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Grupo Oncoclínicas
Latin American Cooperative Group, LACOG
Porto Alegre, Brazil

Ask-the-Expert Webinar

Mechanism of action of CDK4/6 inhibitors and the complex effects within breast cancers/alteration of tumor biology

WILEY Breast Cancer Knowledge Hub

Disclosures

Grants/research support: (to the institution) Nektar, Pfizer, Polyphor, Amgen, Daiichi Sankyo, Sanofi, Exelixis, Regeneron, Novartis, GSK, Janssen, OBI Pharma, Lilly, Seagen, Roche, BMS, MSD, Merck Serono, Astra Zeneca, Novocure, Aveo Oncology, Takeda, TRIO, PharmaMar, Celgene, PPD, Syneos Health, Labcorp, ICON, IQVIA, Parexel, Nuvisan, PSI, Worldwide, Gilead Sciences, Bayer, Servier.

Academic Research Projects: CPO, PUCRS, LACOG, GBECAM.

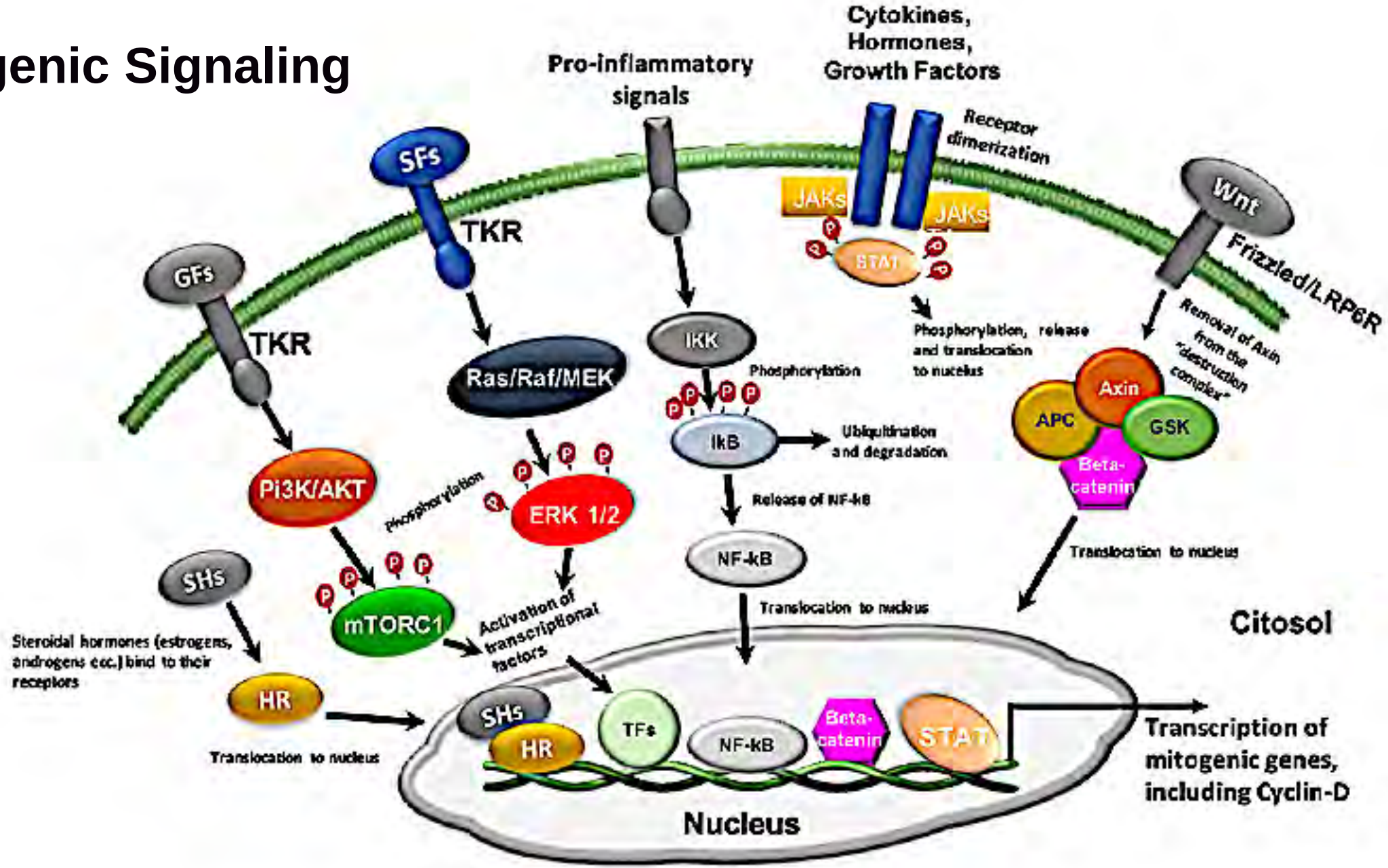
Ownership or Stocks: Tummi, MEDSir

Advisory Boards and Consulting: Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai, Bayer, MSD, Astra Zeneca, Zodiac, Lilly, Sanofi, Daiichi.

Learning Objectives

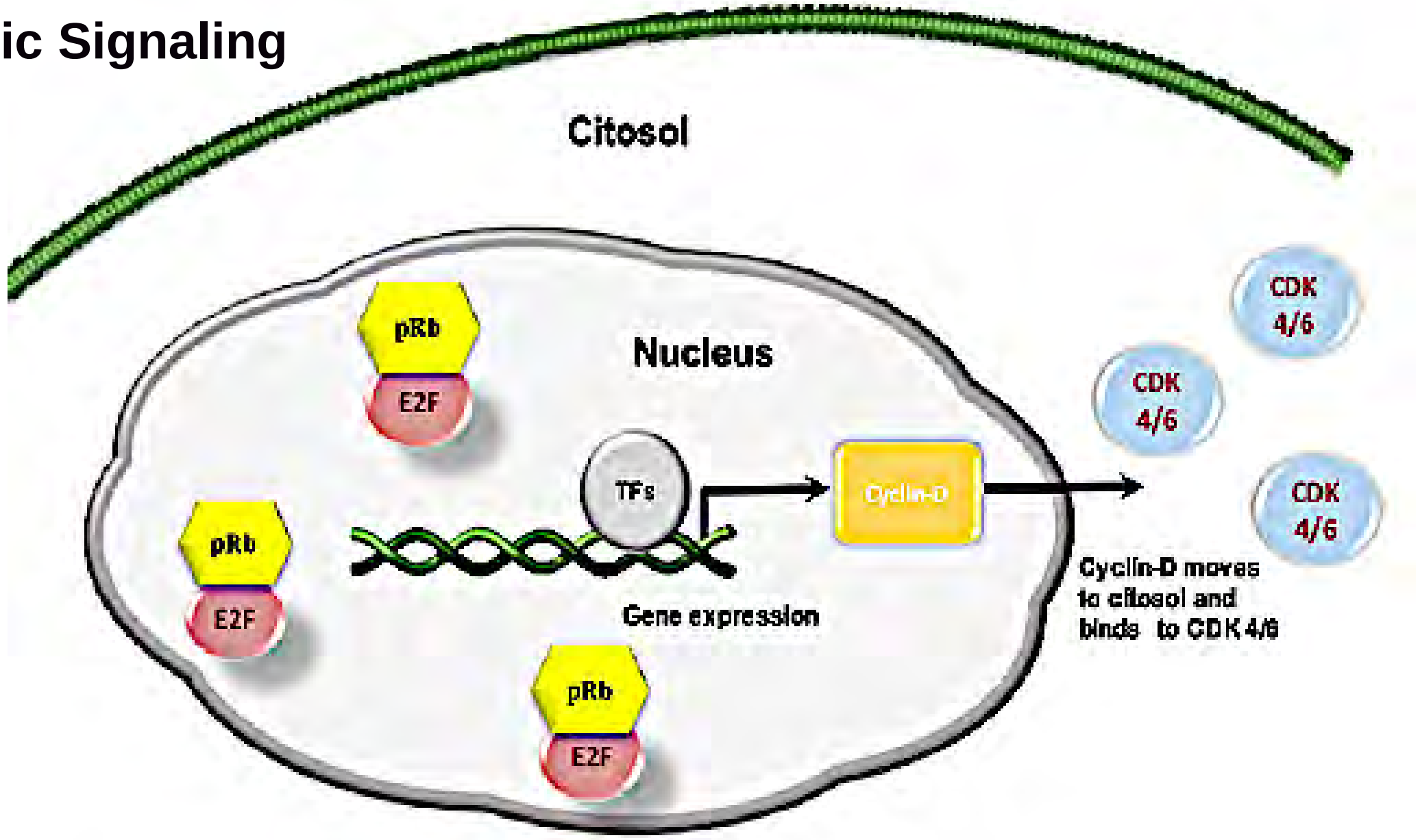
- Understand the basic mechanisms of cell cycle and cellular mitogenic control
- Recognize some of the complex cellular signaling involved in cancer
- Be able to identify the basic mechanisms of action of the CDK4/6 inhibitors
- Address the evolving understanding of the multiple potential mechanisms of resistance to CDK4/6 inhibition

Mitogenic Signaling



Schettini F, et al. Frontiers Oncology 2018 Dec 12;8:608.

Mitogenic Signaling



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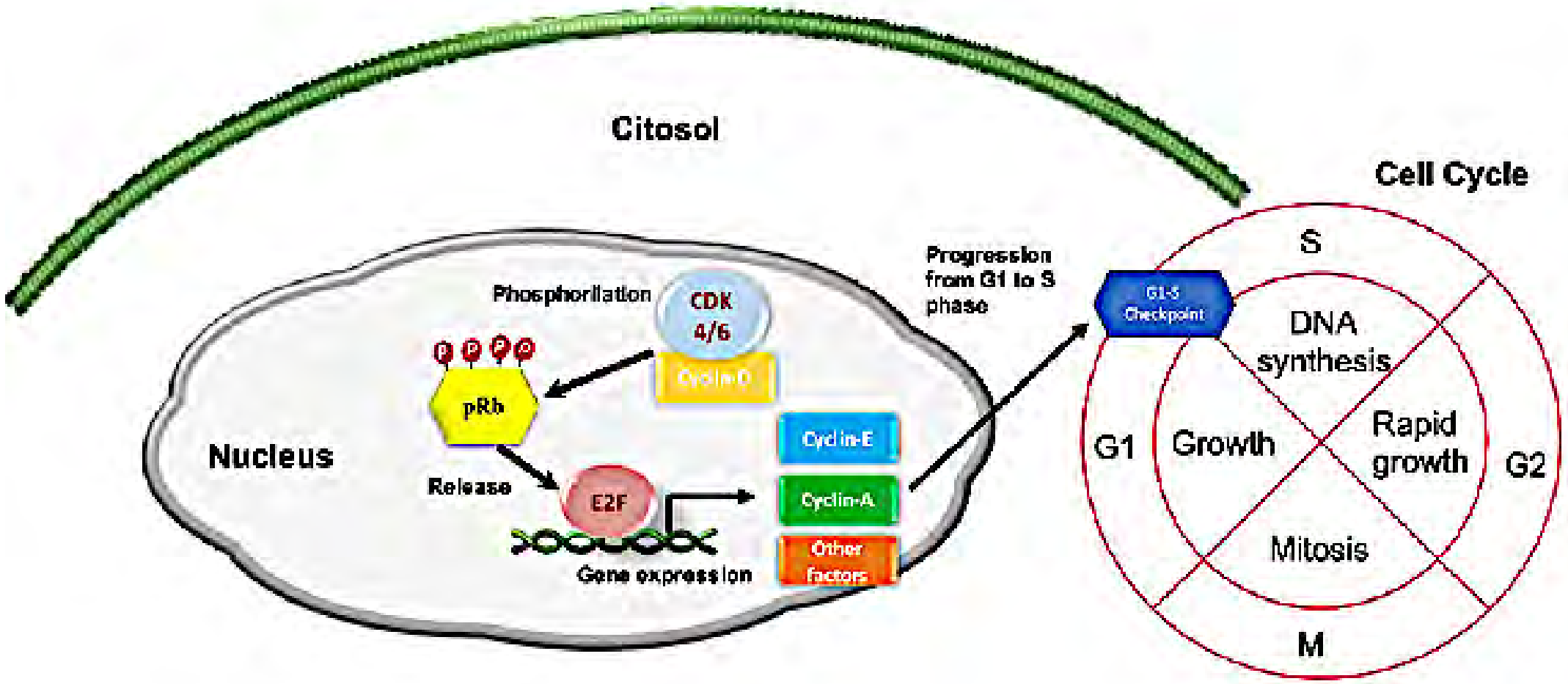
Mitogenic Signaling



Schettini F, et al. Frontiers Oncology 2018 Dec 12;8:608.

Cell Cycle

Sequence of cellular events that occur in an orderly fashion and result in cell growth and cell division

Cell cycle machinery is conserved across evolution/species
Cell Cycle events occur in a highly controlled
orderly succession of sequenced phases

Intephase (G1, S and G2) and M Phase

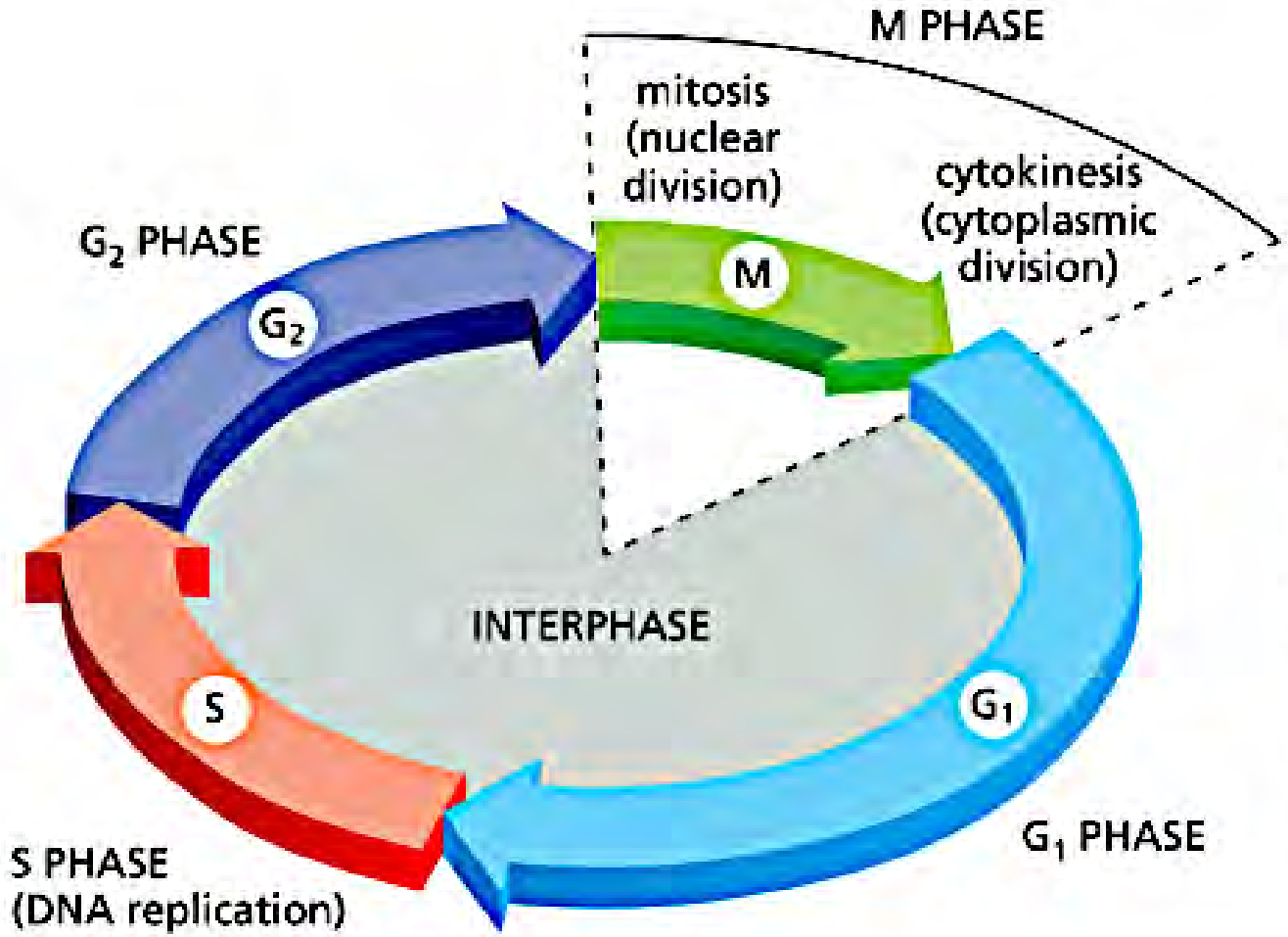


Figure 17–4 The four phases of the cell cycle. In most cells, gap phases separate the major events of S phase and M phase. G_1 is the gap between M phase and S phase, while G_2 is the gap between S phase and M phase.

Molecular Biology of the Cell. Alberts B, et al. Garland Science, 6th Ed. 2017.

Control of the Cell Cycle

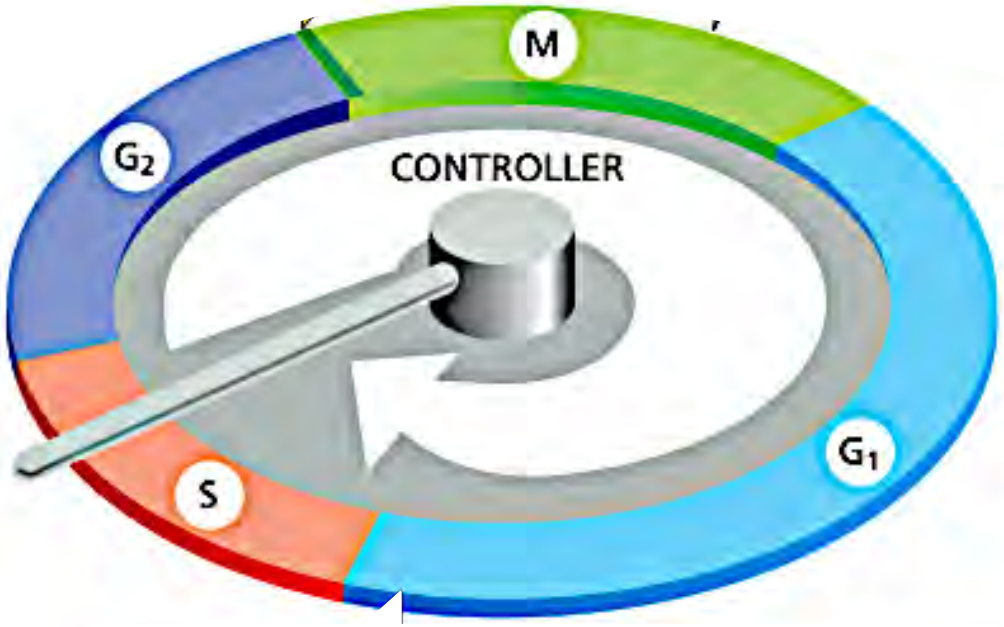
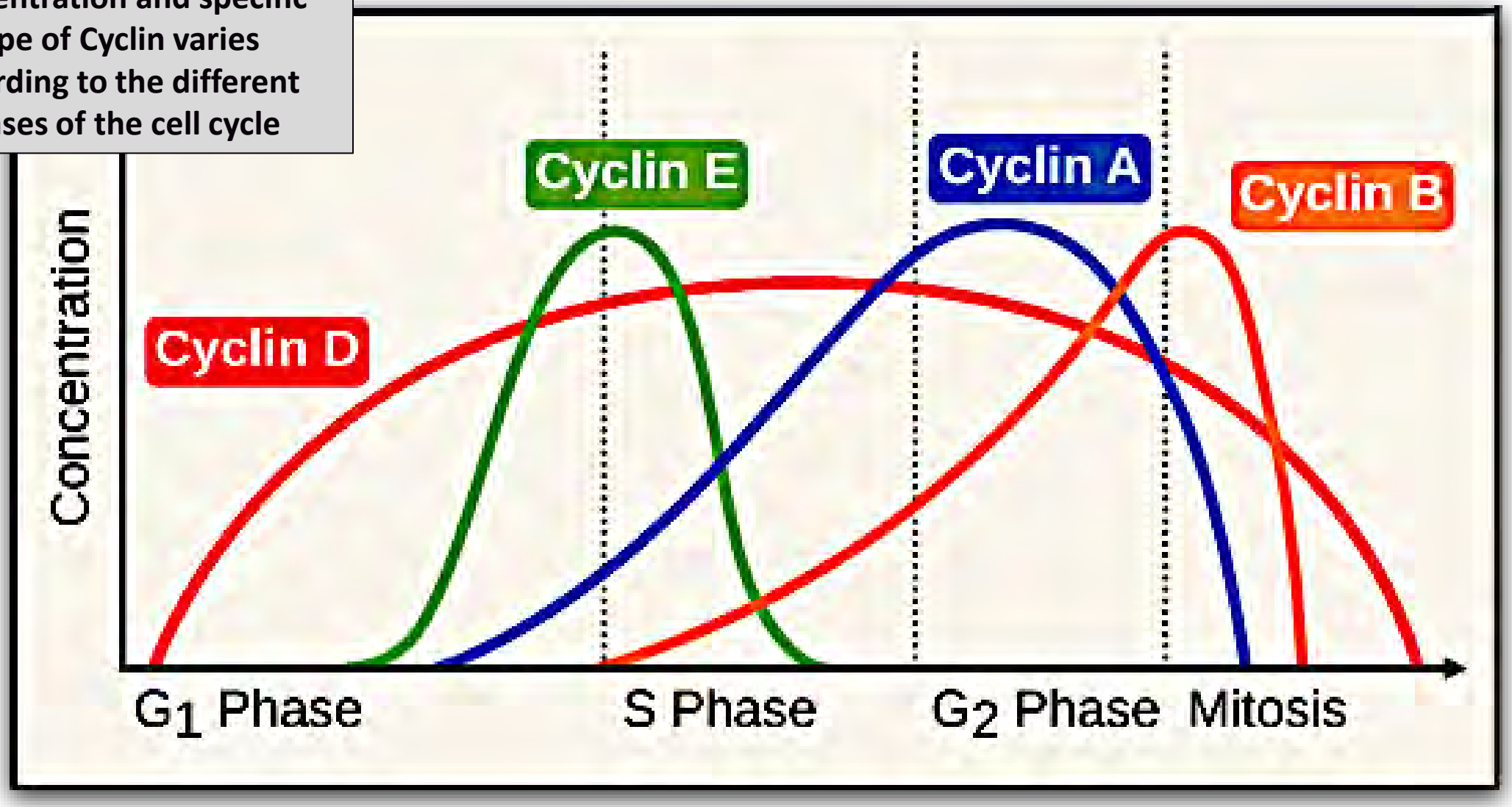


Figure 17–9 The control of the cell cycle. A cell-cycle control system triggers the essential processes of the cycle—such as DNA replication, mitosis, and cytokinesis. The control system is represented here as a central arm—the controller—that rotates clockwise, triggering essential processes when it reaches specific transitions on the outer dial *(yellow boxes)*. Information about the completion of cell-cycle events, as well as signals from the environment, can cause the control system to arrest the cycle at these transitions.

Molecular Biology of the Cell. Alberts B, et al. Garland Science, 6th Ed. 2017.

