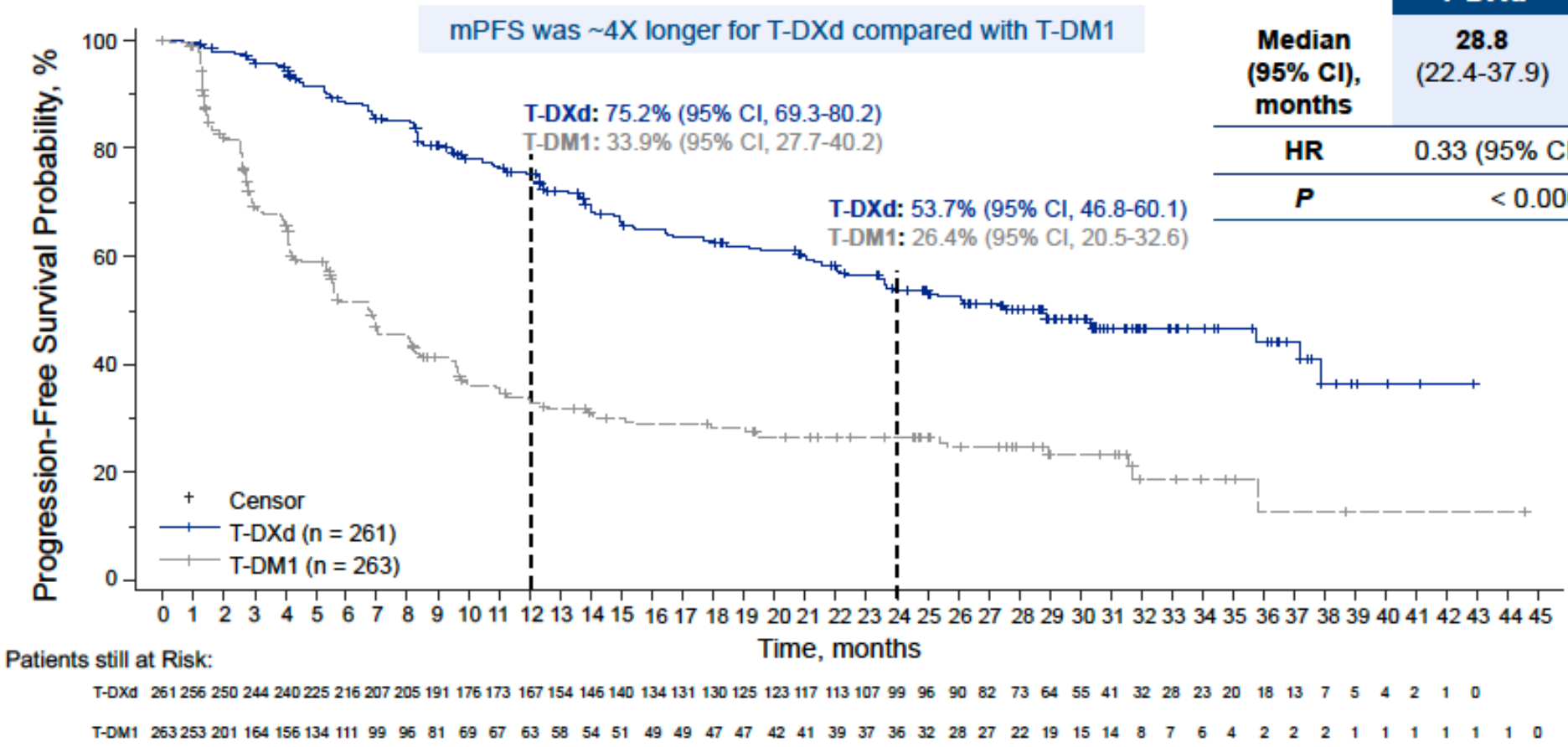
DESTINY-Breast03: updated primary endpoint PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

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DESTINY-Breast03:PFS 2 and Post-study Anticancer Treatment

	T-DXd n = 261	T-DM1 n = 263
Median PFS2 by investigator,[a] mo (95% CI)	40.5 (40.5-NE)	25.7 (18.5-34.0)
	HR, 0.47 (95% CI, 0.35-0.62)	
Patients who discontinued treatment, n (%)	182 (70.8)	243 (93.1)
Any post-study anticancer treatment,[b] n (%)	130 (71.4)	191 (78.6)
Trastuzumab	43 (23.6)	90 (37.0)
T-DXd	3 (1.6)	42 (17.3)
T-DM1	64 (35.2)	24 (9.9)
Pertuzumab	15 (8.2)	28 (11.5)
Taxane	13 (7.1)	32 (13.2)
Taxane and trastuzumab	7 (3.8)	28 (11.5)
Other anti-HER2[c]	39 (21.4)	88 (36.2)
Anti-HER2 TKI	38 (20.9)	87 (35.8)
Other anti-HER2 antibody or ADC	1 (0.5)	4 (1.6)
Hormone therapy	25 (13.7)	30 (12.3)
Other systemic therapy	75 (41.2)	147 (60.5)

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DESTINY-Breast03: Updated Safety summary

Lung toxicity ILD in 15% (Esmo 21 : 10.5%)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

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Take Home from SABCS 22 for ER+HER-MBC

- CDK4/6 inhibitors should be considered in all 1rst line ER+HER2- MBC
- in 2nd line
  - SERDs have a place beyond CDK4/6i but not for all and the population with **ESR1m + prolonged benefit to CDK4/6i (>12m)** seems to derive the most benefit.
  - **AKT pathway inhibition** has a place after CDK4/6i. Benefit seen in CDK4/6i short responders. Biomarkers?
  - CDK4/6i after CDK4/6i data are still too weak for the clinic. Which partner needs switching?

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Take Home from SABCS for HER2+ MBC

- Trastuzumab Deruxtecan confirms positive clinical impact in PFS and OS in HER2+MBC from the second line onwards.
- ILD remains a concern. Screening guidelines and continuous education of the oncology teams should be implemented.