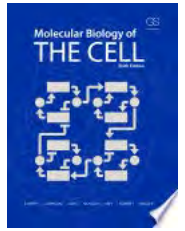
Cyclin Expression During the Cell Cycle

Concentration and specific type of Cyclin varies according to the different phases of the cell cycle

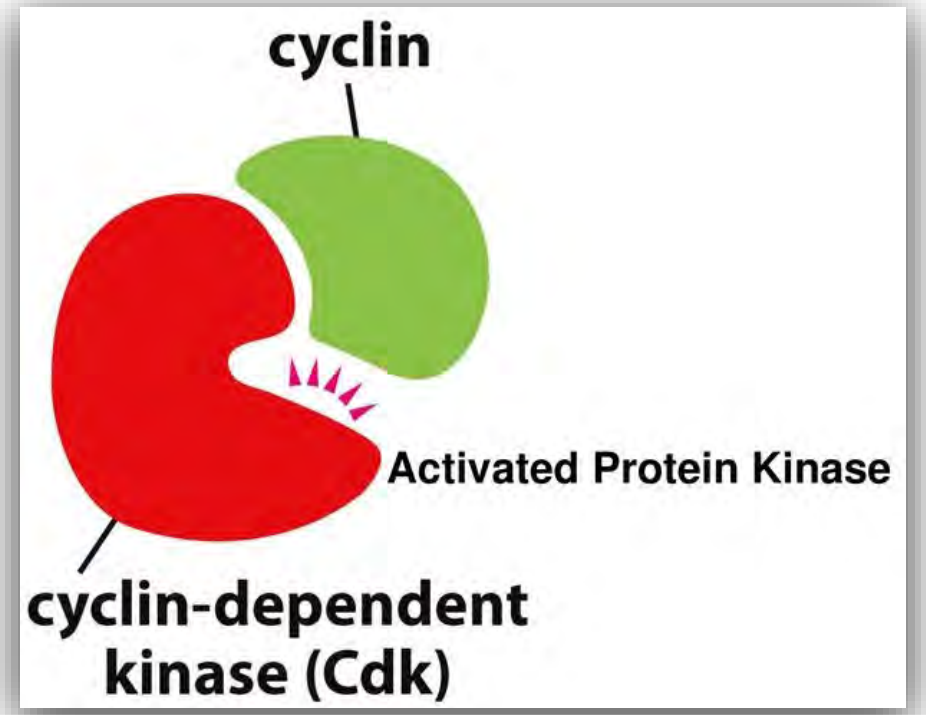


https://blog.praxilabs.com/2021/07/06/cell-cycle-regulation-en/

Cyclins and Cyclin Dependent Kinases (CDKs)

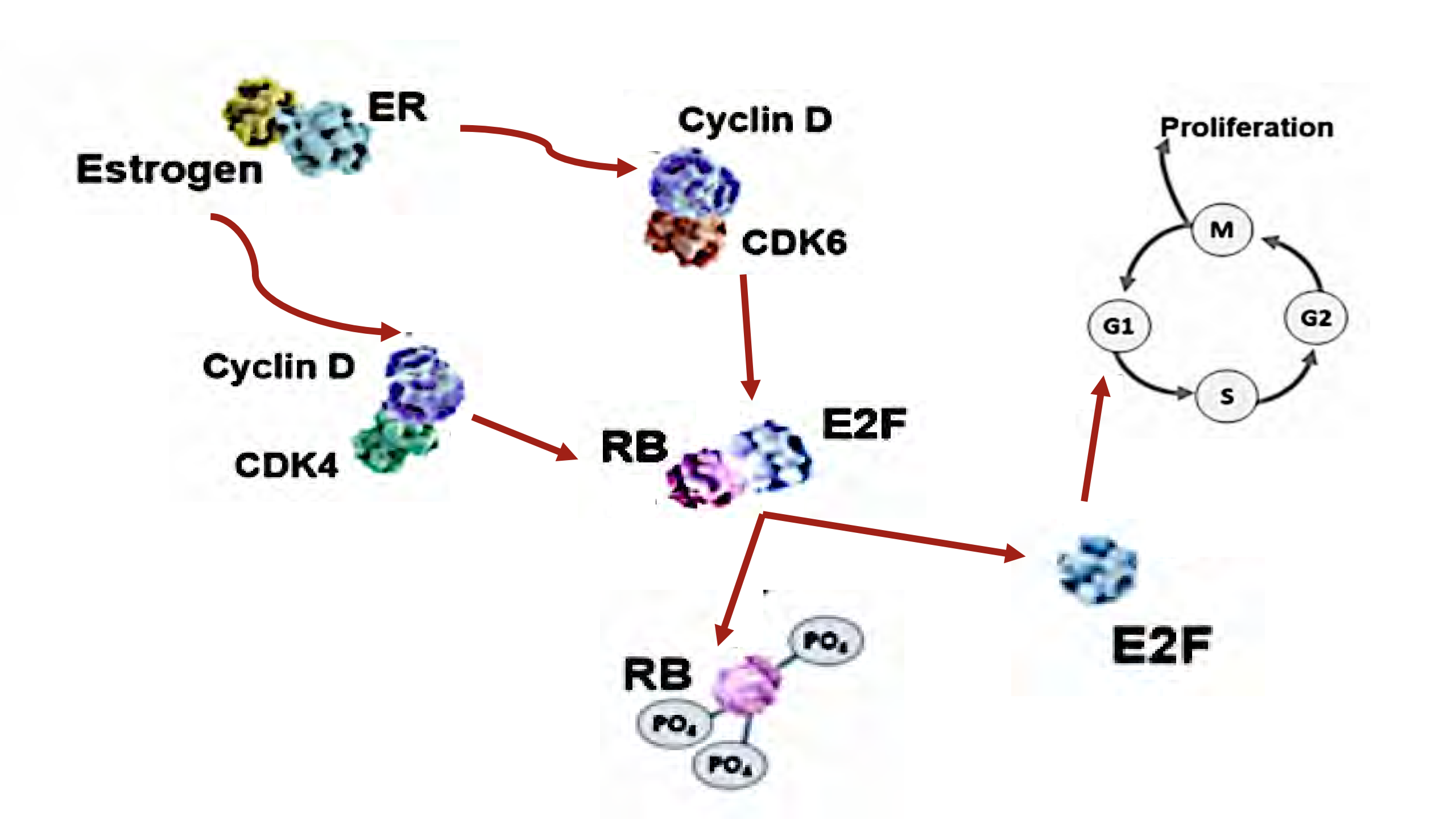


Cdk	Associated Cyclin	Cell-Cycle Stage
Cdk1	Cyclin A, B	G_2/M
Cdk2	Cyclin A, D, E; cyclin H	G_1/S; S; G_2/M
Cdk3	Ik3–1, Ik3–2	G_1
Cdk4	Cyclin D	G_1/S; S
Cdk5	Cyclin D	G_1/S
Cdk6	Cycin D	G_1/S; S
Cdk7	Cyclin H	G_1/S; transcriptional regulation
Cdk8	Cyclin C	G_1/S; G_2/M, transcriptional regulation
Cdk9	Cyclin T1, T2	Acts on differentiation, interaction with tat, the transcriptional regulator of the HIV virus
Cdk10	Interacts with ets-2[25]	G_2/M[27]
Cdk11	RanBPM, RNPS1[26] casein kinase[58], cyclin L	Promotes apoptosis
Cdk12	Cyclin L1 and L2	Regulates alternative splicing[29]
Cdk13	Cyclin L	Regulates alternative splicing[10]



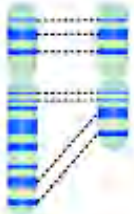
Serine - threonine Kinases

https://blog.praxilabs.com/2021/07/06/cell-cycle-regulation-en/
Molecular Biology of the Cell. Alberts B, et al. Garland Science, 6th Ed. 2017/

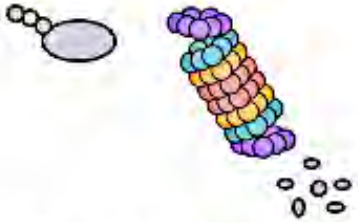

ER
Estrogen
Cyclin D
CDK6
Cyclin D
CDK4
RB
E2F
Proliferation
M
G1
G2
S
RB
PO4
PO4
PO4
E2F

Genomic alterations

Gene amplification
e.g., *CCND1* (Cyclin D1), *CDK4* and/or *CDK6*



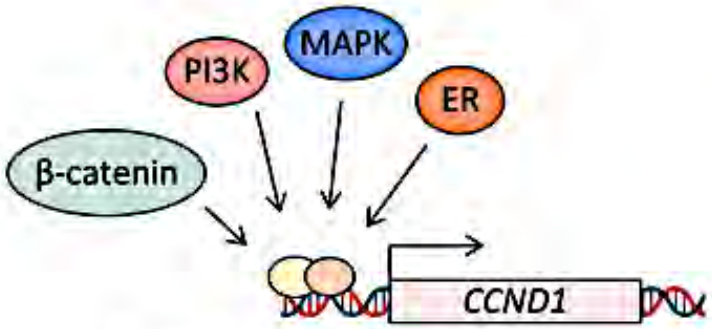
Gene deletion
e.g., *CDKN2A* (p16INK4A) and/or *CDKN2B* (p15INK4B)



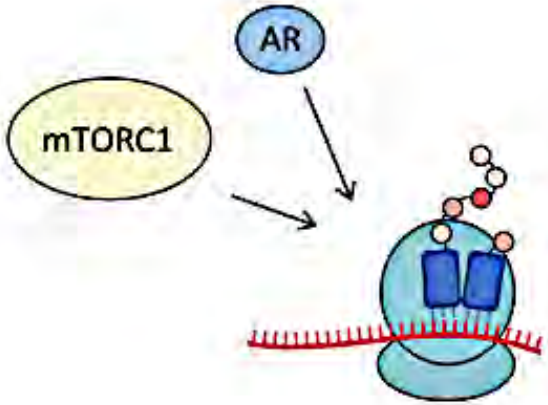
Stabilizing Cyclin D1 mutations e.g., impaired ubiquitination

Activating mutations
e.g., reduced Cyclin D1 nuclear export

Upstream signaling



Transcriptional up-regulation of Cyclin D
e.g., via MAPK, PI3K, ER, β-catenin

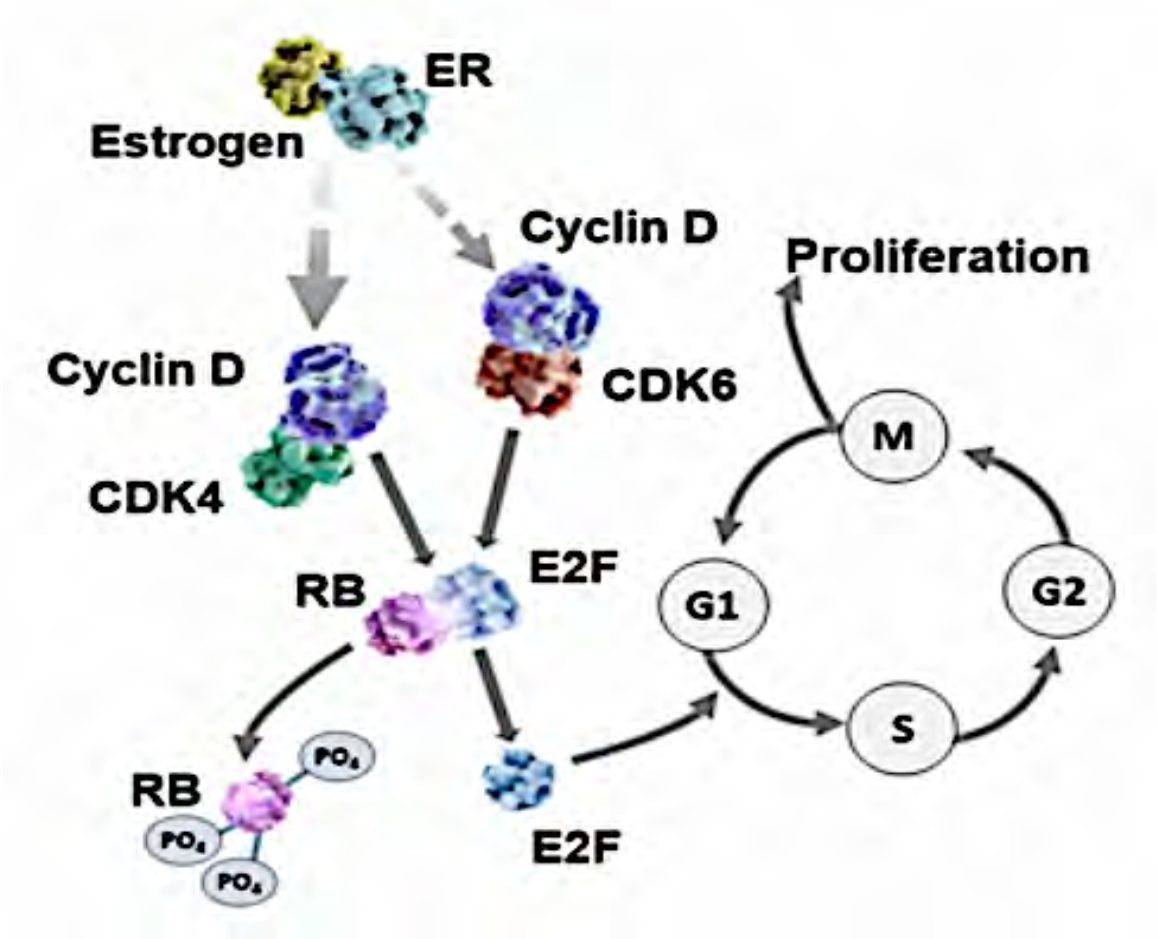


Increased translation of Cyclin genes
e.g., via mTORC1, AR

Major mechanisms responsible for dysregulated CDK4/6 activity in cancer include genomic alterations as well as activation of upstream signaling pathways that may up-regulate this pathway at the transcriptional, translational and post-translational levels.

Goel S, et al. Nat Rev Cancer. Author manuscript; available in PMC 2022 December 01.

ER, Cyclin D, CDK4/6, Rb and E2F

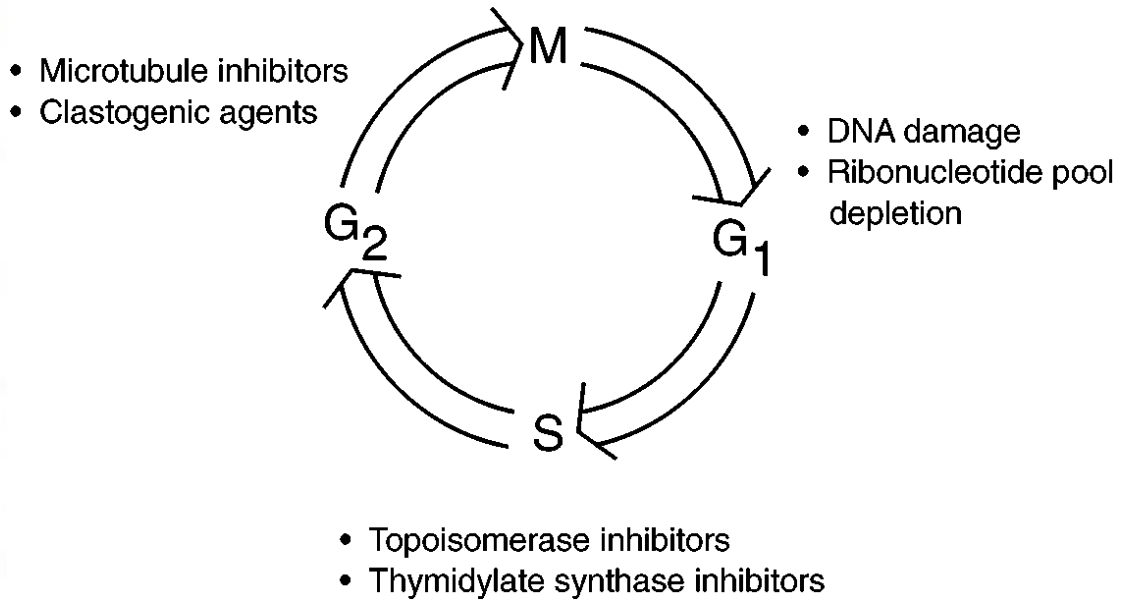


- The growth of HR+ breast cancer is particularly dependent on Cyclin D1, a direct transcriptional target of ER
- Cyclin D1 activates CDK 4/6 resulting in Rb phosphorylation, release of E2F, G1–S phase transition and entry into the cell cycle[1]
- Resistance to endocrine therapy is associated with continued dependence on Cyclin D1 & CDK 4/6

1. Hosford SR, Miller TW. *Pharmgenomics Pers Med.* 2014;7:203-215; 2. Knudsen ES, Wang JY. *Clin Cancer Res*. 2010;16(4):1094-1099; 3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18(3):333-345; 4. Miller TW, et al. *Cancer Discov*. 2011;1(4):338-351; 5. Lange CA, Yee D. *Endocr Relat Cancer*. 2011;18(4):C19-C24; 6. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146.

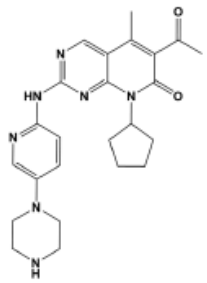
The Cell Cycle (Proliferation) has Always been a Preferred Target of Anticancer Drugs

Class of compounds	Mechanism of action	Prototypical drugs	Cell cycle impact
DNA damaging agents	Induction of DNA alkylation and crosslinks Clastogenic	Cisplatin Nitrogen mustard Cyclophosphamide Chlorambucil	p53-mediated G1/S arrest/apoptosis or G2/M arrest Up-regulation of p21 and sequestration of PCNA
Microtubule inhibitors	Inhibition of tubulin polymerization and disruption of spindle formation	Taxol/paclitaxel Nocodazole Vincristine/vinblastine	Arrest at the mitotic spindle assembly checkpoint associated with stabilization of cyclinB/cdc2
Ribonucleotide pool depletion	Purine nucleoside analogs that inhibit: DNA polymerase Ribonucleotide reductase DNA chain elongation	Hydroxyurea Gemcitibine Difluorodeoxyuridine	p53-mediated up-regulation of p21 and arrest at G1 checkpoint Cell killing in checkpoint defective cells that proceed into S
Antimetabolites	Inhibition of thymidylate synthase and DNA synthesis	Methotrexate Cytosine arabinoside 5-Fluorouracil	p53-mediated S-phase arrest Apoptosis in checkpoint-defective cells that incorporate antimetabolites
Topoisomerase inhibitors	Inhibition of DNA topoisomerase and DNA replication	Camptothecin Etoposide Bufalin	S-phase damage resulting in arrest at S-phase or G2/M checkpoints Up-regulation of p16 and arrest at G1/S checkpoint

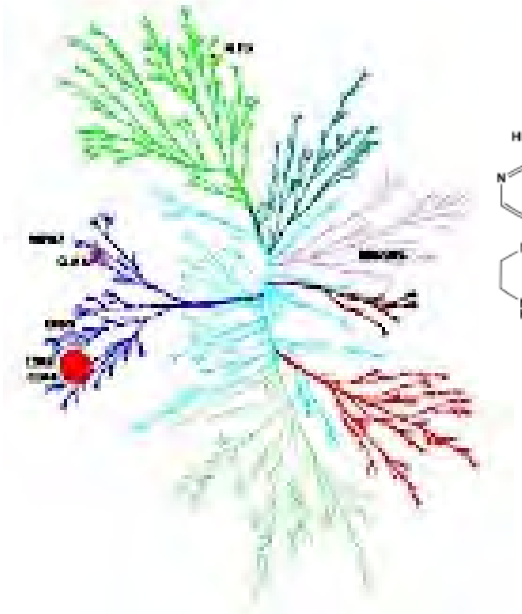


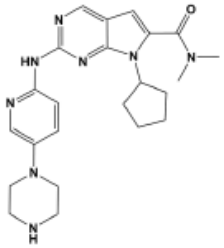
Johnson DG, Walker CL. Annu. Rev. Pharmacol. Toxicol. 1999. 39:295–312

CDK4/6 Inhibitors

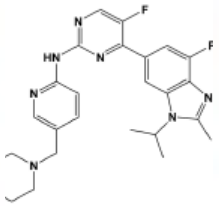


Palbociclib
PD-332991

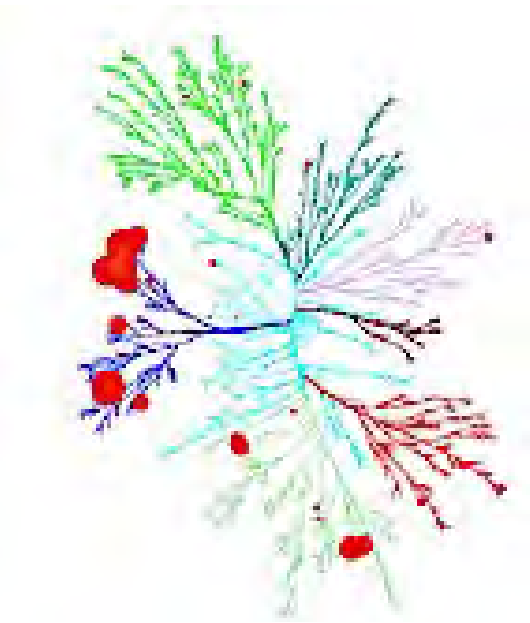




Ribociclib
LEE011



Abemaciclib
LY2835219



Palbociclib (PD-0332991)
CDK1: >10 µM
CDK2: >10 µM
CDK4: 9–11 nM
CDK5: >10 µM
CDK6: 15 nM
CDK7: ND
CDK9: ND

Ribociclib (LEE011)
CDK1: >100 µM
CDK2: >50 µM
CDK4: 10 nM
CDK5: ND
CDK6: 39 nM
CDK7: ND
CDK9: ND

Abemaciclib (LY-2835219)
CDK1: >1 µM
CDK2: >500 nM
CDK4: 2 nM
CDK5: ND
CDK6: 5 nM
CDK7: 300 nM
CDK9: 57 nM

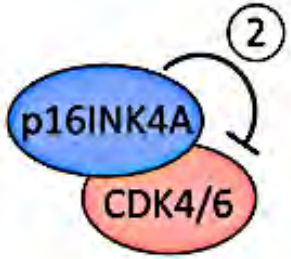
FDA Approved 2015

FDA Approved 2017

FDA Approved 2017

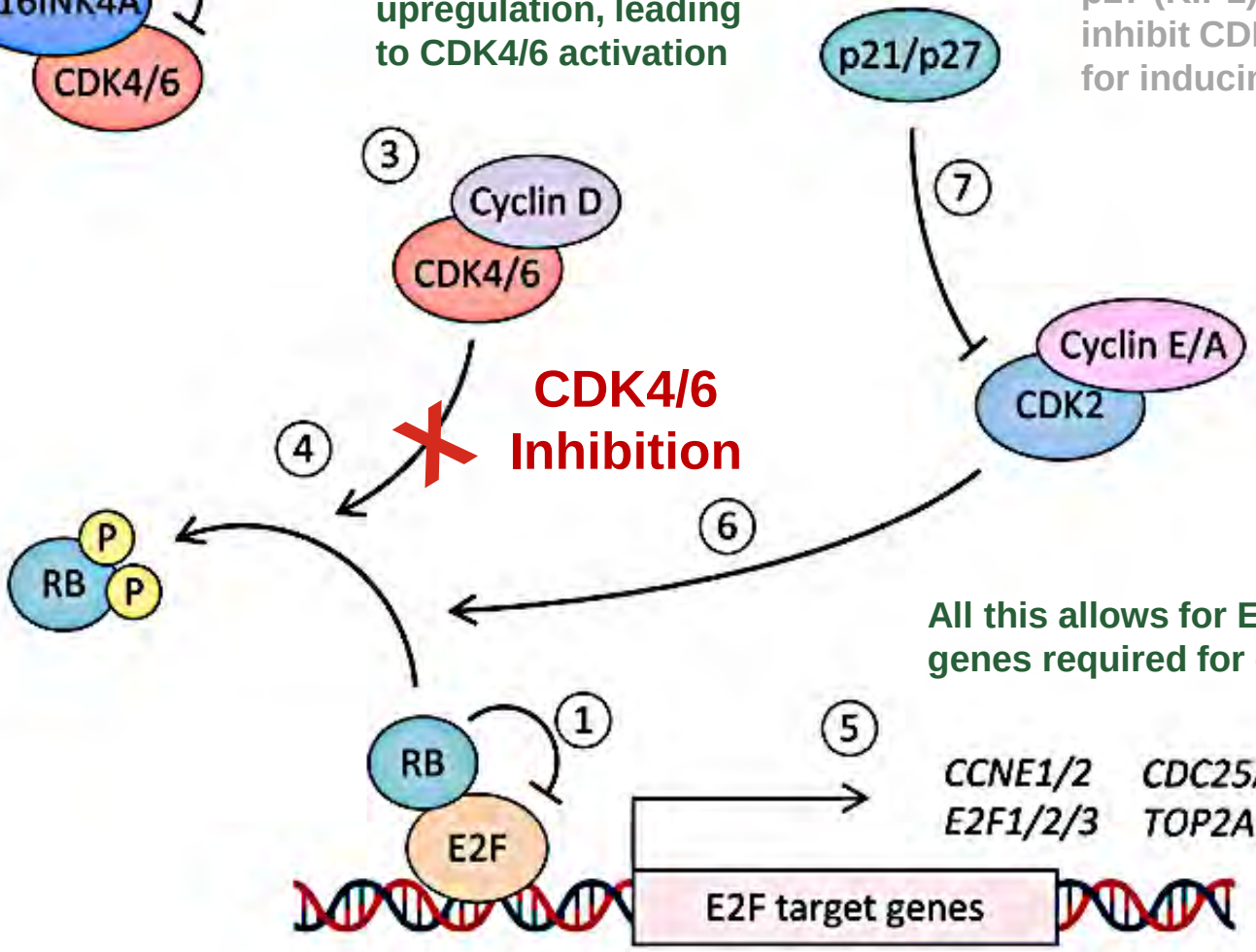
1. Fry DW et al. Mol Cancer Ther. 2004;3:1427. 2. Gelbert LM et al. Invest New Drugs. 2014;32:825. 3. Kim S et al. Mol Cancer Ther. 2013;12(11 Suppl):PR02.

The INK4 family of cell cycle inhibitors bind to monomeric CDK4 and CDK6 to form inactive binary complexes



Mitogen or growth factor stimulation drives cyclin D upregulation, leading to CDK4/6 activation

WAF1 and CIP/KIP family proteins, such as p21 (WAF1), p27 (KIP1) and p57 (KIP2), inhibit CDK2 and are important for inducing cell cycle arrest



RB phosphorylation by cyclin E–CDK2 and cyclin A–CDK2 complexes further enhances RB phosphorylation

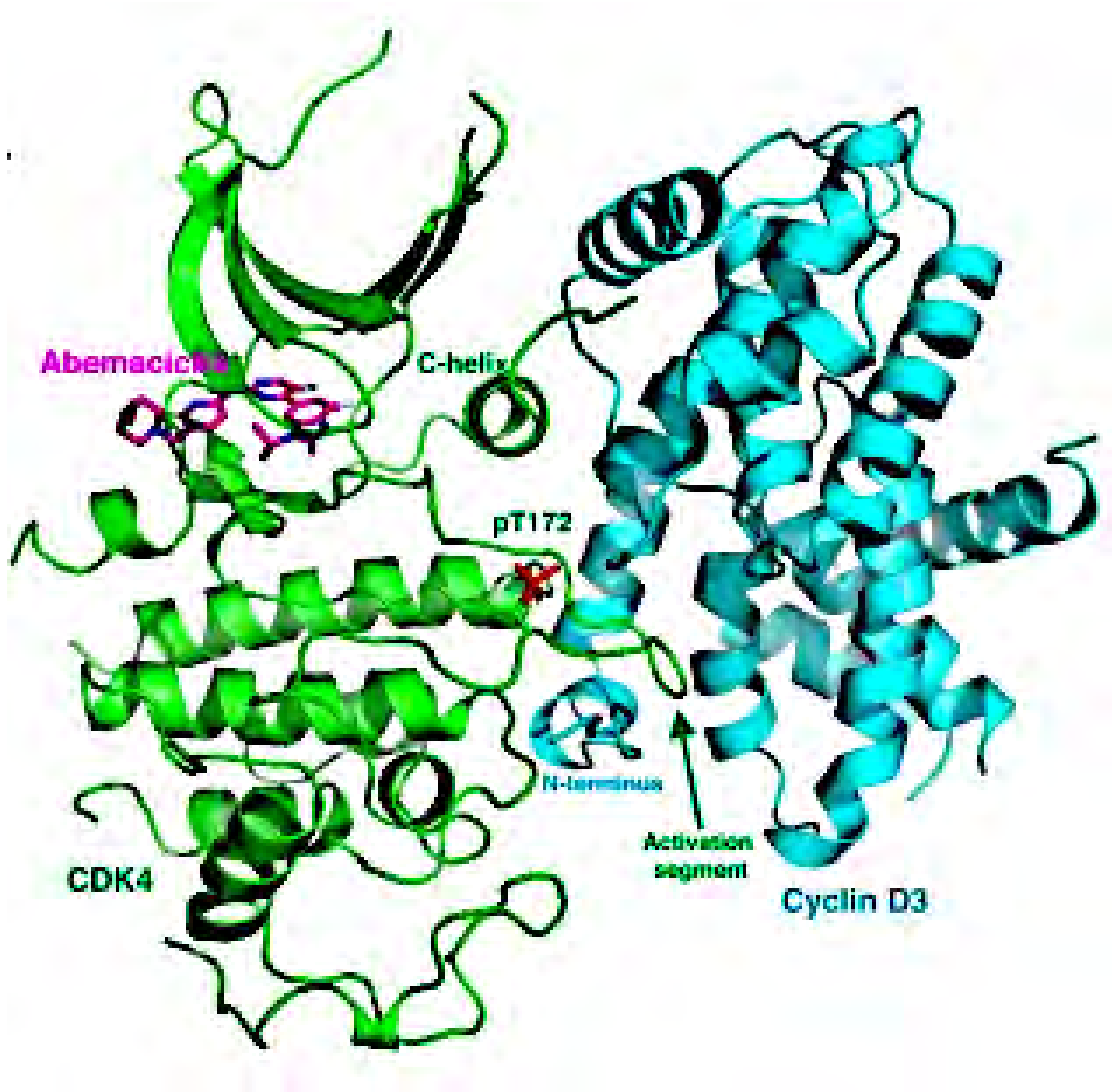
RB phosphorylation by cyclin D–CDK4/6 complexes promotes dissociation of RB–E2F binding

All this allows for E2Fmediated expression of genes required for cell cycle progression

Hypophosphorylated RB binds to and represses E2F family transcription factors

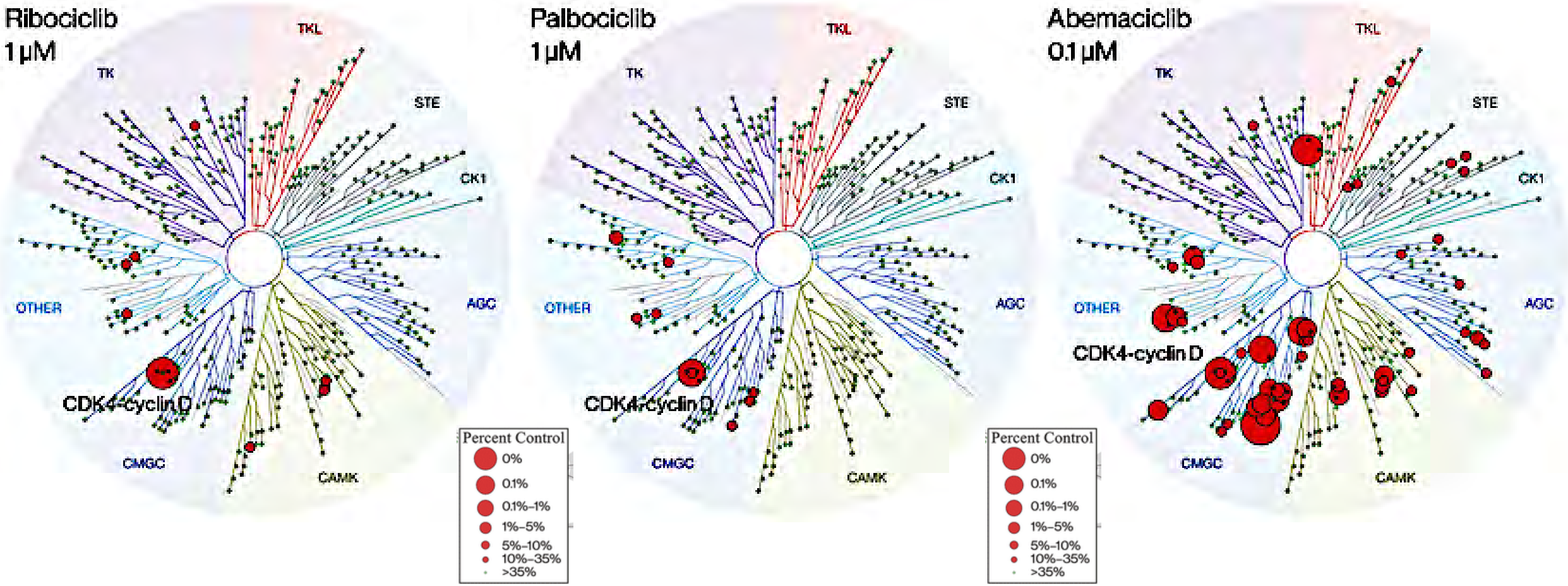
Goel S, et al. Nat Rev Cancer. Author manuscript; available in PMC 2022 December 01.

MOA of CDK-4 Inhibitors

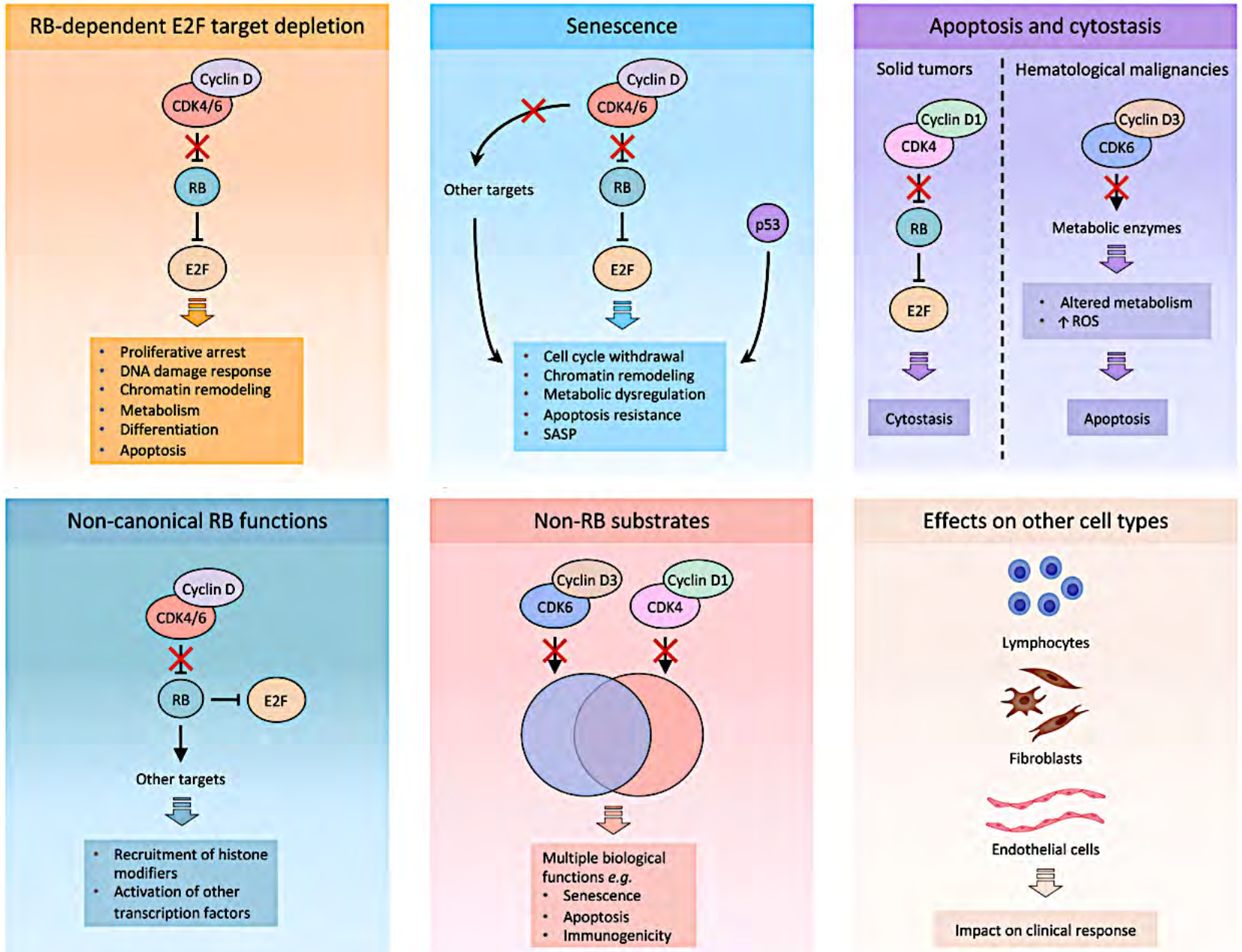


Gharbi SI, et al. npj Breast Cancer **volume 8**, Article number: 126 (2022)

CDK4/6 Inhibitor Kinome Maps



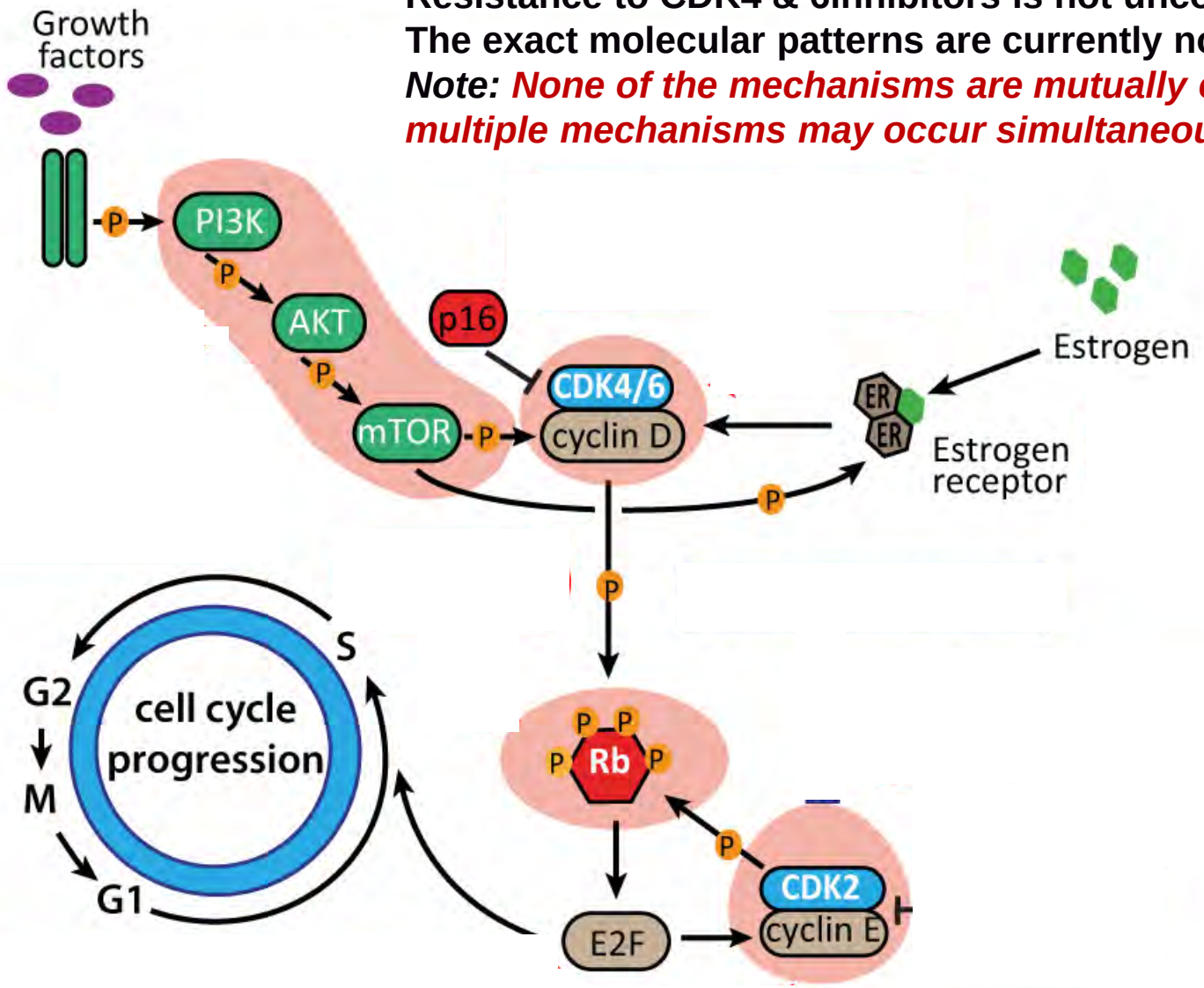
Kim, S, et al. October 2018, Oncotarget 9(81)
DOI:10.18632/oncotarget.26215



Goel S, et al. Nat Rev Cancer. Author manuscript; available in PMC 2022 December 01.

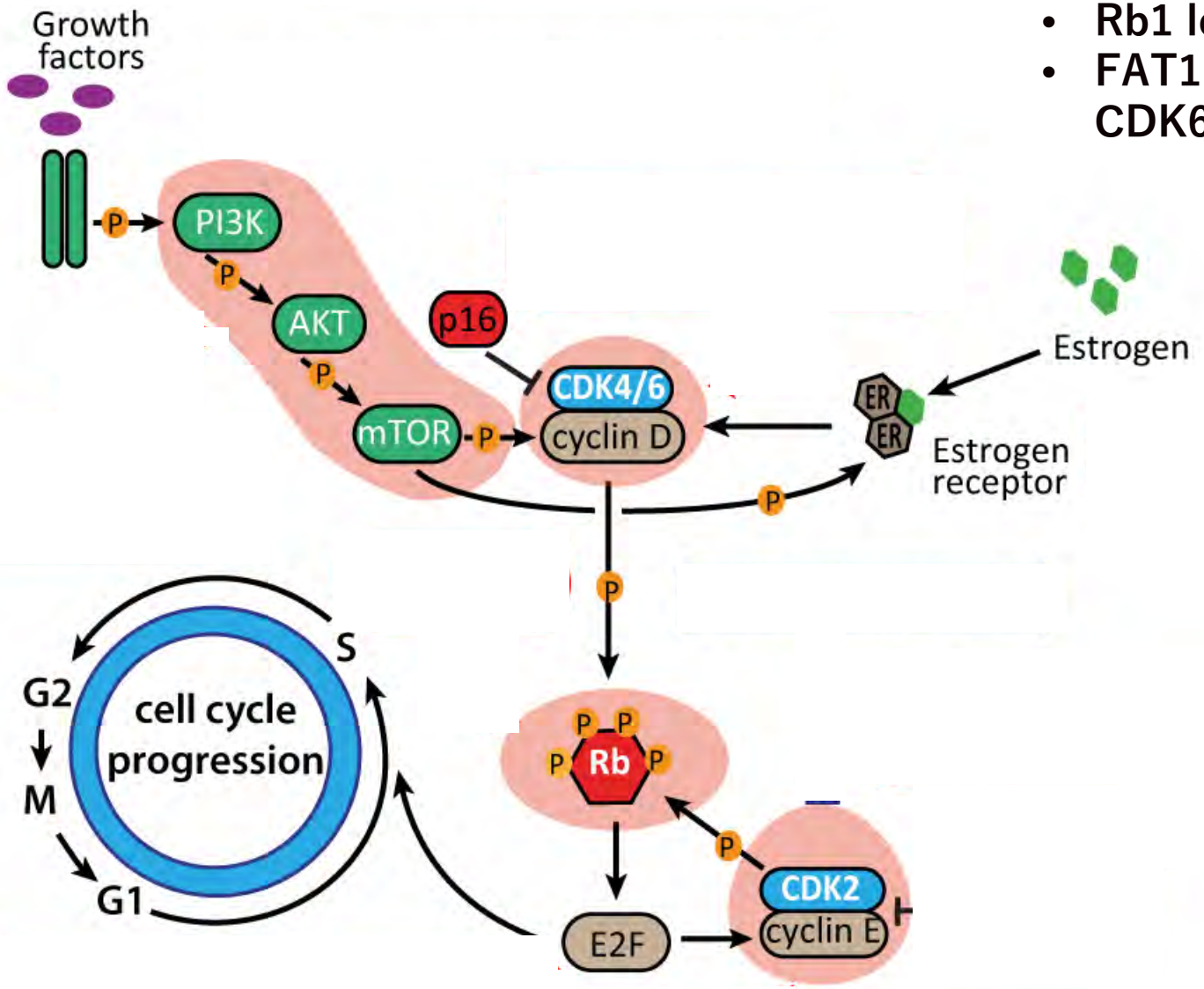
Resistance to CDK4 & 6inhibitors is not uncommon.
The exact molecular patterns are currently not well understood.
Note:* *None of the mechanisms are mutually exclusive and multiple mechanisms may occur simultaneously.

- **Abnormalities in the Central Mechanisms of CDK4/6i action (Rb, CDK4/6, Cyclin D)**
- **Cell Cycle Compensatory Mechanisms**
- **Compensatory Mechanisms in related pathways (non-Cell Cycle)**



Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15–R30.

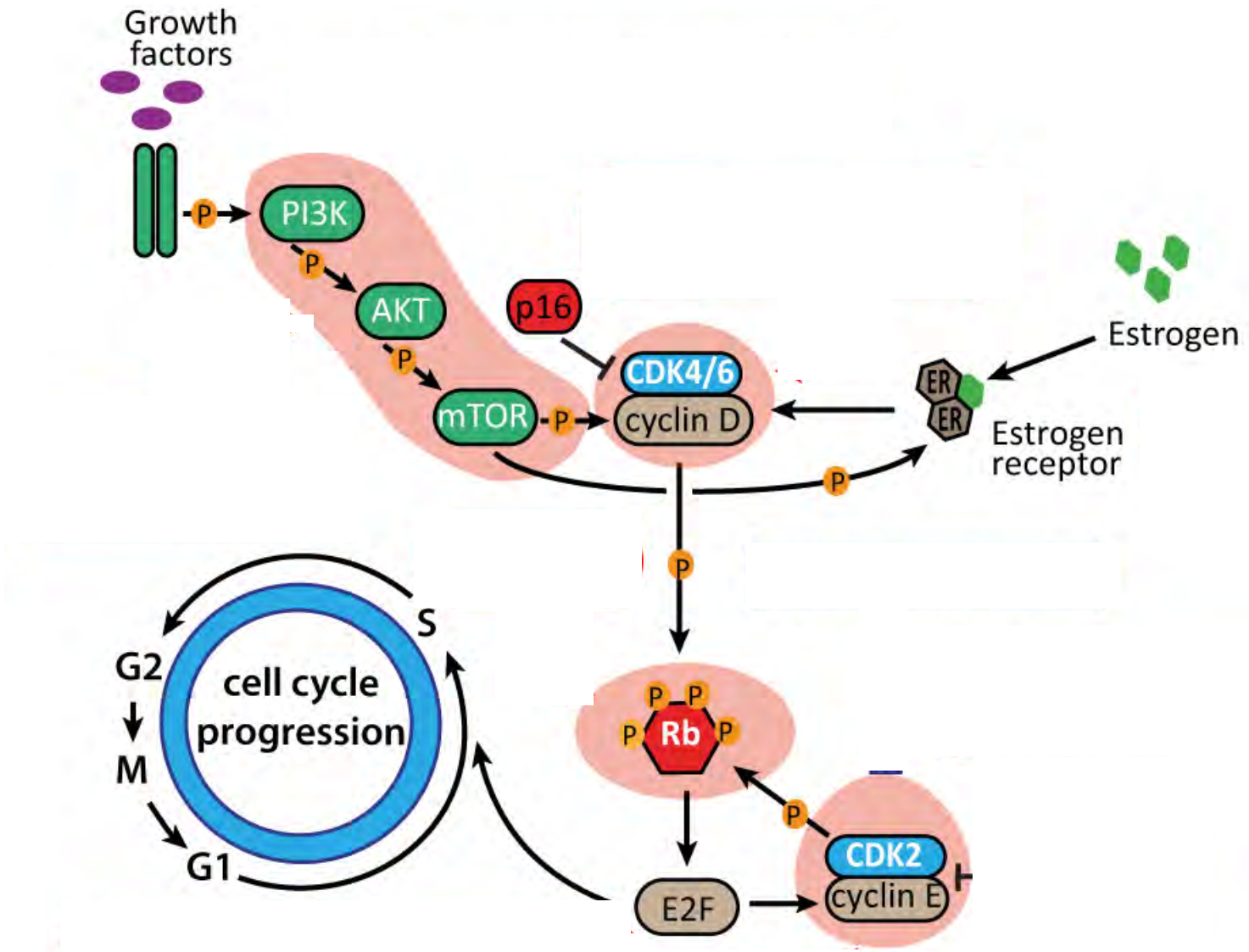
- **Abnormalities in the Central Mechanisms of CDK4/6i action (Rb, CDK4/6, Cyclin D)**



- **Rb1 loss in 4.7% PALOMA 3**
- **FAT1 loss (6%) can induce CDK6 overexpression**

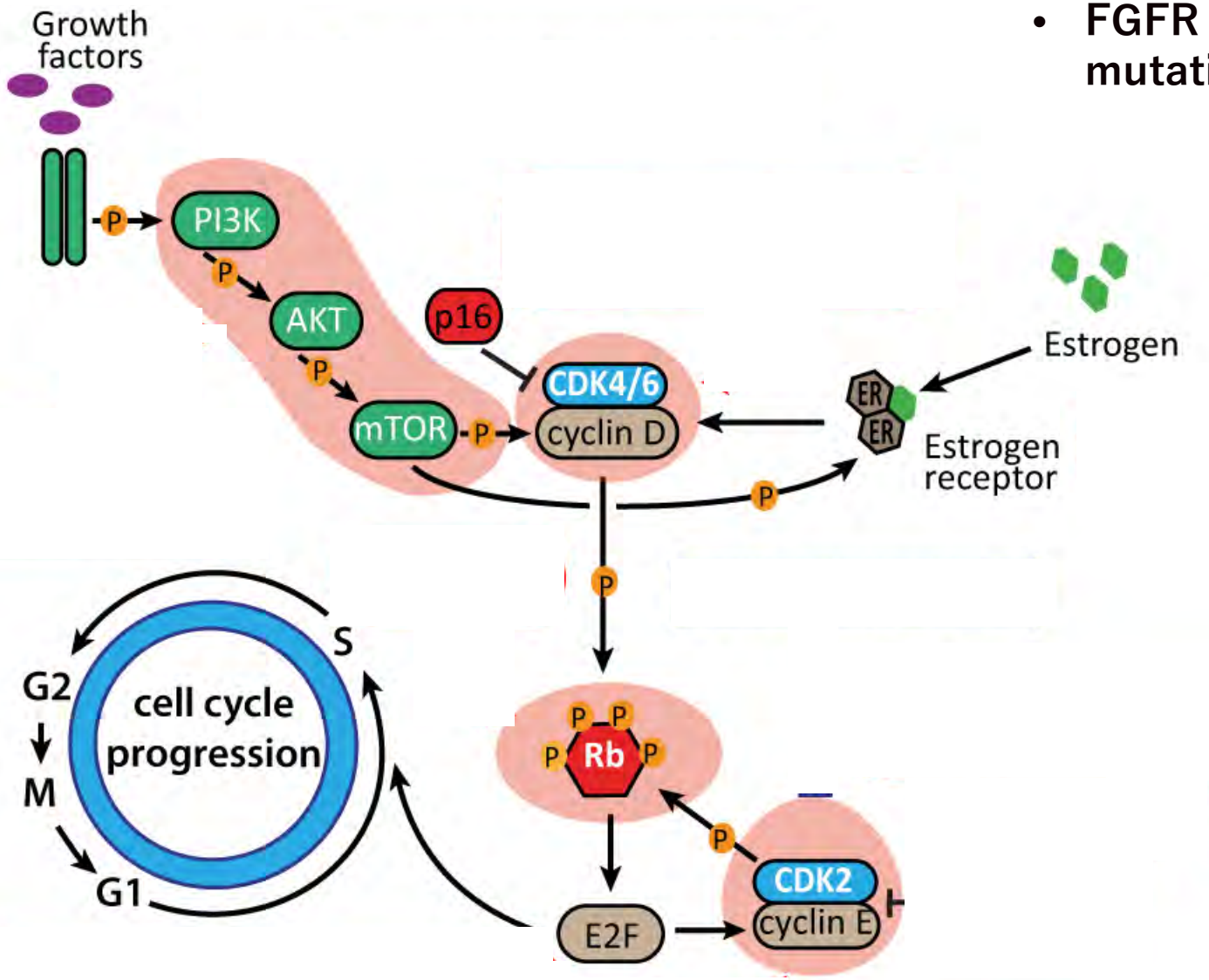
Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15–R30.

- **Cell Cycle Compensatory Mechanisms**



Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15–R30.

- **FGFR amplification or mutations**



- **Compensatory Mechanisms in related pathways (non-Cell Cycle)**

Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15–R30.

Take Home Messages

- The Cell Cycle is a well conserved, organized and tightly regulated series of enzymatic reactions that result in cell growth and division.
- The Cell Cycle is structured in carefully sequenced and very well recognized phases.
- Cyclins, Cyclin-dependent Kinases (CDKs) and different inhibitor proteins are the main molecular components of the Cell Cycle machinery and define specific and critical checkpoints that prevent inappropriate cell division.

Take Home Messages

- Cell Cycle abnormalities are a characteristic of cancer
- Most our therapies interfere at different levels with cell cycle machinery
- New generation CDK4/6 inhibitors have revolutionized therapy and outcomes in HR+ breast cancer
- Better understanding of the mechanism of action of these agents is critical to further improve clinical results by informing their mechanisms of resistance and define both optimal sequencing strategies and best possible combination partners.

WILEY

Giuseppe Curigliano, MD, PhD

Professor of Medical Oncology at University of Milan, Italy

Chief of the Clinical Division of Early Drug Development at European Institute of Oncology, Milan, Italy

Ask-the-Expert Webinar

Novel agents in HR+ / HER2 negative MBC

WILEY Breast Cancer Knowledge Hub

Disclosures

- Board Member : Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my Institute : MSD, Astra Zeneca
- Speakers bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None

Learning Objectives

- At the end of this webinar, learners will be able to

- Describe/Explain/Identify/List
- Explaining treatment options beyond CDK 4-6 inhibitors in HR+/HER2 – MBC
- Understanding magnitude of clinical benefit and toxicity of these agents
- Defining a treatment algorithm beyond progression to CDK 4-6 inhibitors

Continuing CDK4/6i Post Progression: Primary Results of the MAINTAIN Trial

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and Blood Markers, including circulating tumor DNA

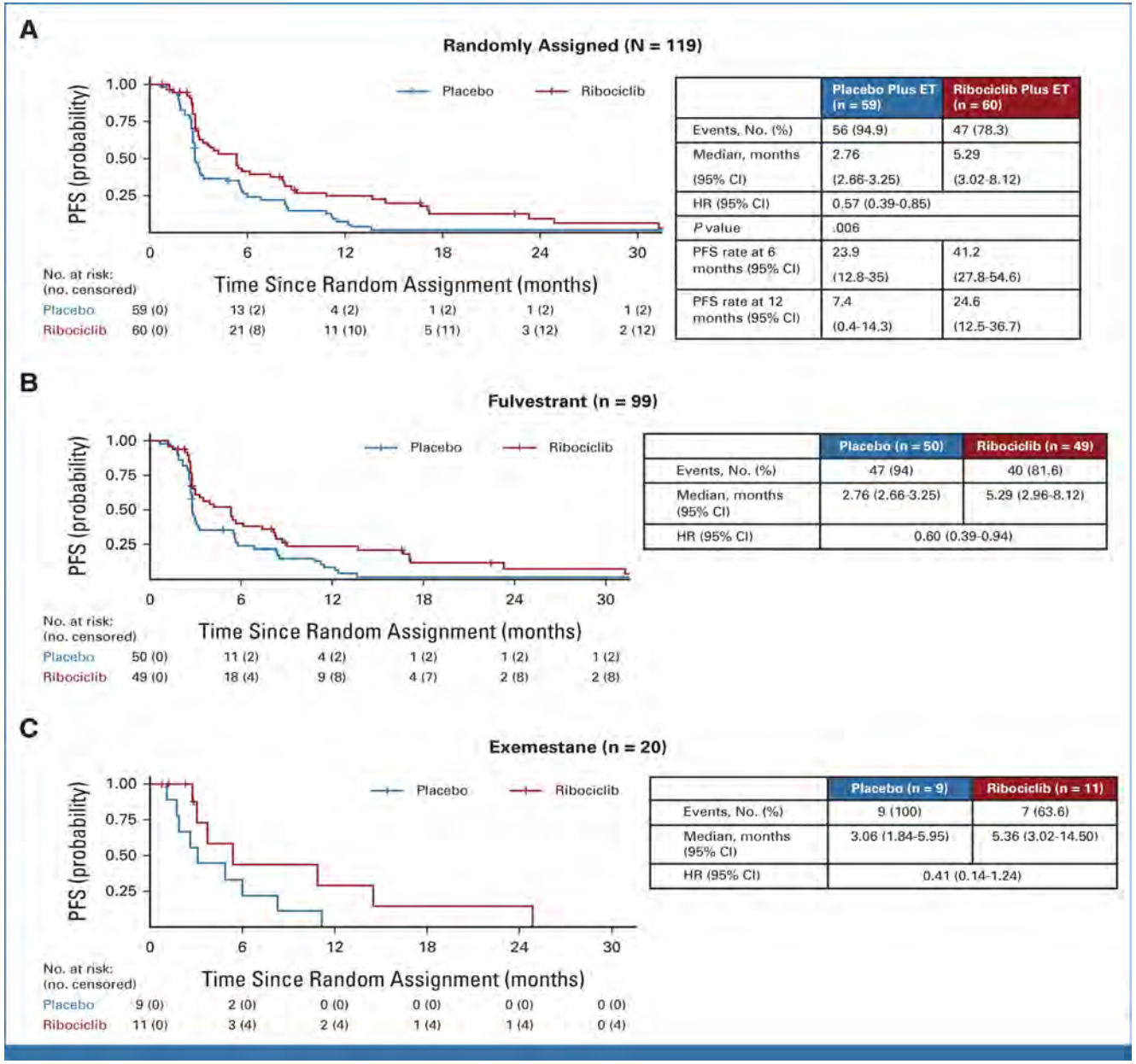
170 screened, 119 randomized
9 remain on rx, 1=placebo and 8=ribociclib
99 received fulvestrant
20 received exemestane

- Investigator initiated trial, 13 US sites
- Primary endpoint PFS, scans q 12 wks
- Median FU 18.2 mo
- 54 v 35% de novo MBC
- Visceral mets ~60%
- 12 v 7% chemo for MBC
- 10 v 2% intervening Rx post CDK4/6i
- 64 v 70% prior CDK4/6i>12 months

Non-approved medication information in Japan is contained in this slide.

Kalinsky et al, JCO 2023

MAINTAIN TRIAL

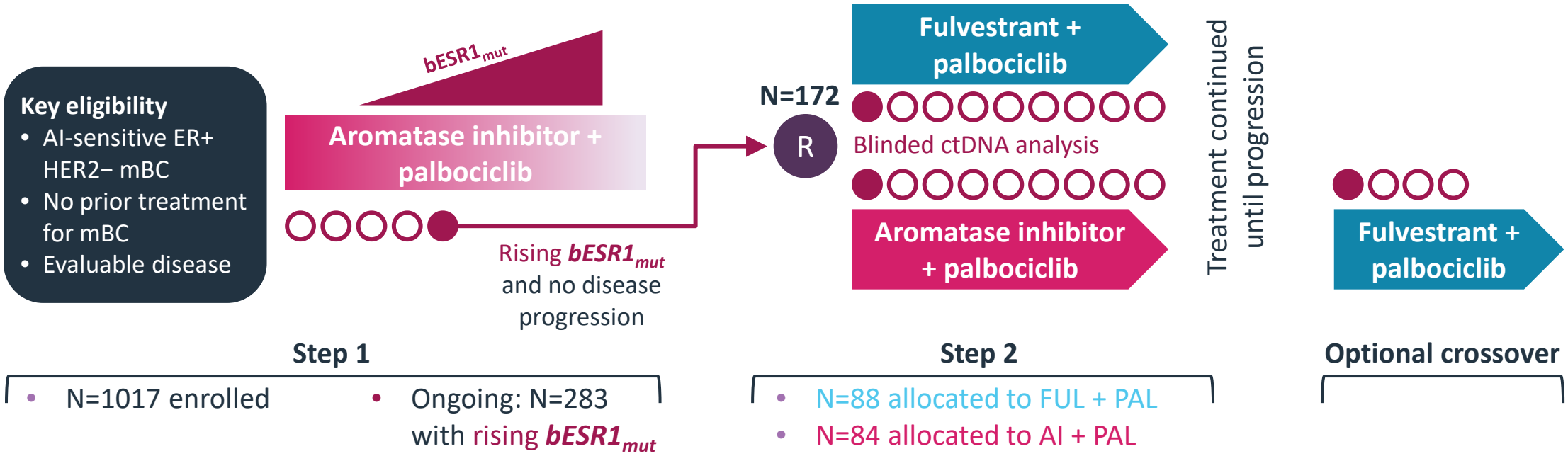


Published in: Kevin Kalinsky DOI: 10.1200/JCO.22.02392

Non-approved medication information in Japan is contained in this slide.

PADA-1: Characterization of *ESR1* mutations with aromatase inhibitor or fulvestrant + palbociclib therapy

PADA-1 strategy: Target rising $bESR1_{mut}$ when they become detectable during first-line AI + palbociclib treatment

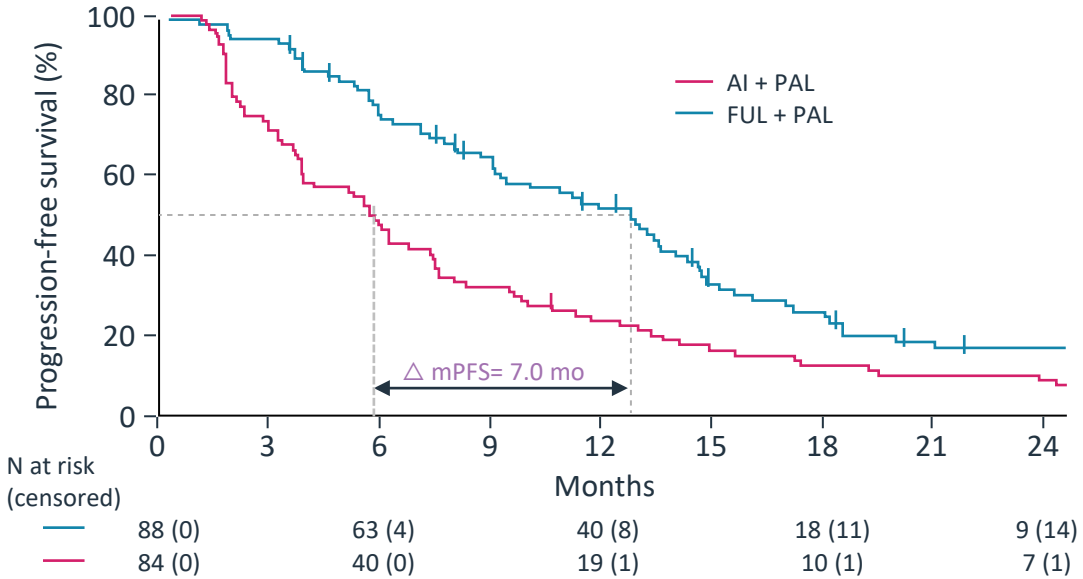


Bidard FC, et al. ASCO 2023. Abstract 1002

PADA-1: Updated PFS results

Updated PFS results (primary endpoint)

Data cutoff June 2022: Median F/U 28.2 mo; N=152 PFS events



	ASCO 2023 analysis		2021 analysis[1]	
	FUL + PAL	AI + PAL	FUL + PAL	AI + PAL
mPFS, mo (95% CI)	12.8 (9.3–14.7)	5.8 (3.9–7.5)	11.9	5.7
HR (95% CI)	0.54 (0.38–0.75)		0.61	
Optional crossover (n=49) mPFS (95% CI)	3.5 (2.4–5.4)			

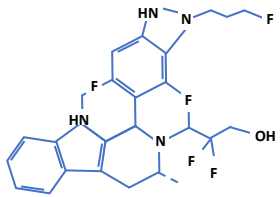
1. Bidard, et al. Lancet Oncol 2022

Bidard FC, et al. ASCO 2023. Abstract 1002

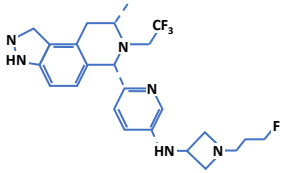
A number of next-generation oral SERDs are being developed to address the unmet needs in HR+ BC

Oral SERDs under investigation in Phase III trials[1–6]

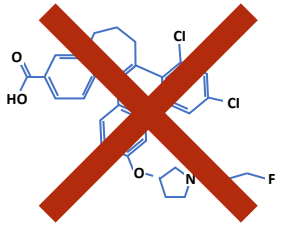
Giredestrant



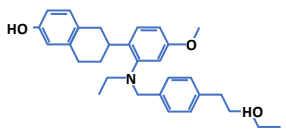
Camizestrant



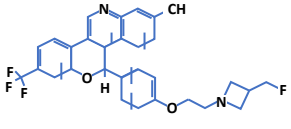
Amcenestrant (discontinued)*



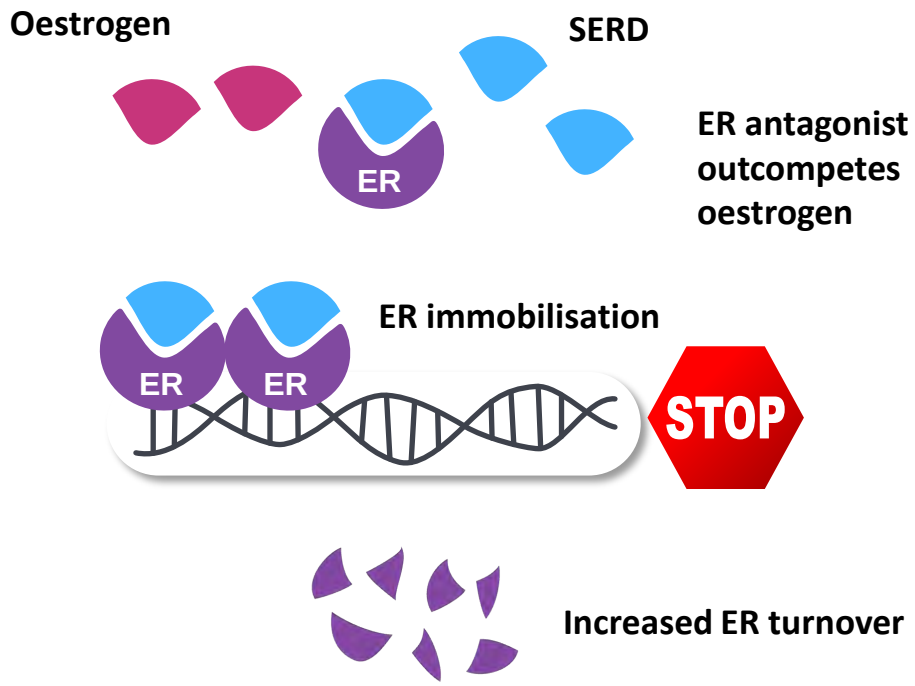
Elacestrant



Imlunestrant



Mechanism of action[8]



SERDs are capable of full suppression of ligand-dependent and ligand-independent (*ESR1*-mutant) ER activity

* Sanofi announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[7]

BC, breast cancer; ER, oestrogen receptor; HR, hormone receptor; SERD, selective oestrogen receptor degrader.

1. https://clinicaltrials.gov/ct2/show/NCT04546009 (accessed July 2022); 2. https://clinicaltrials.gov/ct2/show/NCT04478266 (accessed July 2022);
3. https://clinicaltrials.gov/ct2/show/NCT04711252 (accessed July 2022); 4. https://clinicaltrials.gov/ct2/show/NCT04964934 (accessed July 2022);
5. https://clinicaltrials.gov/ct2/show/NCT03778931 (accessed July 2022); 6. https://clinicaltrials.gov/ct2/show/NCT04975308 (accessed July 2022); 7. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022); 8. Guan J, *et al. Cell* 2019.

Oral SERD Trial Landscape in Pretreated mBC

	EMERALD	SERENA-2	EMBER-3	AMEERA-3	acelERA
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant +/-** abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

Non-approved medication information in Japan is contained in this slide.

- AI, aromatase inhibitor.

Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

Next-generation oral SERDS are being evaluated in patients with HR+, HER2– mBC

	acelERA BC[1,2] (Phase II; N = 303)	AMEERA-3*[,3,4] (Phase II; N = 290)	EMERALD[5,6] (Phase III; N = 477)
Oral SERD	Giredestrant 30 mg PO qd	Amcenestrant 400 mg PO qd	Elacestrant 400 mg PO qd
Comparator arm	Fulvestrant or AI	Fulvestrant, AI or tamoxifen	Fulvestrant or AI
Prior treatment for mBC	1–2 lines of systemic therapy (1 line of ET; ≤1 targeted therapy/CT)	0–2 lines of ET; ≥80%with prior CDK4/6i; ≤1 targeted therapy/CT	1–2 lines of ET (one of which in combination with a CDK4/6i)
Patients	Males and pre-/peri-/post-menopausal females	Males and pre-/peri-/post-menopausal females	Males and postmenopausal females
	39% with *ESR1* mutations†	43% with *ESR1* mutations‡	48% with *ESR1* mutations (47% planned per protocol§)
Primary endpoint(s)	PFS (all patients)		PFS (all patients; *ESR1*mut population)

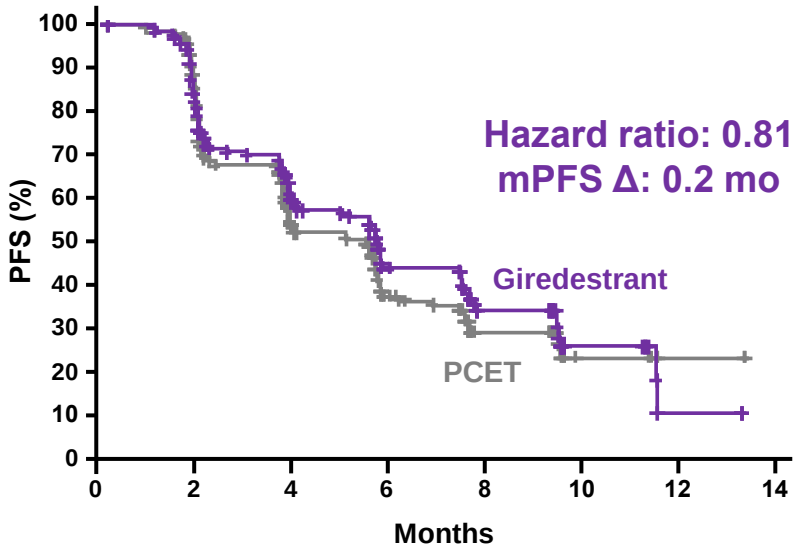
* Sanofi announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[7]
† 232 patients with *ESR1* status known.[2]
‡ 280 patients with *ESR1* status known.[4]
§ This represents an enriched proportion of patients with *ESR1* mutations; within this population, 20–40% would be expected to have *ESR1* mutations.[8]
AI, aromatase inhibitor; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ET, endocrine therapy; HR, hormone receptor; mBC, metastatic breast cancer; PFS, progression-free survival; PO, orally; qd, once daily; SERD, selective oestrogen receptor degrader.

Non-approved medication information in Japan is contained in this slide.

1. https://clinicaltrials.gov/ct2/show/NCT04576455 (accessed July 2022); 2. Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation); 3. https://clinicaltrials.gov/ct2/show/NCT04059484 (accessed July 2022); 4. Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation); 5. https://clinicaltrials.gov/ct2/show/NCT03778931 (accessed July 2022); 6. Bidard F-C, *et al. J Clin Oncol* 2022; 7. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022); 8. Brett JO, *et al. Breast Cancer Res* 2021.

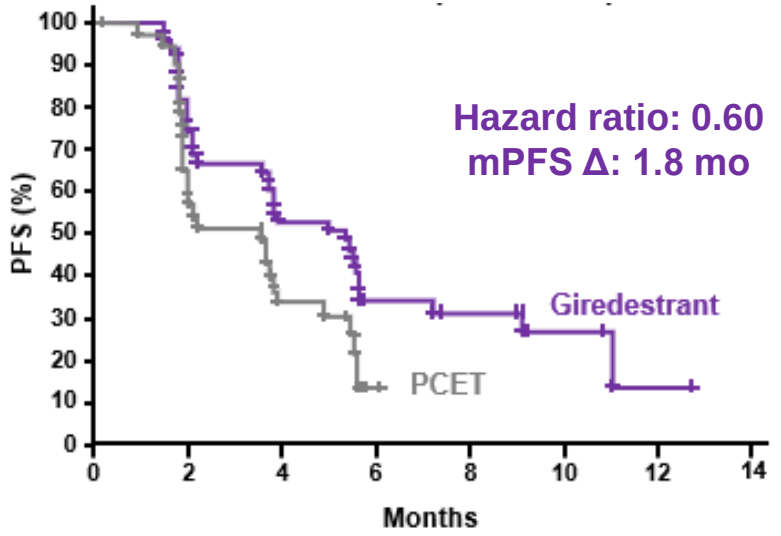
acelERA BC: Giredestrant

1° EP: PFS (ITT)



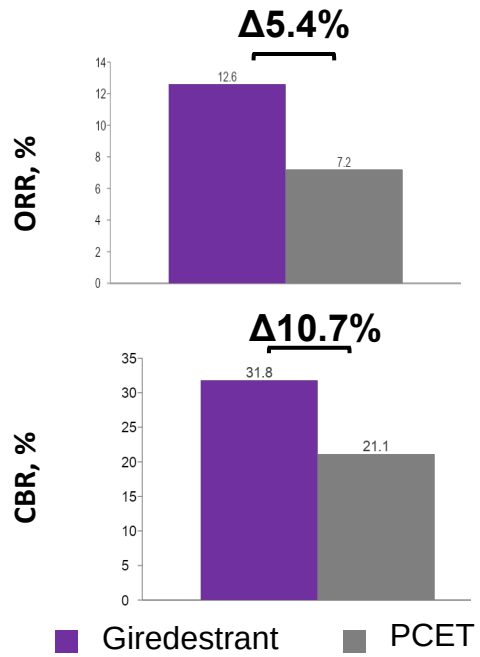
	Giredestrant (n = 151)	PCET (n = 152)
95% CI for hazard ratio	0.60, 1.10	
P value	0.176	
mPFS, mo	5.6	5.4

2° EP: PFS (*ESR1*mut)



	Giredestrant (n = 51)	PCET (n = 39)
95% CI for hazard ratio	0.35, 1.03	
P value	0.0610	
mPFS, mo	5.3	3.5

2° EP: ORR and CBR*



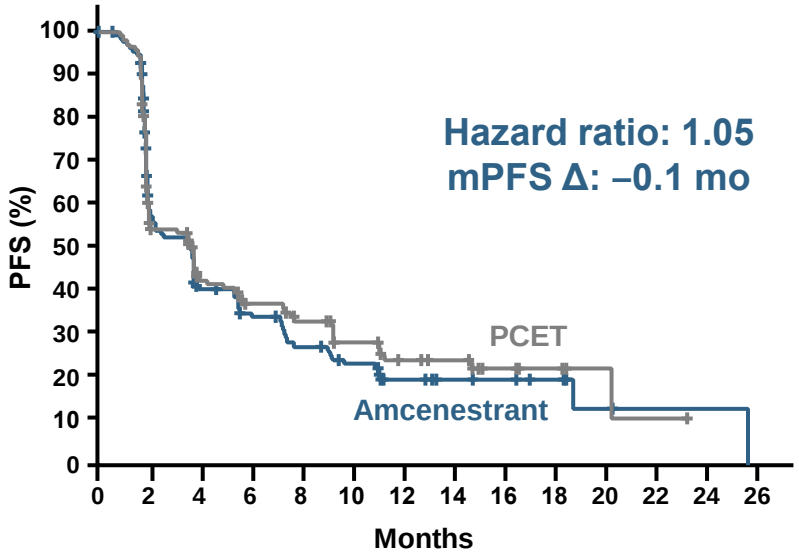
- **PFS data in subgroups were generally consistent with the ITT population**
- **Mature OS data not yet available**

Non-approved medication information in Japan is contained in this slide.

* CBR included all patients with confirmed PR/CR or SD of ≥6 months as determined by the investigator per Response Evaluation Criteria in Solid Tumors v1.1.
1°, primary; BC, breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependant kinase 4/6 inhibitor; CI, confidence interval; CR, complete response; EP, endpoint; HR, hormone receptor; ITT, intention-to-treat; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; PR, partial response; SD, stable disease; SERD, selective oestrogen receptor degrader.
Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation).

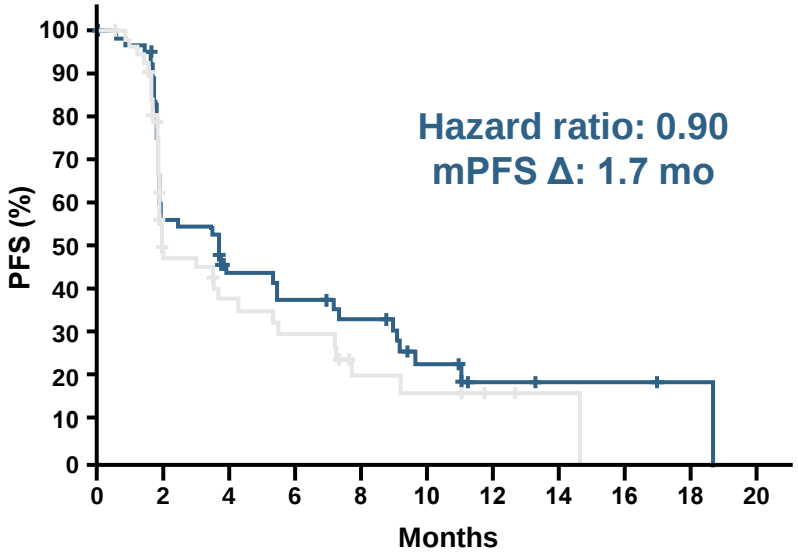
Amcenestrant: AMEERA 3

1° EP: PFS (ITT)



	Amcenestrant (n = 143)	PCET (n = 147)
95% CI for hazard ratio	0.79, 1.40	
P value	0.644	
mPFS, mo	3.6	3.7

2° EP: PFS (*ESR1*mut)



	Amcenestrant (n = 65)	PCET (n = 55)
95% CI for hazard ratio	0.565, 1.435	
mPFS, mo	3.7	2.0

ORR and CBR not reported for AMEERA-3

- **PFS data in subgroups were generally consistent with the ITT population**
- **Mature OS data not yet available**

Non-approved medication information in Japan is contained in this slide.

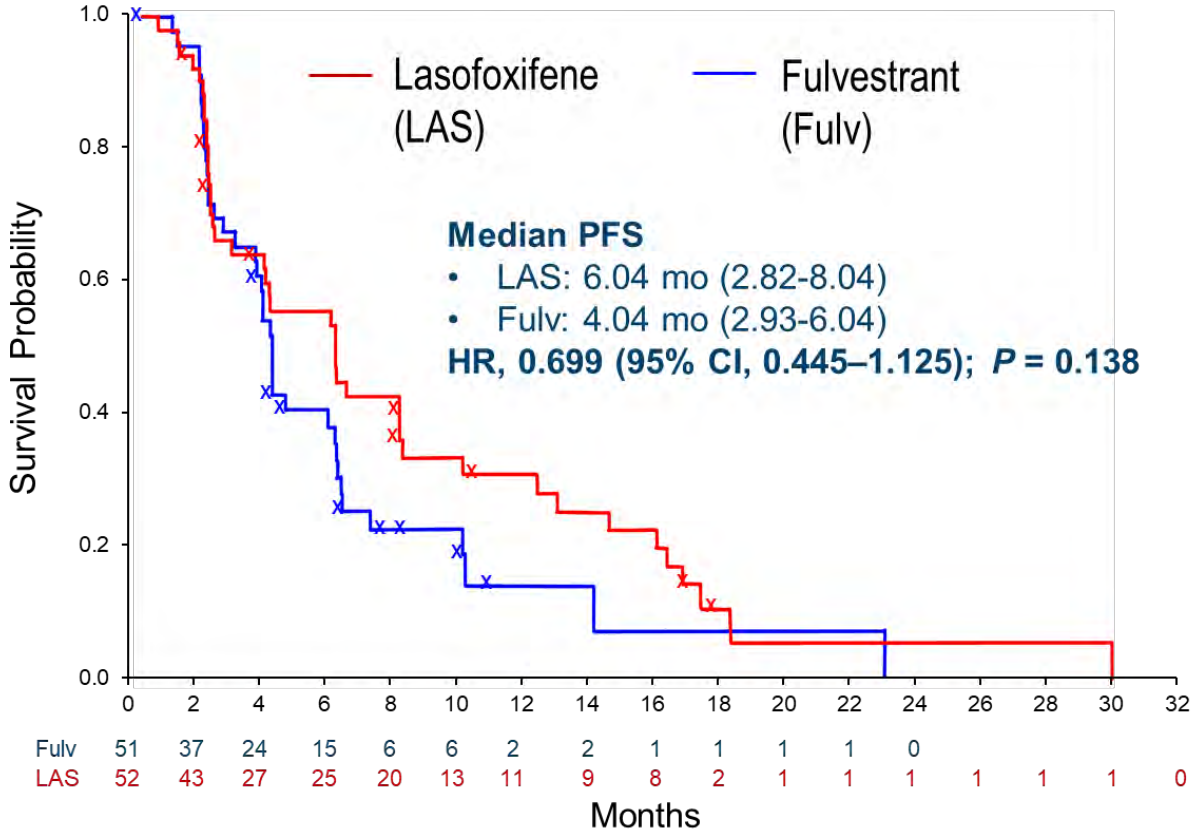
* Sanofi announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[2]

1°, primary; BC, breast cancer; CI, confidence interval; EP, endpoint; HR, hormone receptor; ITT, intention-to-treat; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation. 2. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022).

ELAINE-1: Lasofoxifene vs Fulvestrant in ER+/HER2- LA/MBC with *ESR1* Mutation and Disease Progression on AI and CDK4/6i

Primary Endpoint: PFS



Maximum Tumor Response

- ORR for LAS vs Fulv was 13.2% vs 2.9% (*P* = .12)
- CBR (≥24 weeks) for LAS vs Fulv was 36.5% vs 21.6% (*P* = .12)

Exploratory ctDNA Analyses

- 61 patients' *ESR1*-mutant allele fraction (MAF) assessed
- LAS median relative change ↓ 87.1% vs Fulv ↓ 14.7%

Safety

- Most AEs were Grade 1/2
- Most common TAES: nausea, fatigue, arthralgia, hot flush
- No thrombotic events occurred

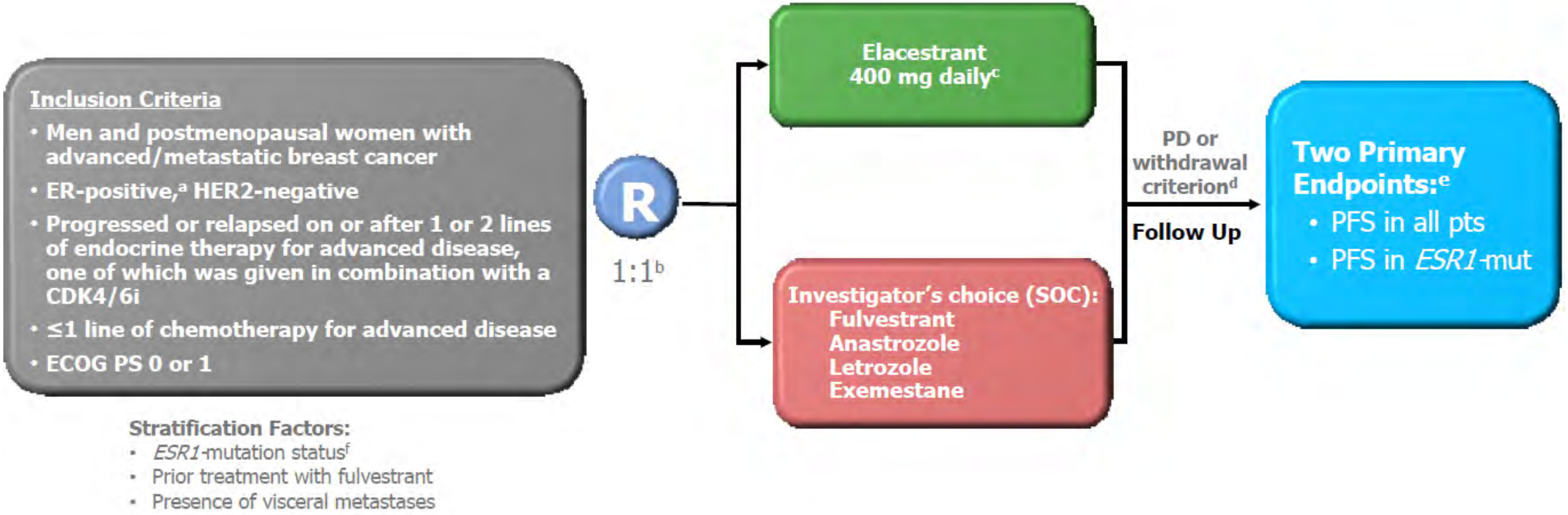
Non-approved medication information in Japan is contained in this slide.

Goetz MP et al. ESMO 2022. Abstract LBA20.

Elacestrant vs Endocrine Therapy in ER+/HER2− mBC *EMERALD*

- **EMERALD is a phase 3 trial of elacestrant vs SOC ET in patients with ER+/HER2− mBC**

Updated results by duration of prior CDK4/6 inhibitor therapy in the metastatic setting



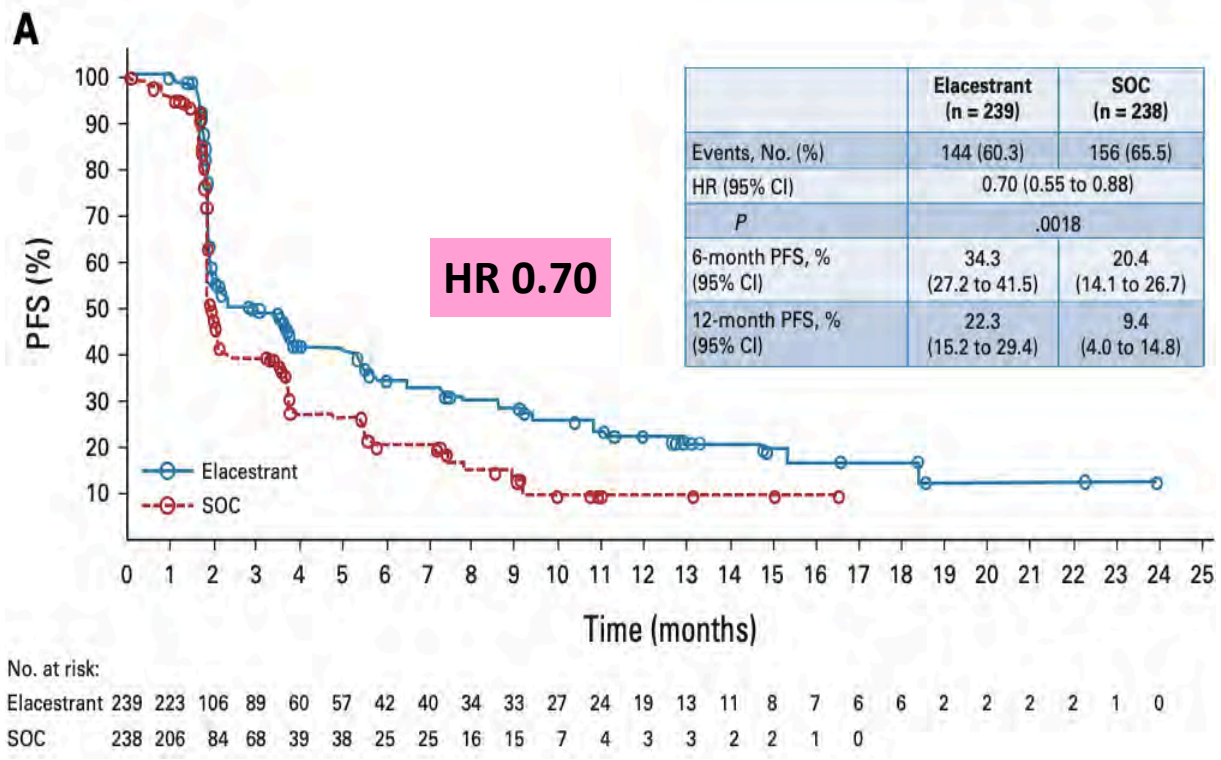
Non-approved medication information in Japan is contained in this slide.

- ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; SOC, standard of care.

Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

EMERALD PRIMARY ENDPOINT: PFS

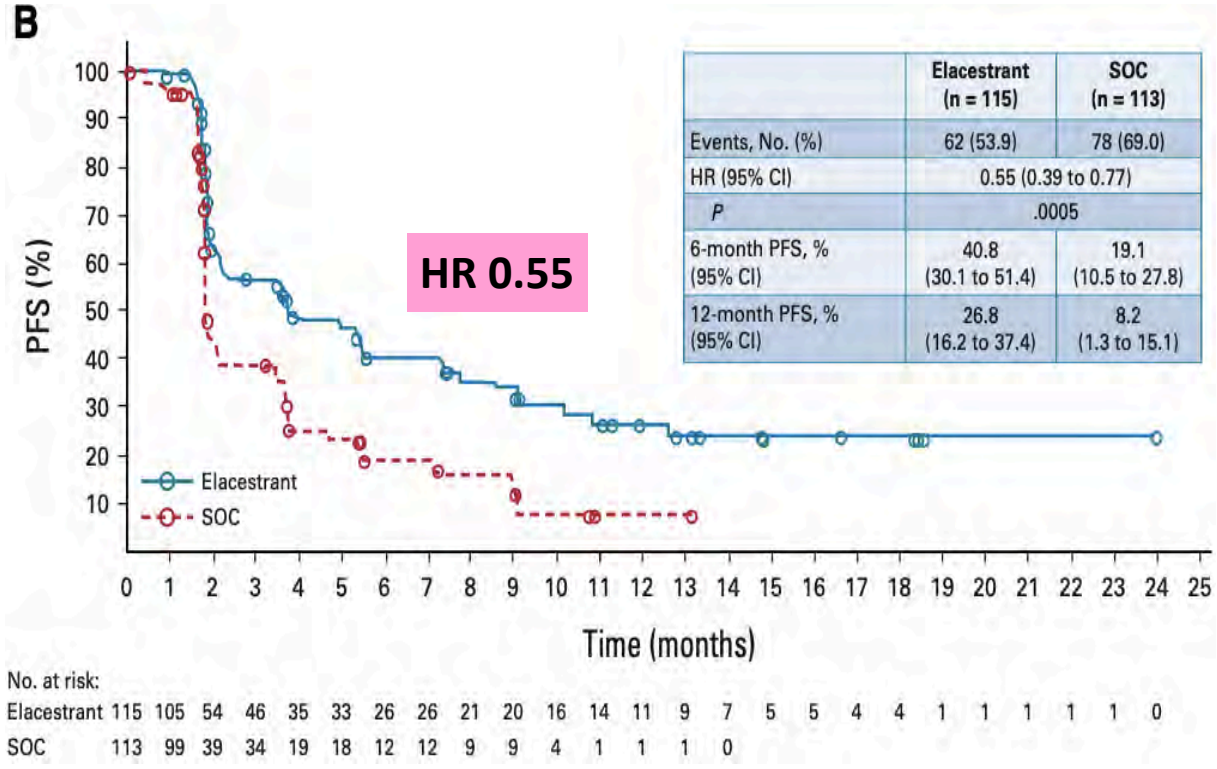
All patients (ITT)



HR 0.70

	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)

Patients with ESR1mut



HR 0.55

	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)

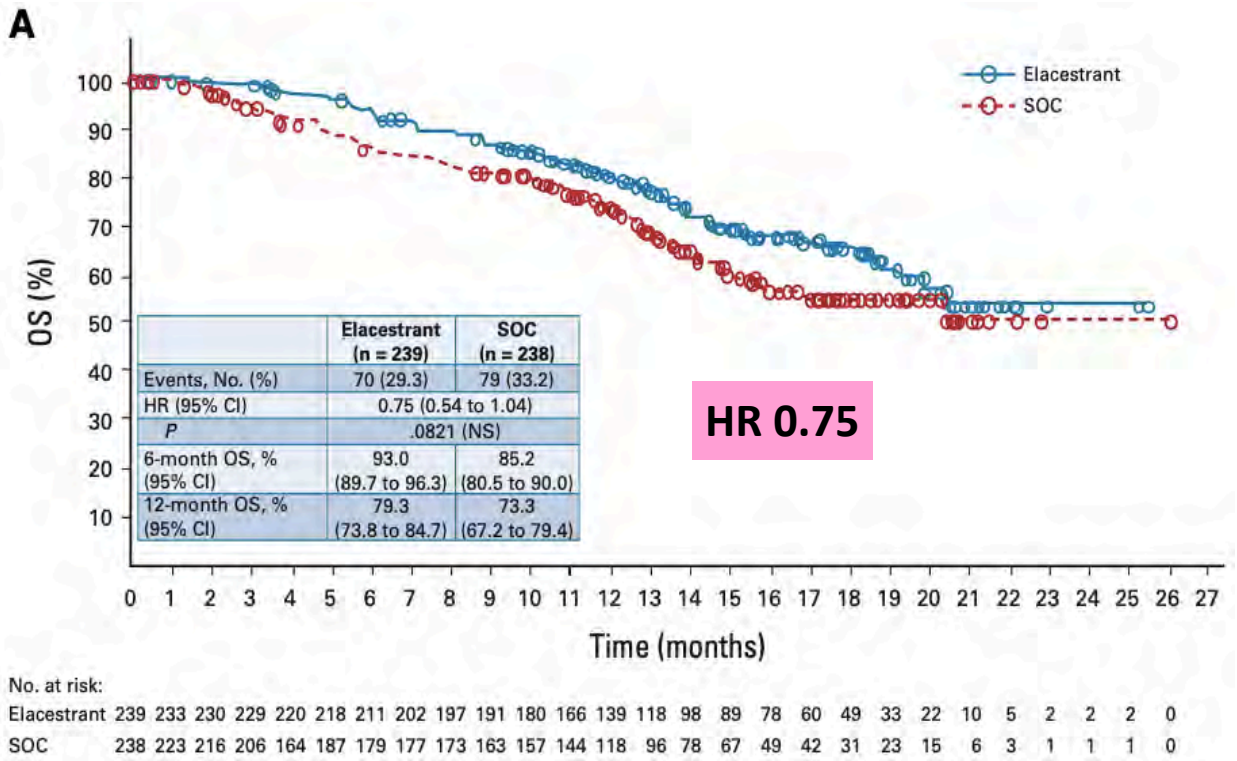
Non-approved medication information in Japan is contained in this slide.

Elacestrant demonstrated a significant improvement vs. SOC

Bidard FC et al. *J Clin Oncol* 2022;40(28):3246-3256.

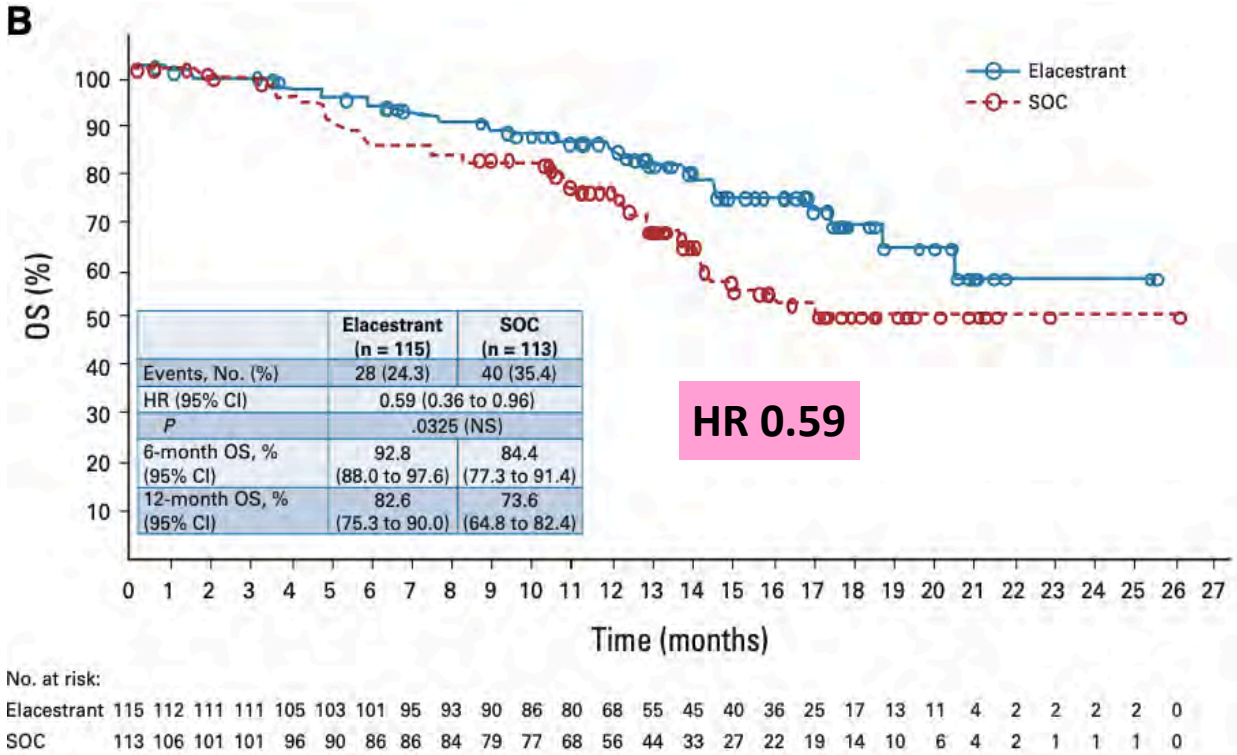
EMERALD: OS (INTERIM ANALYSIS)

All patients (ITT)



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	70 (29.3)	79 (33.2)
HR (95% CI)	0.75 (0.54 to 1.04)	
P	.0821 (NS)	
6-month OS, % (95% CI)	93.0 (89.7 to 96.3)	85.2 (80.5 to 90.0)
12-month OS, % (95% CI)	79.3 (73.8 to 84.7)	73.3 (67.2 to 79.4)

Patients with ESR1mut



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	28 (24.3)	40 (35.4)
HR (95% CI)	0.59 (0.36 to 0.96)	
P	.0325 (NS)	
6-month OS, % (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS, % (95% CI)	82.6 (75.3 to 90.0)	73.6 (64.8 to 82.4)

- While no statistically significant differences were noted at the α=0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups. Final analysis with mature data is expected to take place in late 2022/early 2023.

Non-approved medication information in Japan is contained in this slide.

Bidard FC et al. *J Clin Oncol* 2022;40(28):3246-3256.

EMERALD: Elacestrant

PFS by Duration of CDK4/6i in All Patients

	Duration on CDK4/6i in the metastatic setting					
	At Least 6 Months (87.5%)		At Least 12 Months (66.7%)		At Least 18 Months (46.7%)	
	Elacestrant (n=202)	SOC Hormonal Therapy (n=205)	Elacestrant (n=150)	SOC Hormonal Therapy (n=160)	Elacestrant (n=98)	SOC Hormonal Therapy (n=119)
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months, % (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months, % (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

- Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

Non-approved medication information in Japan is contained in this slide.

EMERALD: Elacestrant
PFS by Duration of CDK4/6i in ESR-1 mutant population

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)		At Least 18 Months (50.0%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

- Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

Non-approved medication information in Japan is contained in this slide.

EMERALD: Elacestrant
Safety

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

AEs:

- Most AEs were grade 1 or 2
- Low-grade nausea was common in both treatment arms
- No grade 4 TRAEs

Treatment discontinuation:

- Elacestrant: 3.4%
- SOC: 0.9%

- No hematologic safety signal was observed
- No incidence of bradycardia

- Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

Non-approved medication information in Japan is contained in this slide.

THERAPEUTIC ALGORITHM IN HR+/HER2- MBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Breast Cancer

NCCN Guidelines Index
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Discussion

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[x]	*ESR1* mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[y] Entrectinib[y]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[z,aa] Dostarlimab-gxly[bb]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[z,aa]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[cc]	Category 2A	

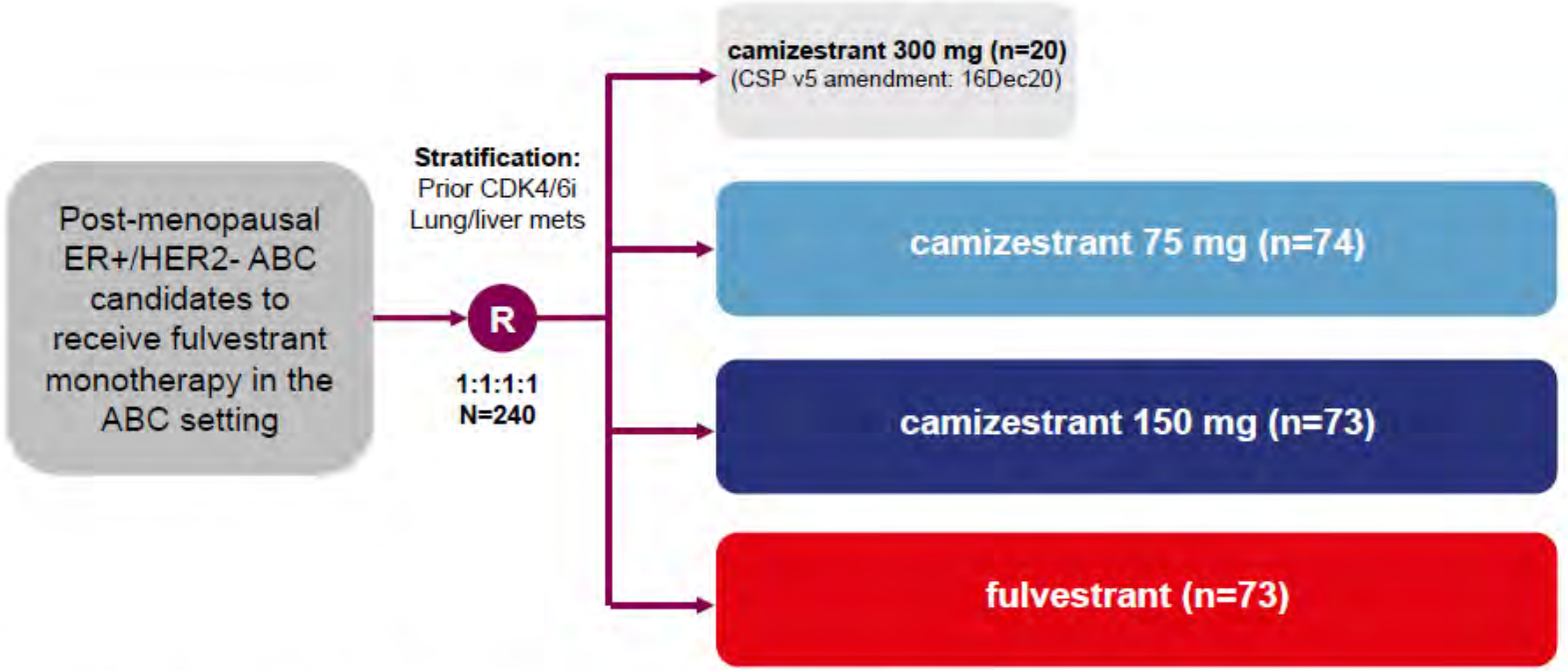
Non-approved medication information in Japan is contained in this slide.

Camizestrant Postmenopausal ER+/HER2− mBC: *SERENA-2*

- **SERENA-2 is a phase 2 study of camizestrant vs fulvestrant in postmenopausal advanced ER+/HER2− breast cancer**

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



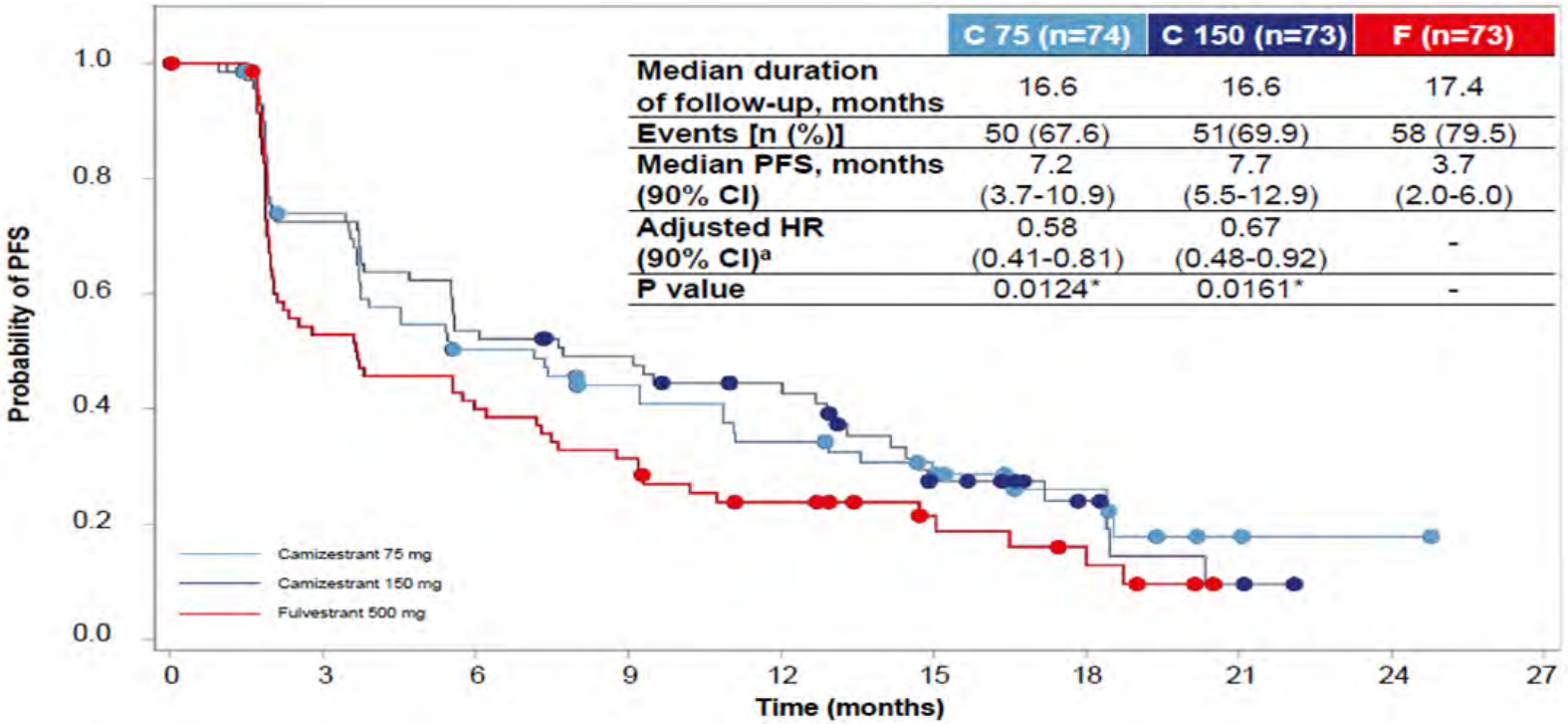
- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

- ABC, advanced breast cancer; CT, chemotherapy; SERD, selective estrogen receptor degrader.
*Disease progression assessed by the investigator and defined using RECIST, version 1.1
Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-02.

Non-approved medication information in Japan is contained in this slide.

SERENA-2: Camizestrant: *PFS*

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*	-

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		

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

Camizestrant at both 75 and 150 mg doses improves PFS over fulvestrant in postmenopausal women with ER+/HER2− ABC

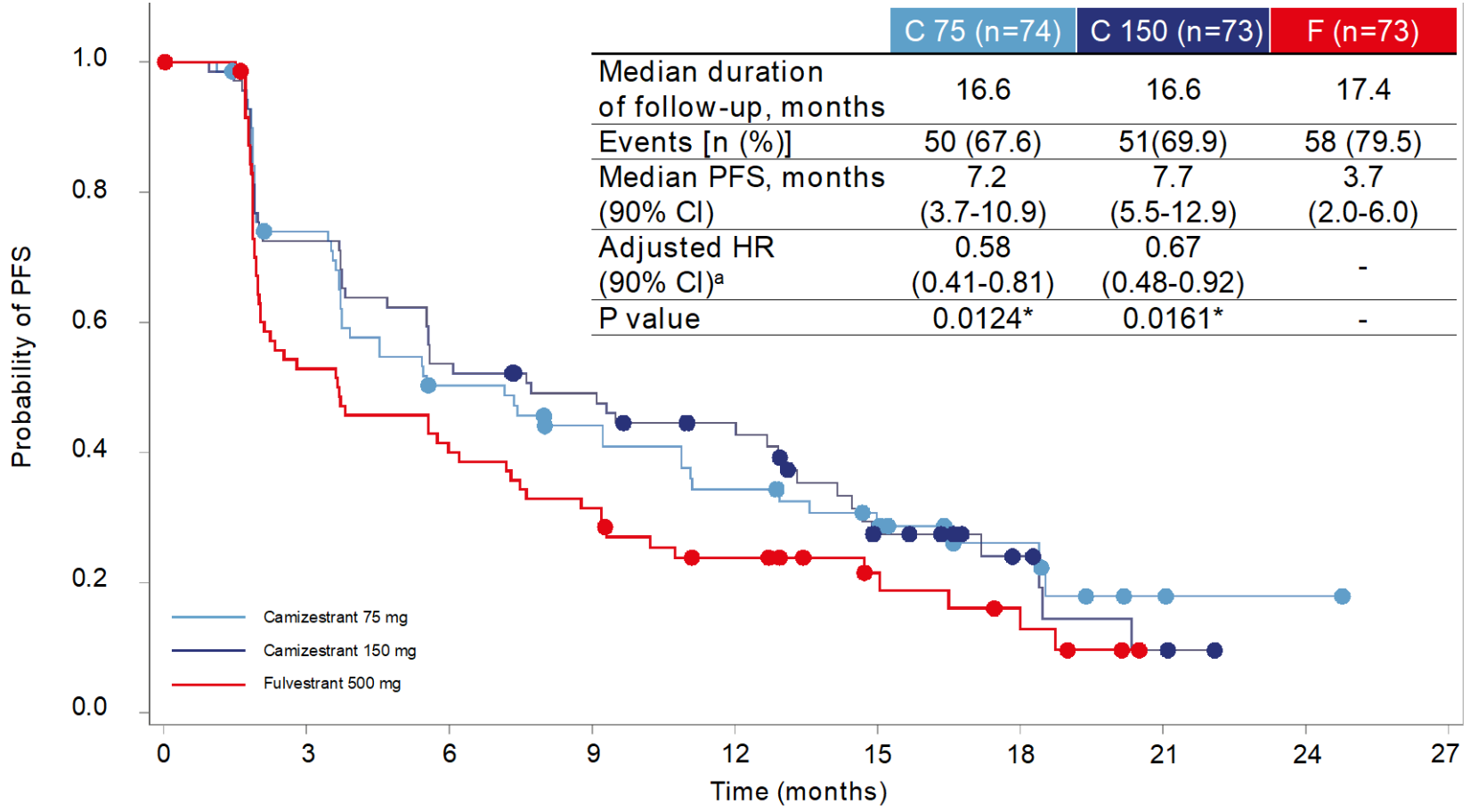
- PFS by IA:
  - Cam 75 mg: 7.2 months; hazard ratio 0.58
  - Cam 150 mg: 7.7 months; hazard ratio 0.67
  - Fulvestrant: 3.7 months
- *PFS by BICR: consistent with PFS by IA*

- BICR, blinded independent central review; Cam, camizestrant; IA, investigator assessment.

Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-02.

Non-approved medication information in Japan is contained in this slide.

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT



	C 75 (n=74)	C 150 (n=73)	F (n=73)
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P value	0.0124*	0.0161*	-

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		

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

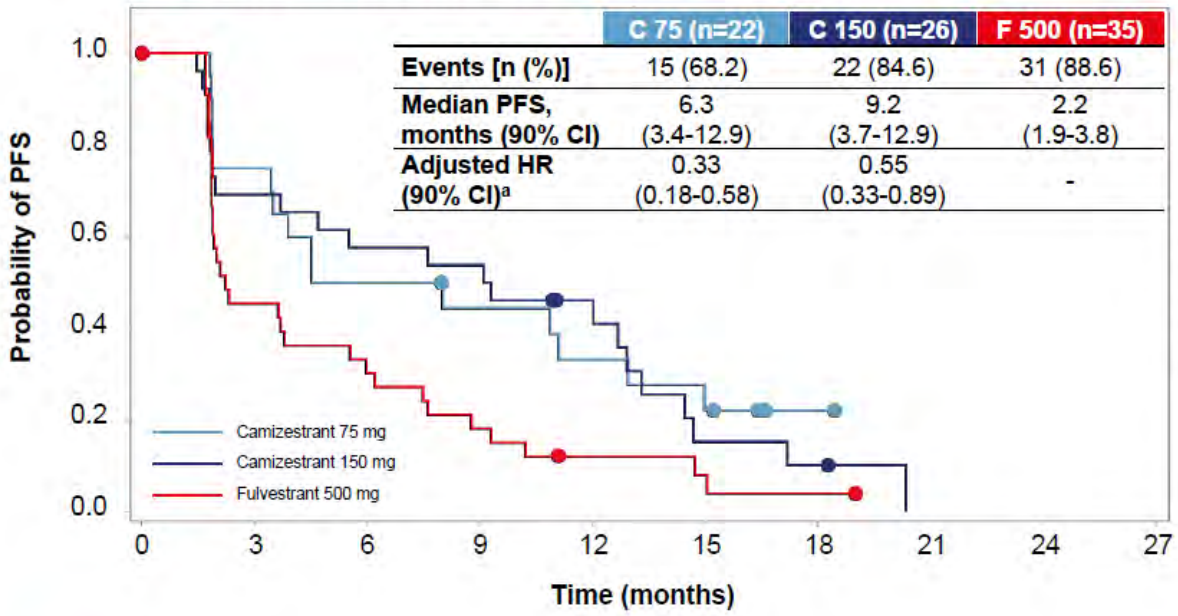
CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

Olivera M et al. SABCS 2022.

Non-approved medication information in Japan is contained in this slide.

PFS BY DETECTABLE ESR1m

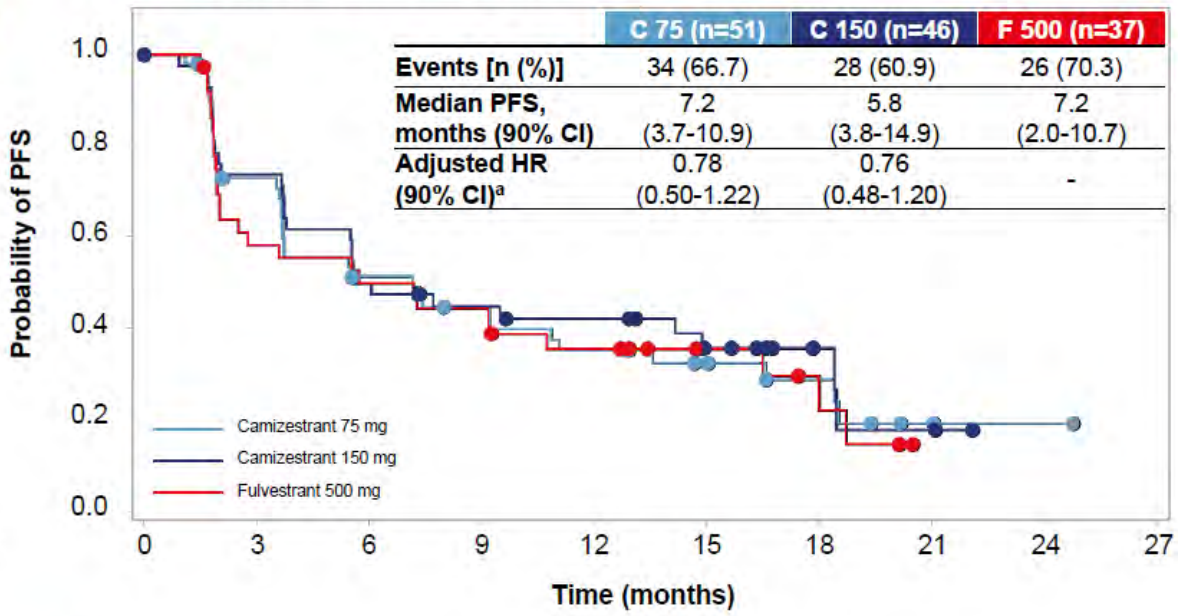
*ESR1*m detectable at baseline



	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)	-

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)	-

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	

Olivera M et al. SABCS 2022.

Non-approved medication information in Japan is contained in this slide.

SERENA-2: Camizestrant
ORR and CBR

Group	n	Number (%) of patients with response	Adjusted response rate (%)	Comparison against fulvestrant		
				Odds ratio	90% CI	2-sided p-value
ORR						
Camizestrant 75 mg	70	11 (15.7)	15.7	1.43	0.63-3.33	0.4789
Camizestrant 150 mg	65	13 (20.0)	20.3	1.96	0.88-4.51	0.1675
Fulvestrant	68	8 (11.8)	11.5			
CBR24						
Camizestrant 75 mg	74	35 (47.3)	48.8	1.48	0.84-2.64	0.2554
Camizestrant 150 mg	73	36 (49.3)	51.0	1.62	0.91-2.89	0.1658
Fulvestrant	73	28 (38.4)	39.1			

- Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-02. Non-approved medication information in Japan is contained in this slide.

SERENA-2: Camizestrant
Safety

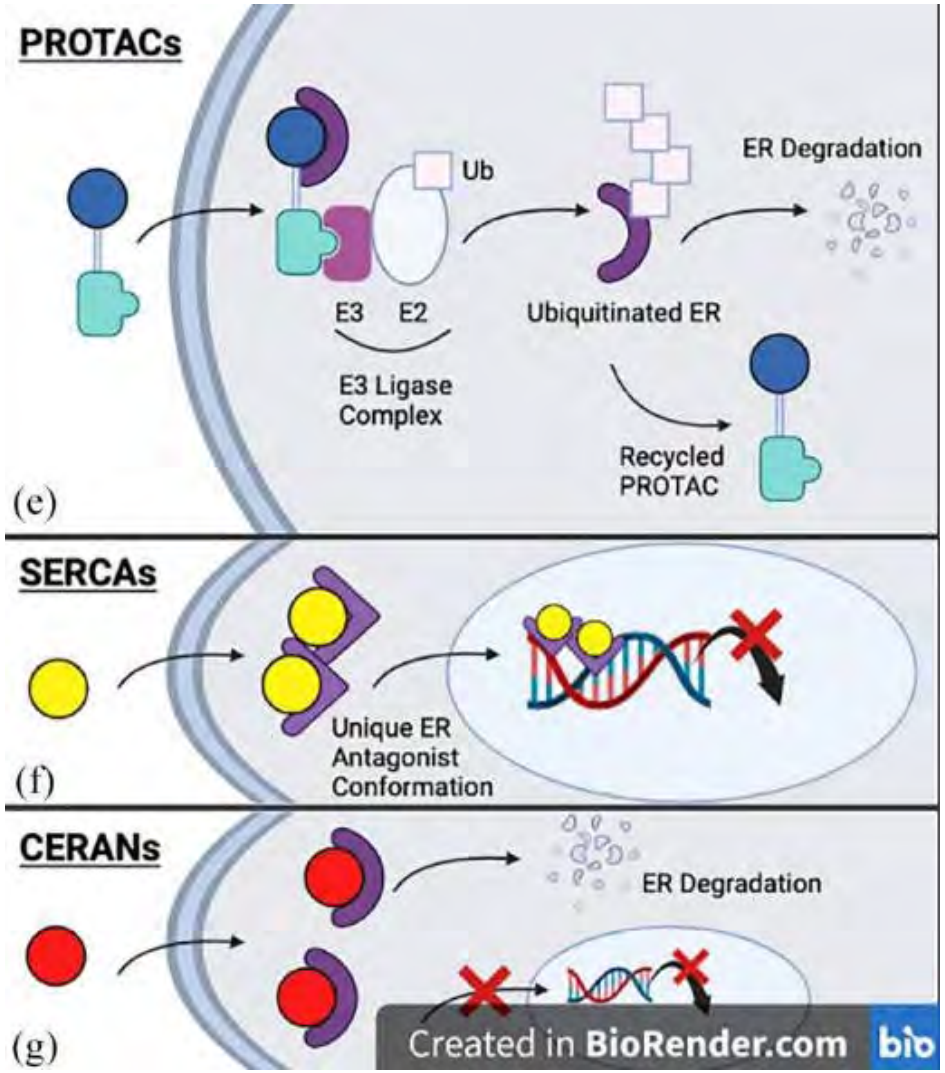
AE, n (%)	C 75 (n=74)		C 150 (n=73)		C 300 (n=20)		F 500 (n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	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

- ALT, alanine transaminase.

Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-02.

Non-approved medication information in Japan is contained in this slide.

NOVEL ENDOCRINE THERAPIES



Lloyd MR et al. *Ther Adv Med Oncol* 2022;14:17588359221113694.

ARV-471 in ER+/HER2- Advanced BC
VERITAC

- **First-in-human, open-label, 3-part study of ARV-471 alone or in combination with palbociclib in patients with ER+/HER2 locally advanced/metastatic BC**

Phase 1 dose escalation (Part A)	Phase 2 cohort expansion (Part B; VERITAC)	Phase 1b combination (Part C)
Treatment • ARV-471 orally	**Treatment** • ARV-471 orally	**Treatment** • ARV-471 plus palbociclib orally
Primary objective • Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds	**Primary objective** • Assess the antitumor activity of ARV-471	**Primary objective** • Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D of the combination

- BC, breast cancer; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Hurvitz SA, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-03.

Non-approved medication information in Japan is contained in this slide.

ARV-471 in ER+/HER2– Advanced BC
VERITAC Phase 2 Expansion

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 (n=35)

ARV-471 500 mg orally QD (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

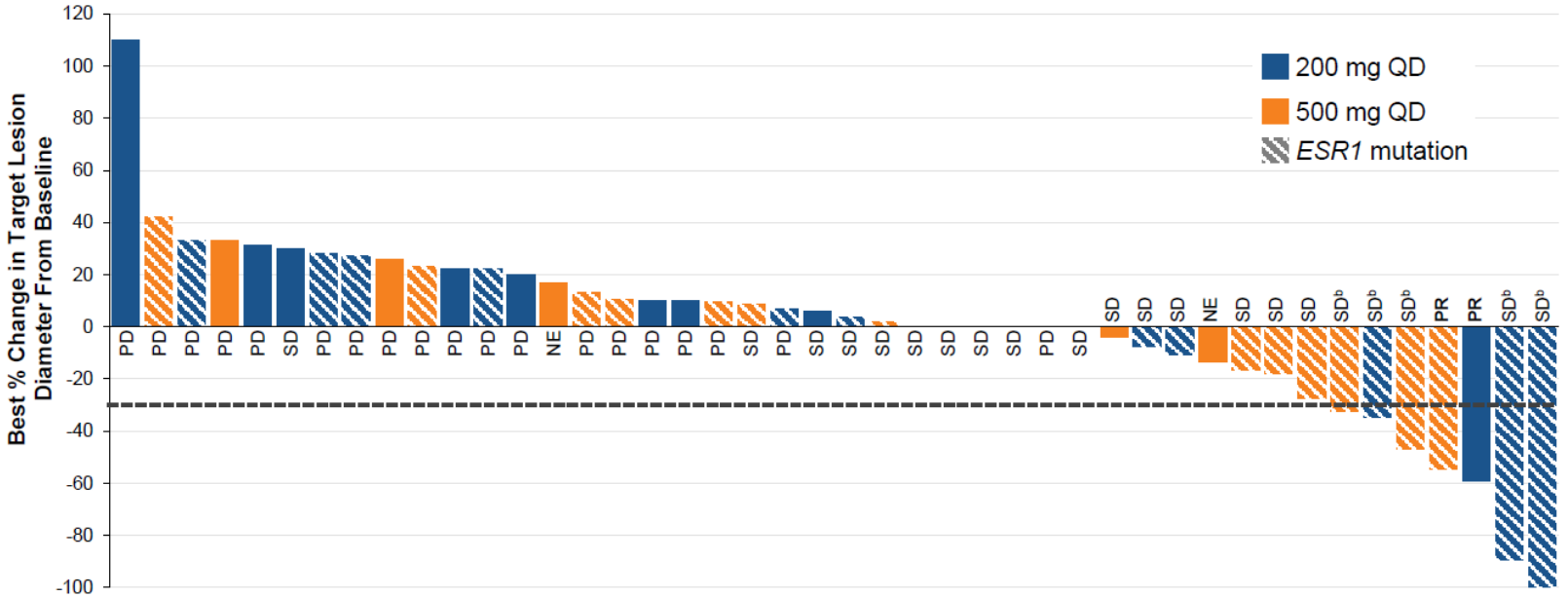
- CR, complete response; DOR, duration of response; PK, pharmacokinetic; PR, partial response; QD, once daily.

Hurvitz SA, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-03.

Non-approved medication information in Japan is contained in this slide.

VERITAC: ARV-471
Response

	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	22	41
CBR, % (95% CI)	47.4 (24.4, 71.1)	54.5 (32.2, 75.6)	51.2 (35.1, 67.1)



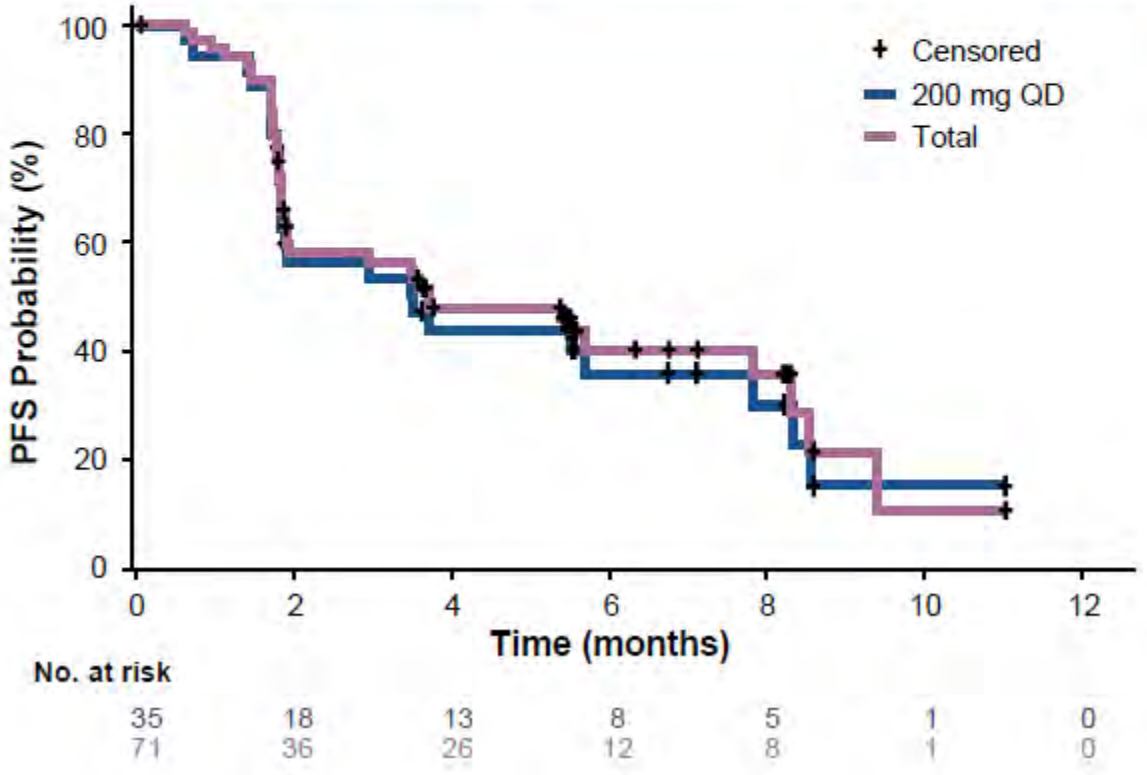
- NE, not evaluable due to missing data for best overall response.

Hurvitz SA, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-03.

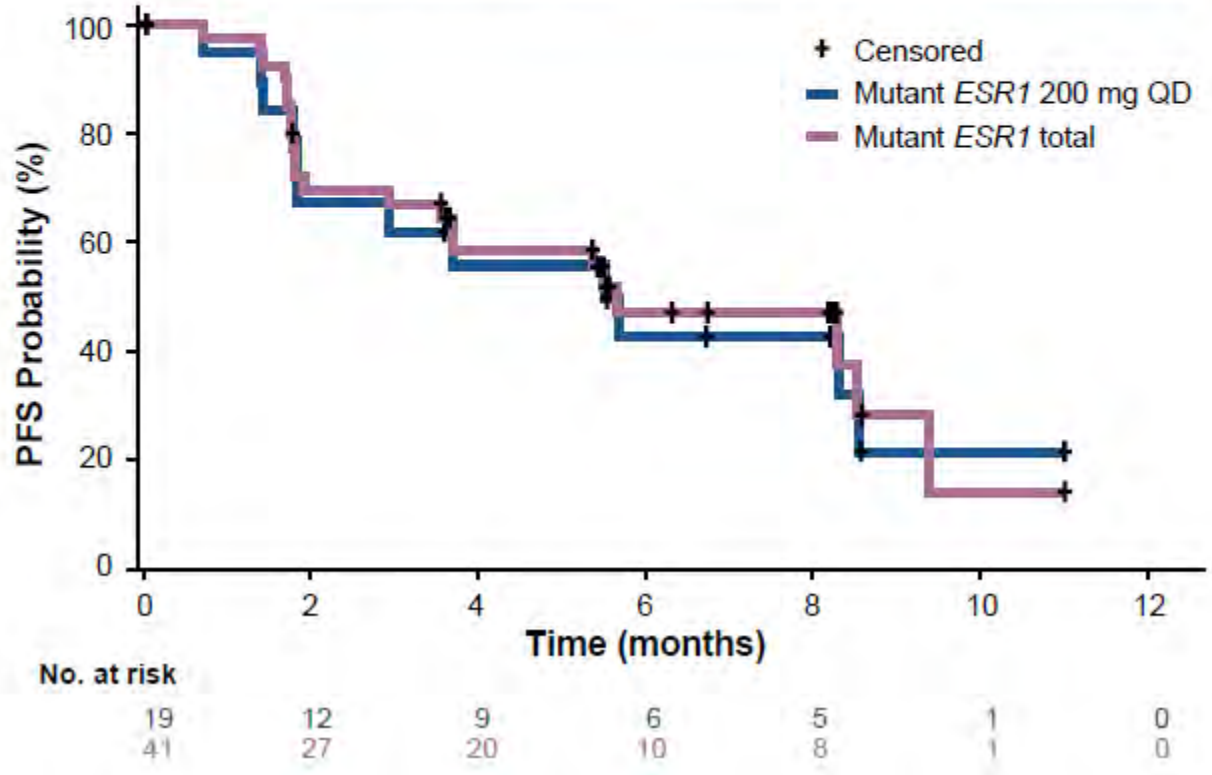
Non-approved medication information in Japan is contained in this slide.

VERITAC: ARV-471
PFS

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)



	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



- mPFS, median progression-free survival.

Hurvitz SA, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-03.

Non-approved medication information in Japan is contained in this slide.

VERITAC: ARV-471
Safety

	200 mg QD (n = 35)			500 mg QD (n = 36)			Total (N = 71)		
n (%), ≥ 10%	Grade 1	Grade 2	Grade 3/4	Grade 1	Grade 2	Grade 3/4	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

- Most AEs were grade 1/2
- Grade ≥ 3 in 22.5% of patients
- ARV-471 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy, favorable tolerability, and robust ER degradation

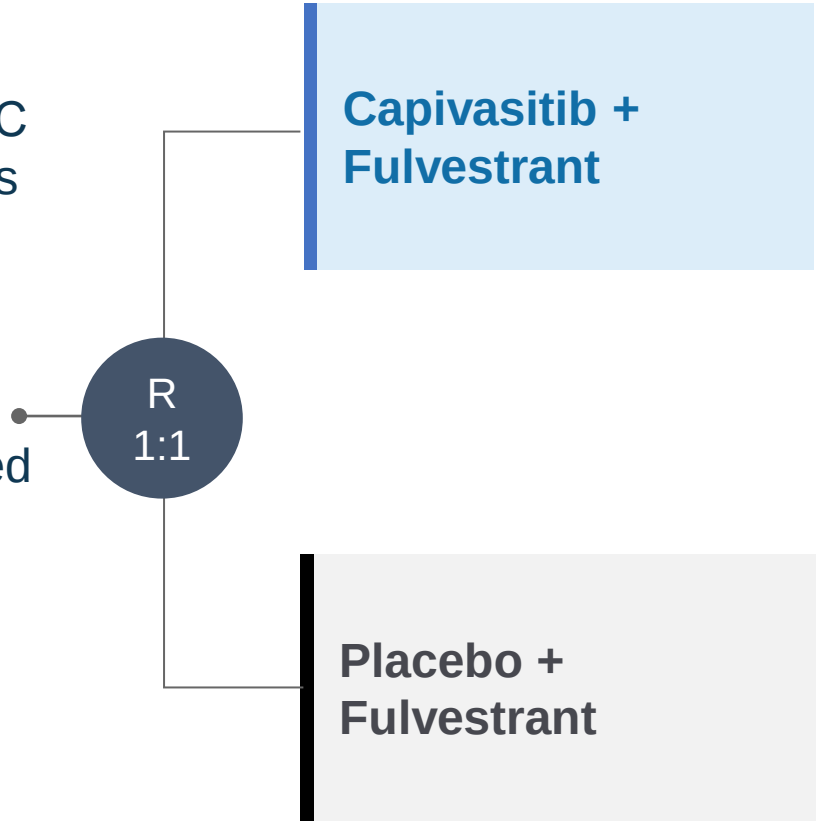
- TRAE, treatment-related adverse event.

Hurvitz SA, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-03.

Non-approved medication information in Japan is contained in this slide.

Capivasertib + Fulvestrant in AI-Resistant HR+/HER2− BC
CAPItello-291 Phase 3

Eligibility criteria
- ER+ and HER2− advanced BC
- Recurrence on or < 12 months from end of adjuvant AI
- ≤ 2 lines of prior endocrine therapy
- ≤ 1 line of chemotherapy
- Prior CDK4/6 inhibitors allowed
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c < 8.0%



Dual primary endpoints
- PFS (IA)
  - Overall
  - AKT pathway-altered tumors

Secondary objectives
- OS
  - Overall
  - AKT pathway-altered tumors
- ORR
  - Overall
  - AKT pathway-altered tumors

- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

CAPItello-291 *Characteristics*

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Median age; years (range)		59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female; n (%)		352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Post menopausal; n (%)		287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
Race; n (%)	White	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
	Asian	95 (26.8)	94 (26.6)	48 (31.0)	35 (26.1)
	Black or African American	4 (1.1)	4 (1.1)	2 (1.3)	1 (0.7)
	Other	55 (15.5)	49 (13.9)	30 (19.4)	22 (16.4)
Region*; n (%)	1	197 (55.5)	198 (56.1)	80 (51.6)	76 (56.7)
	2	68 (19.2)	68 (19.3)	29 (18.7)	24 (17.9)
	3	90 (25.4)	87 (24.6)	46 (29.7)	34 (25.4)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR-	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	ER+/PR unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance; n (%)	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)

- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

CAPItello-291
Prior Treatments

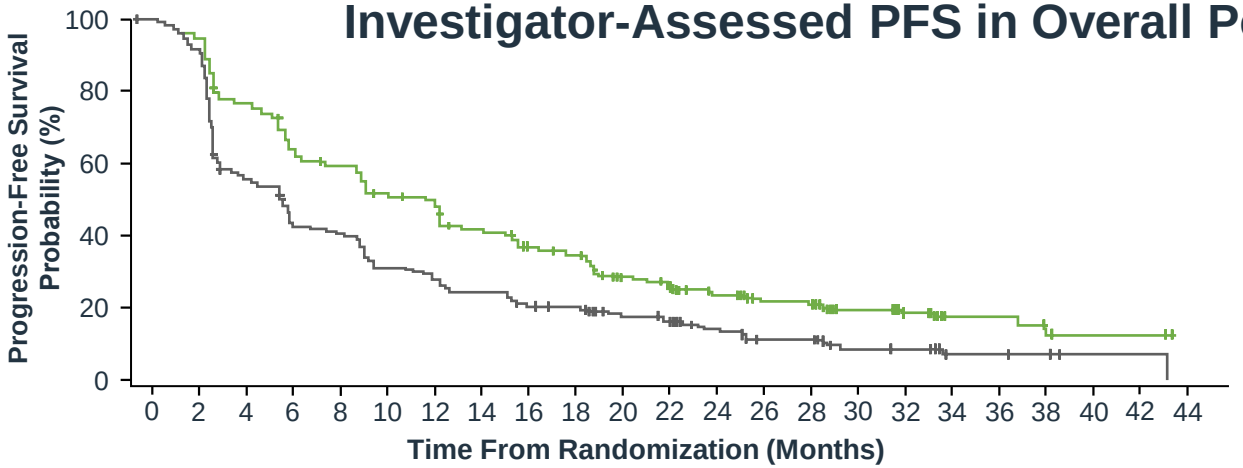
	Overall Population		AKT Pathway Altered	
n, (%)	Capivasertib + Fulvestrant (n = 355)	Placebo + Fulvestrant (n = 350)	Capivasertib + Fulvestrant (n = 155)	Placebo + Fulvestrant (n = 134)
Prior endocrine therapy for ABC				
0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy				
Adjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
Neoadjuvant	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

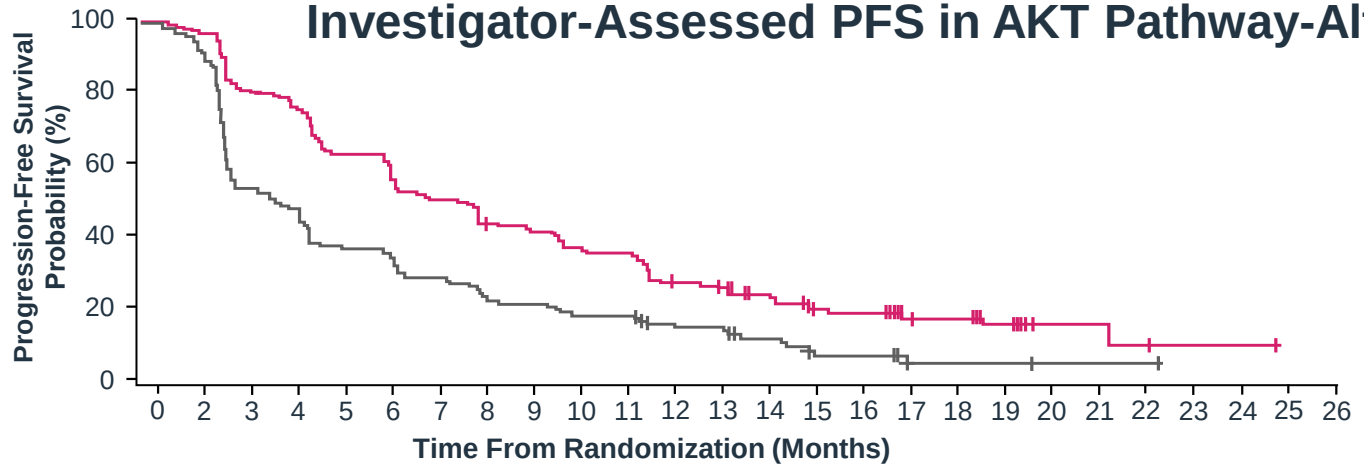
CAPItello-291
Dual Primary Endpoints

Investigator-Assessed PFS in Overall Population



	Capivasertib + Fulvestrant (n = 355)	Placebo + Fulvestrant (n = 353)
PFS events, n	258	293
mPFS, months (95% CI)	7.2 (5.5, 7.4)	3.6 (2.8, 3.7)
Adjusted hazard ratio (95% CI); *P* value	0.60 (0.51, 0.71); < .001	

Investigator-Assessed PFS in AKT Pathway-Altered Population



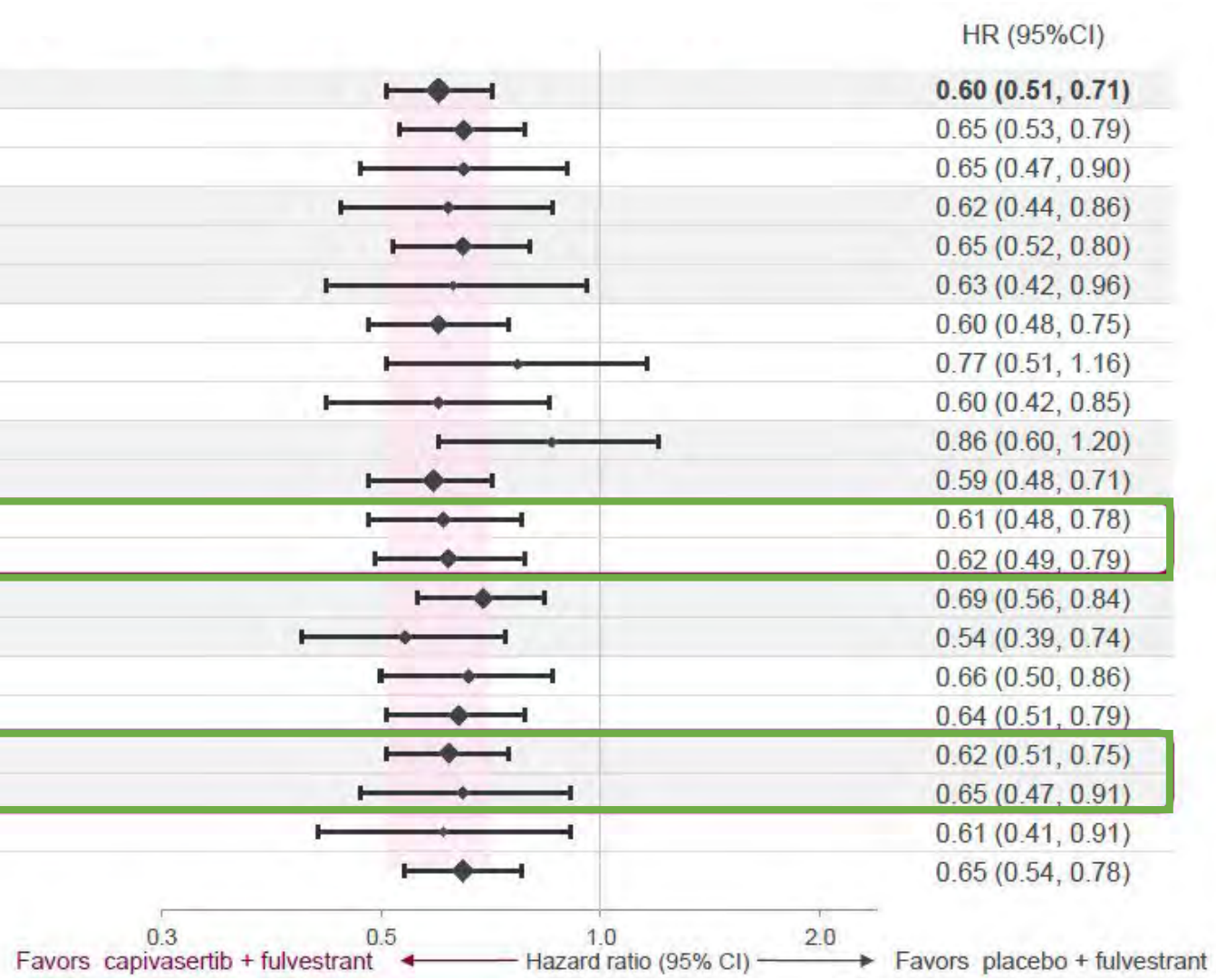
	Capivasertib + Fulvestrant (n = 155)	Placebo + Fulvestrant (n = 134)
PFS events, n	121	115
mPFS, months (95% CI)	7.3 (5.5, 9.0)	3.1 (2.0, 3.7)
Adjusted hazard ratio (95% CI); *P* value	0.50 (0.38, 0.65); < .001	

- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

CAPItello-291
PFS by Subgroups

		Number of patients	HR (95%CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

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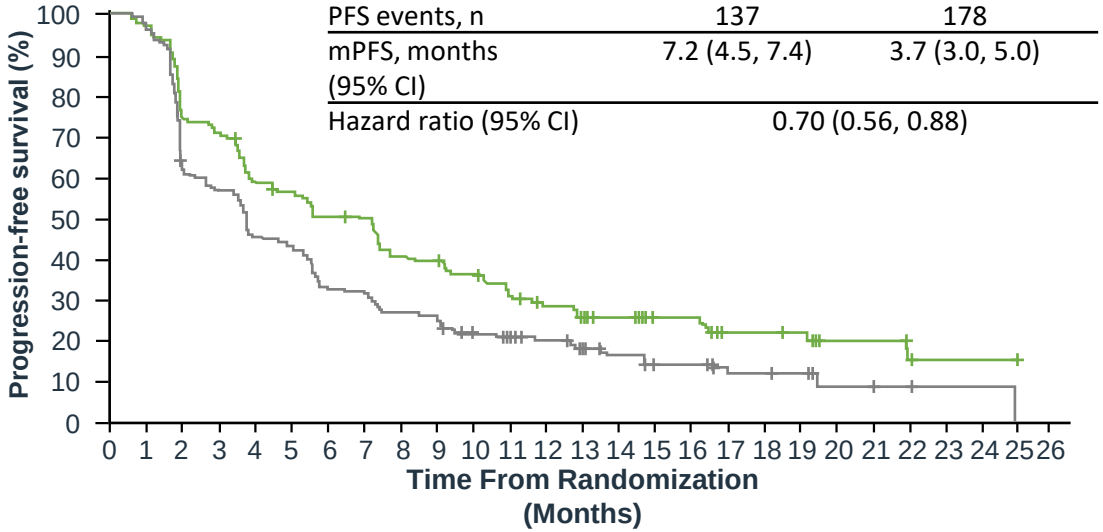
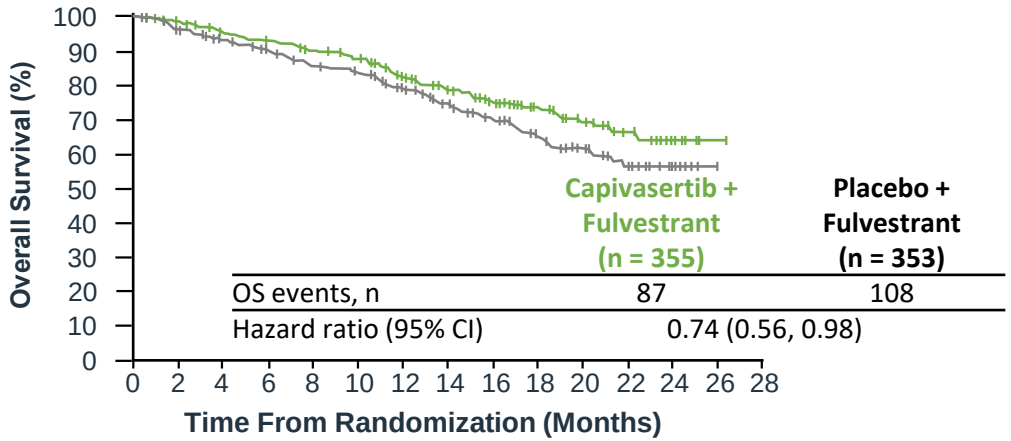
CAPItello-291
Regulatory and Exploratory Analyses

Investigator-Assessed PFS in Non-Altered Population, Including Unknown



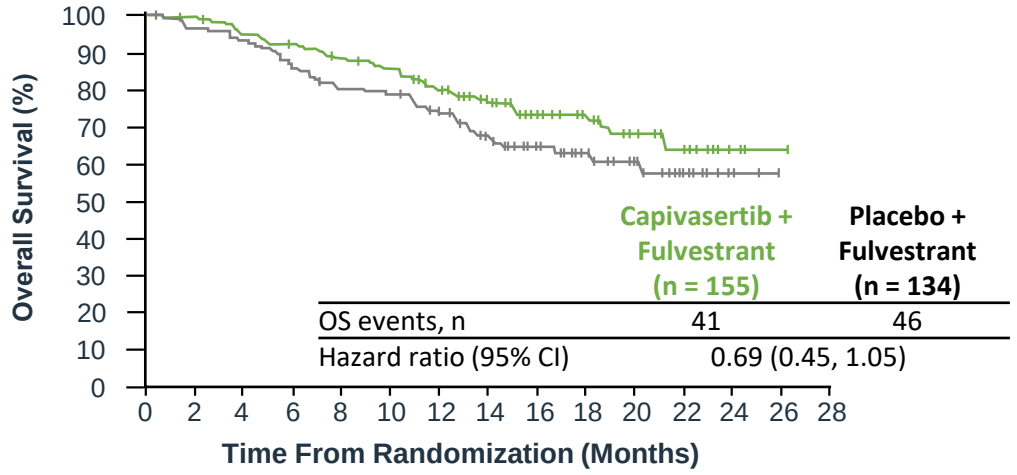
	Capivasertib + Fulvestrant (n = 200)	Placebo + Fulvestrant (n = 219)
PFS events, n	137	178
mPFS, months (95% CI)	7.2 (4.5, 7.4)	3.7 (3.0, 5.0)
Hazard ratio (95% CI)	0.70 (0.56, 0.88)	

OS in Overall Population*



	Capivasertib + Fulvestrant (n = 355)	Placebo + Fulvestrant (n = 353)
OS events, n	87	108
Hazard ratio (95% CI)	0.74 (0.56, 0.98)	

OS in AKT Pathway-Altered Population*



	Capivasertib + Fulvestrant (n = 155)	Placebo + Fulvestrant (n = 134)
OS events, n	41	46
Hazard ratio (95% CI)	0.69 (0.45, 1.05)	

- *Overall 8% maturity, study not powered to detect a difference in OS (regulatory required analysis).
- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

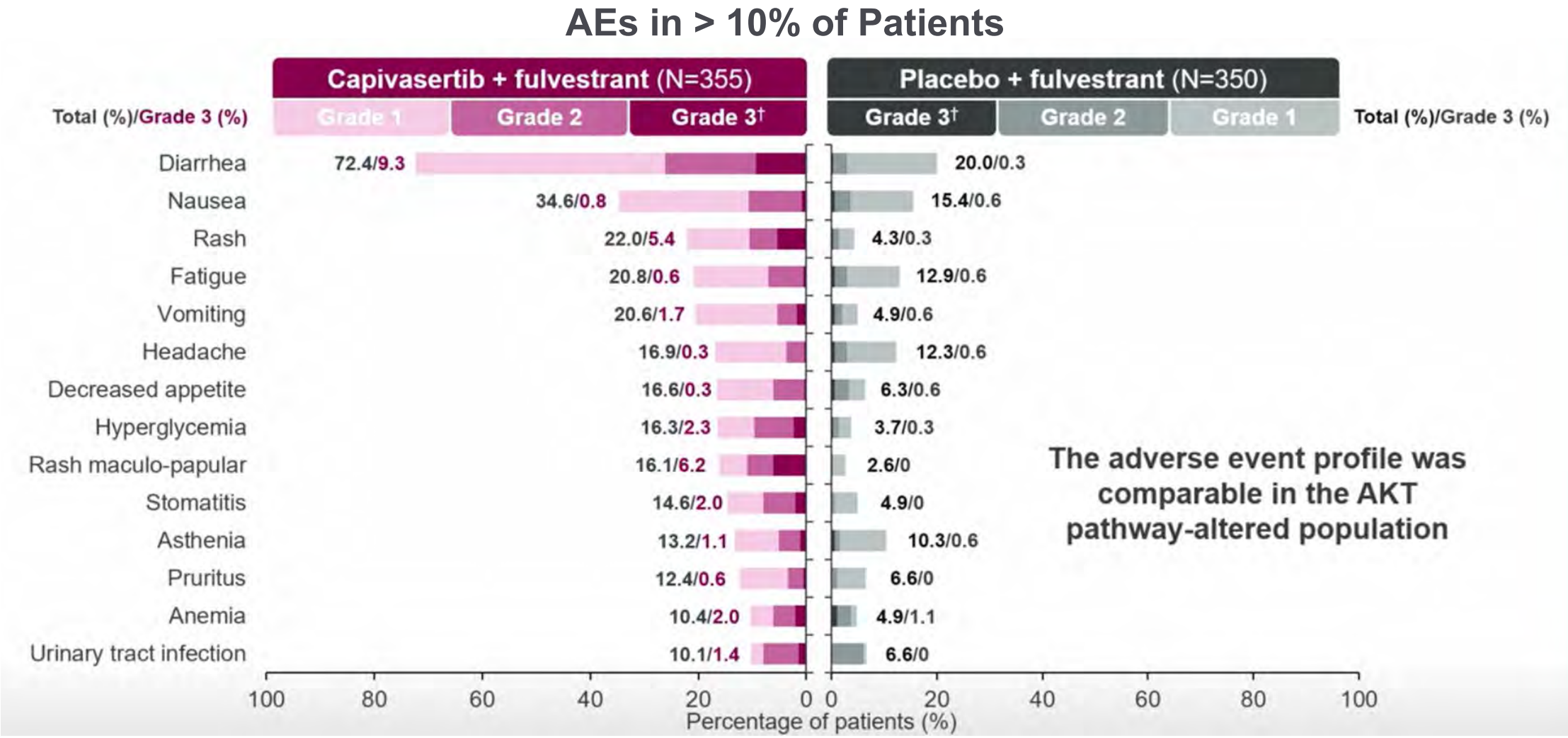
CAPItello-291
Safety Summary

Safety in Overall Population, n (%)	Capivasertib + Fulvestrant (n = 355)	Placebo + Fulvestrant (n = 350)
Any AE	343 (96.6)	288 (82.3)
Any serious AE	57 (16.1)	28 (8.0)
Any AE leading to death	4 (1.1)	1 (0.3)
Any AE 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 AE leading to dose interruption of capivasertib/placebo only	124 (34.9)	36 (10.3)
Any AE leading to dose reduction of capivasertib/placebo only	70 (19.7)	6 (1.7)

- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

CAPItello-291
Adverse Events



- Turner SC, et al. San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-04.

Non-approved medication information in Japan is contained in this slide.

DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint
- PFS by BICR (HR+)

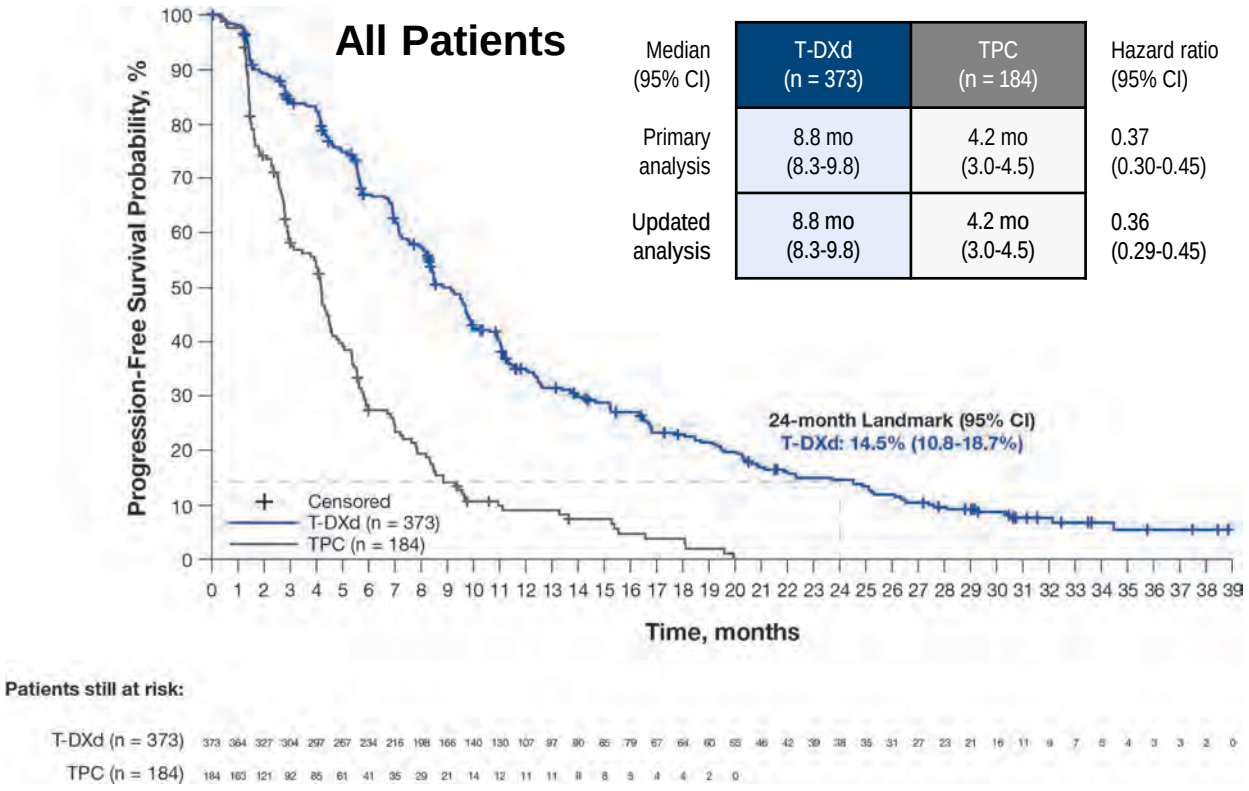
Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

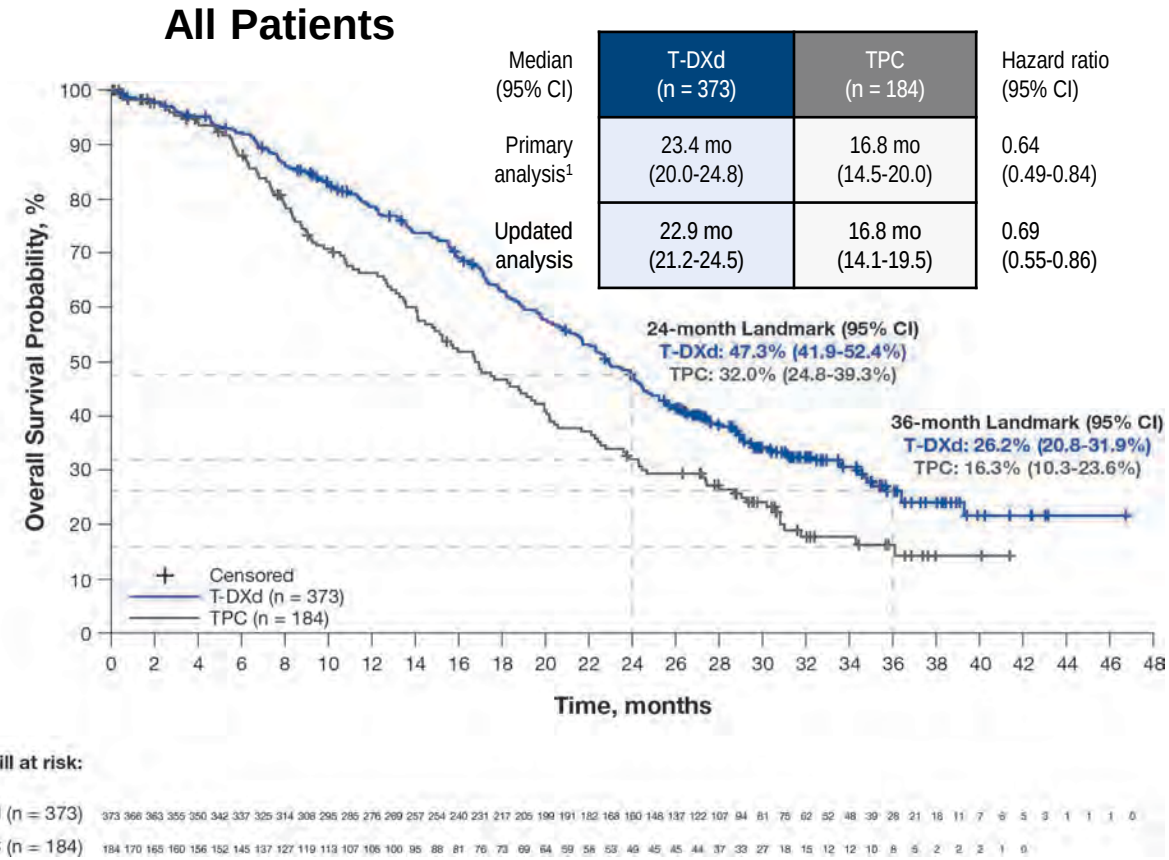
ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.
1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Progression-Free Survival



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.36 (0.29-0.45)

Overall Survival



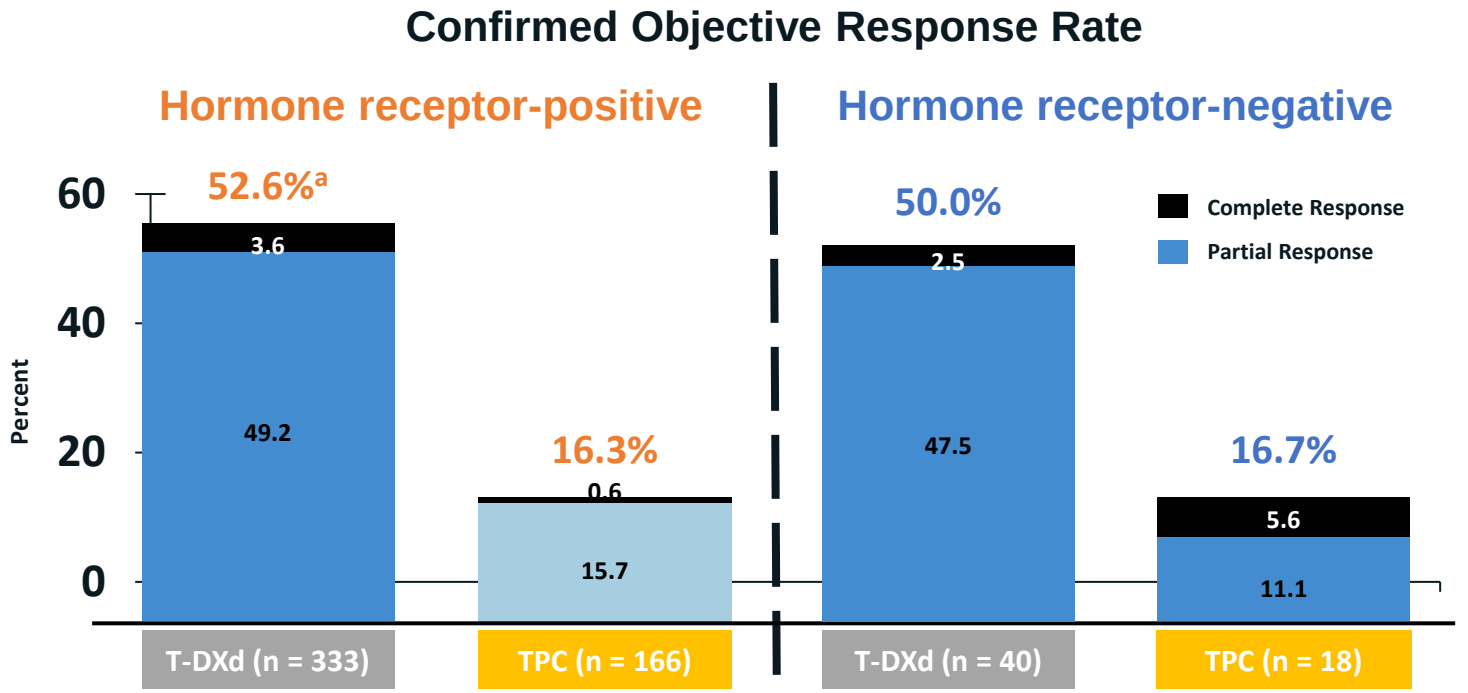
Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	22.9 mo (21.2-24.5)	16.8 mo (14.1-19.5)	0.69 (0.55-0.86)

Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC, regardless of HR status

HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Confirmed ORR



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive Disease, %	7.8	21.1	12.5	33.3
Not Evaluable, %	4.2	12.7	7.5	5.6
Clinical Benefit Rate[b], %	71.2	34.3	62.5	27.8
Duration of Response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.
[a]The response of one patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded central independent review.

Non-approved medication information in Japan is contained in this slide.

Overall Safety Summary

- Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 per patient-year for the T-DXd and TPC arms, respectively
  - This supports that longer T-DXd exposure does not increase toxicity
- Overall, the safety profile is consistent with results from the primary analysis (data cutoff, January 11, 2022)
  - Rates of ILD/pneumonitis remained unchanged with longer follow-up, and rates of left ventricular dysfunction were consistent with previously observed rates

Safety analysis set[a]

n (%)	T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
Grade ≥3	202 (54.4)	116 (67.4)
Serious TEAEs	108 (29.1)	44 (25.6)
TEAEs associated with dose discontinuation	62 (16.7)	14 (8.1)
TEAEs associated with dose interruptions	155 (41.8)	73 (42.4)
TEAEs associated with dose reductions	89 (24.0)	65 (37.8)
TEAEs associated with deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]	14 (3.8)	8 (4.7)

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death that occurred any time from date of first dose through 47 days after the last dose of the study treatment.
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Overall Safety Summary

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  - Rates of ILD/pneumonitis remained unchanged with longer follow-up, and rates of left ventricular dysfunction were consistent with previously observed rates

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0

Safety analysis set[a]

n (%)	T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
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1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

PFS2[a] and Post-Study Anticancer Therapies[b]

	HR+ Cohort		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS2 by investigator, mo (95% CI)	15.5 (13.8-17.2)	10.5 (8.3-11.4)	15.4 (13.6-16.5)	9.7 (8.3-10.8)
Hazard ratio (95% CI)	0.51 (0.40-0.64)		0.51 (0.41-0.64)	
Post-study anticancer therapies				
Systemic treatment, n (%)	247 (74.6)	126 (77.3)	282 (75.6)	144 (78.3)
Targeted therapy[c]	119 (36.0)	70 (42.9)	134 (35.9)	75 (40.8)
CDK4/6 inhibitors	47 (14.2)	27 (16.6)	48 (12.9)	27 (14.7)
ADC	16 (4.8)	15 (9.2)	18 (4.8)	15 (8.2)
T-DXd	2 (0.6)	4 (2.5)	2 (0.5)	4 (2.2)
Sacituzumab govitecan	9 (2.7)	5 (3.1)	11 (2.9)	5 (2.7)
Endocrine therapy	102 (30.8)	56 (34.4)	103 (27.6)	57 (31.0)
Chemotherapy	222 (67.1)	109 (66.9)	257 (68.9)	126 (68.5)
Radiation, n (%)	32 (9.7)	25 (15.3)	37 (9.9)	29 (15.8)
Surgery, n (%)	3 (0.9)	1 (0.6)	5 (1.3)	1 (0.5)

ADC, antibody drug conjugate; CDK, cyclin-dependent kinase; HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first.
[b]Participants may have been treated with more than 1 type of post-study anticancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody drug conjugates, or no subclass specified.

Giuseppe Curigliano, MD PhD

PFS2[a] and Post-Study Anticancer Therapies[b]

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Radiation, n (%)			37 (9.9)	29 (15.8)
Surgery, n (%)			5 (1.3)	1 (0.5)

ADC sequence

How many had discontinued for ILD/Toxicity?

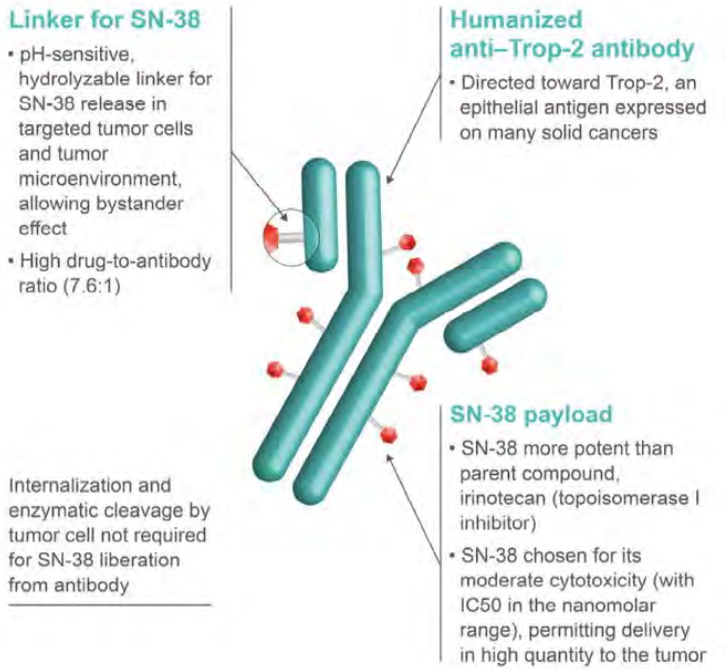
ADC, antibody drug conjugate; CDK, cyclin-dependent kinase; HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first.
[b]Participants may have been treated with more than 1 type of post-study anticancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody drug conjugates, or no subclass specified.

Giuseppe Curigliano, MD PhD

ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)
Payload	Anti-TOPO1
DAR	7.6
Trial	Ph3 RCT (TROPiCS-02)

Sacituzumab govitecan

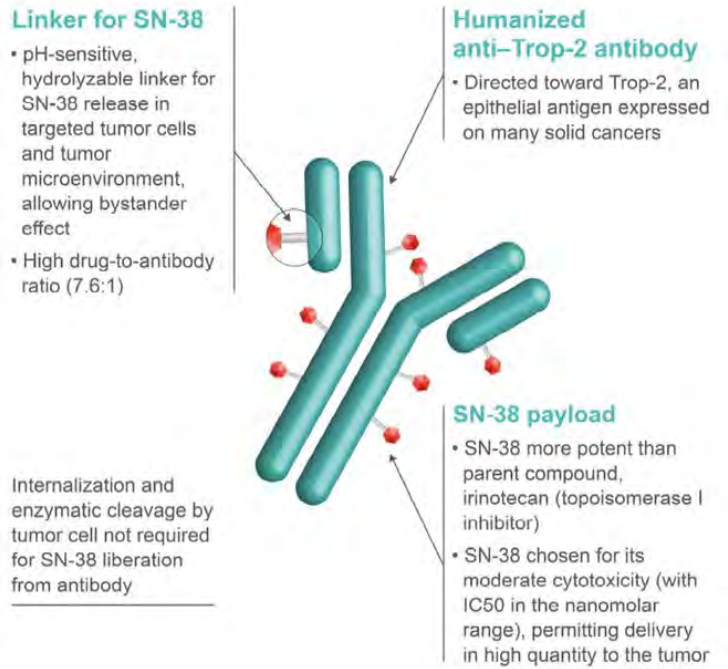


Giuseppe Curigliano, MD PhD

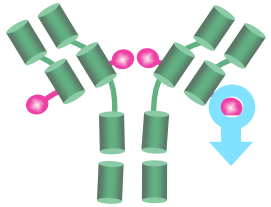
ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	**Ph3 RCT (TROPION-Breast01)**	**Single arm Ph1-2**

Sacituzumab govitecan

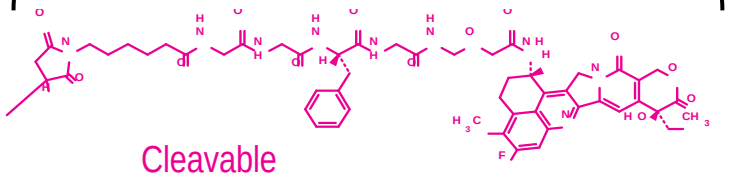


Datopotamab deruxtecan



- Payload mechanism of action: Topo-I inhibitor*
- High potency payload*
- Optimised drug to antibody ratio ≈4*†
- Payload with short systemic half-life*†
- Stable linker-payload*
- Tumour-selective cleavable linker*
- Bystander antitumour effect*

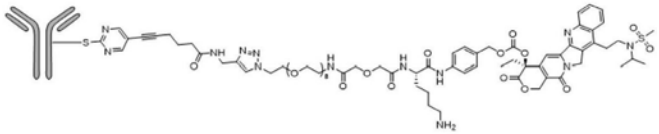
Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

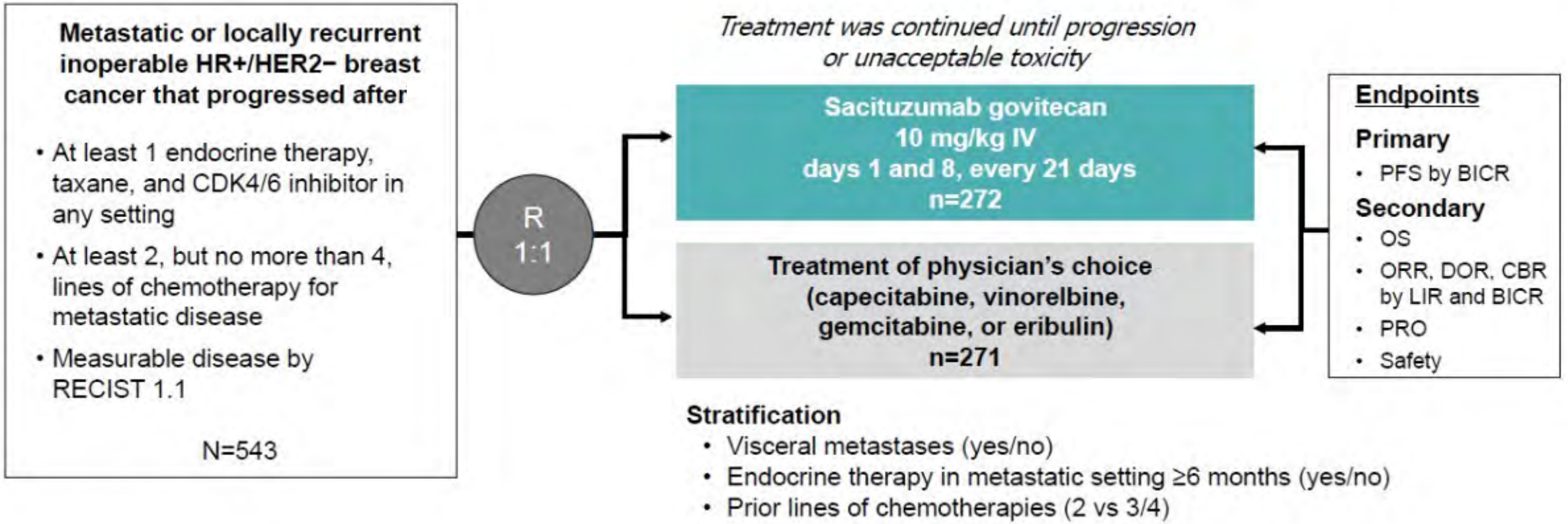
SKB264 (MK-2870)



- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- Payload: belotecan-derivative topoisomerase I inhibitor
- DAR: 7.4

Giuseppe Curigliano, MD PhD

Sacituzumab Govitecan vs TPC in HR+/HER2− mBC TROPiCS-02



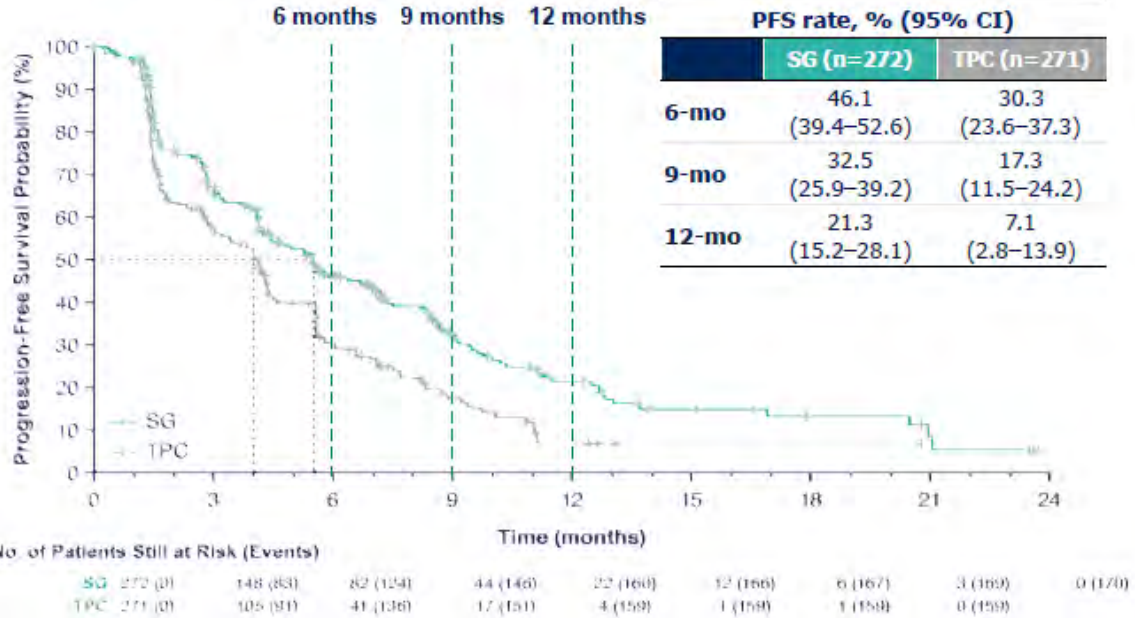
HR, hormone receptor; LIR, local investigator review; PRO, patient-reported outcomes.

Rugo HS, et al. Presented at: SABS; December 6-10, 2022; San Antonio, Texas. Presentation GS5-11.

TROPiCS-02
PFS and OS in ITT

PFS

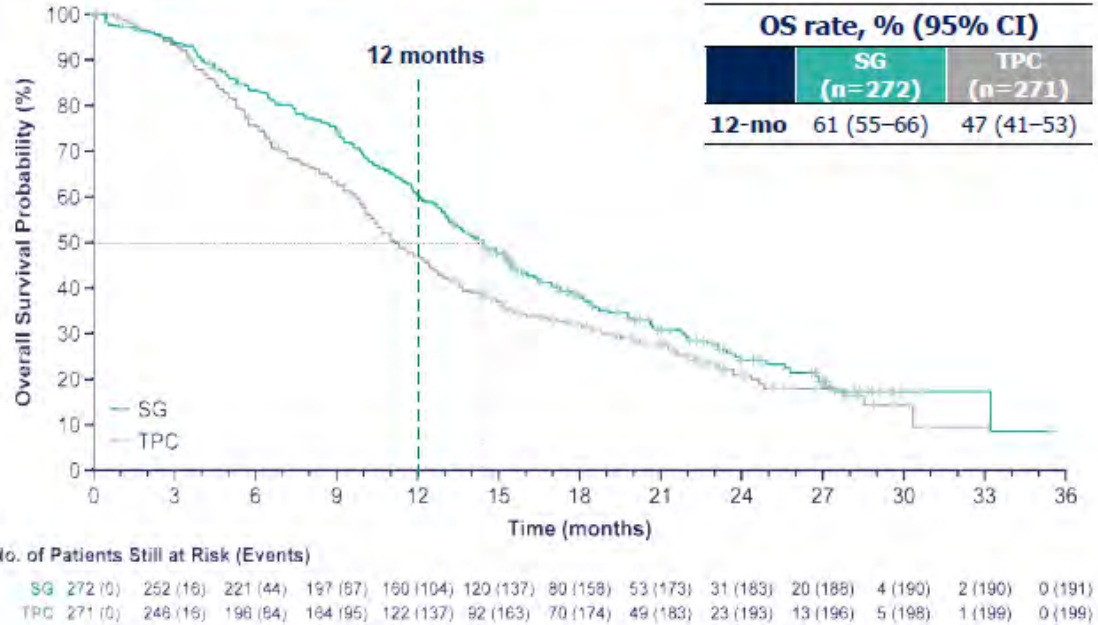
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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)

OS

	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	



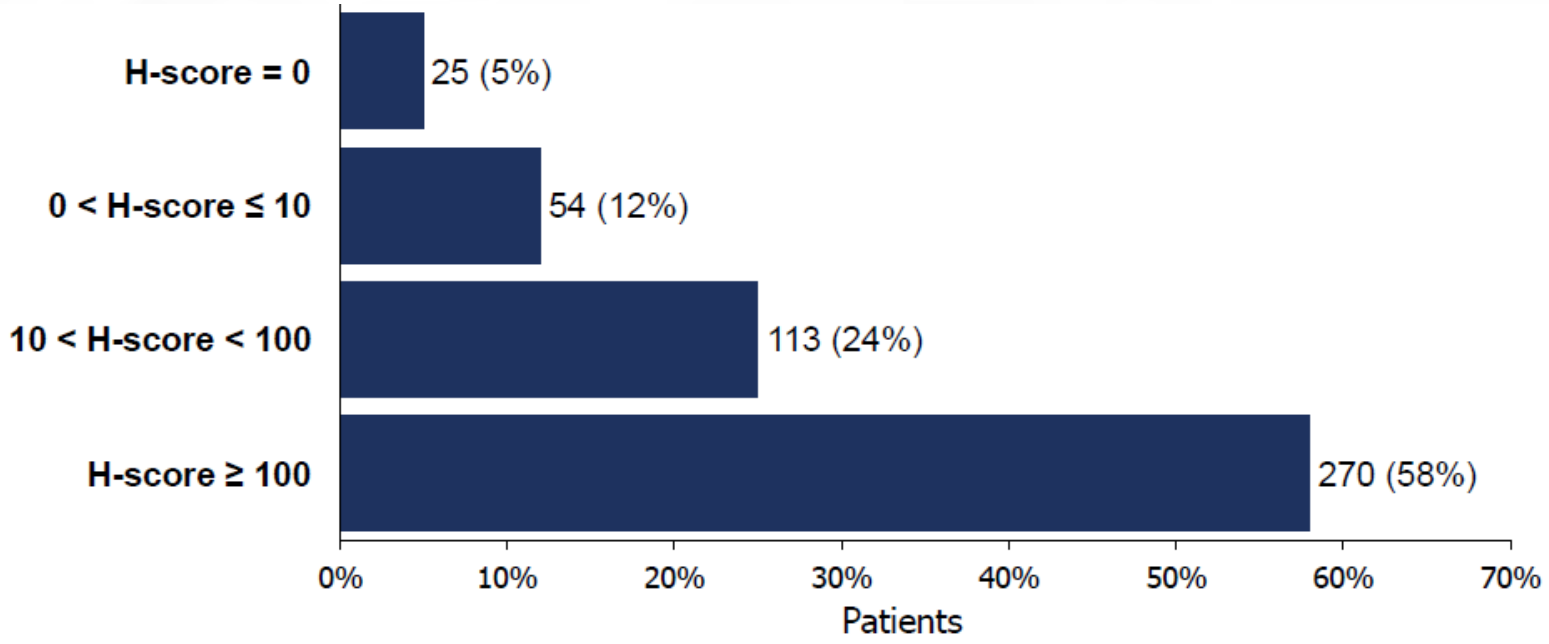
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Rugo HS, et al. Presented at: SABS; December 6-10, 2022; San Antonio, Texas. Presentation GS5-11.

SG vs TPC in HR+/HER2− mBC by TROP-2 Expression TROPiCS-02

TROP-2 Expression Observed in 95% of Evaluable Tissue Samples



PFS and OS benefit of SG over TPC was observed across TROP-2 subgroups (H-score < 100 and ≥ 100) and in tumors with very low TROP-2 expression, including H-score ≤ 10*

TROP-2 H-Score Cutoff 100

PFS: SG vs TPC

- < 100: 5.3 vs 4.0 months; hazard ratio 0.77
- ≥ 100: 6.4 vs 4.1 months; hazard ratio 0.60

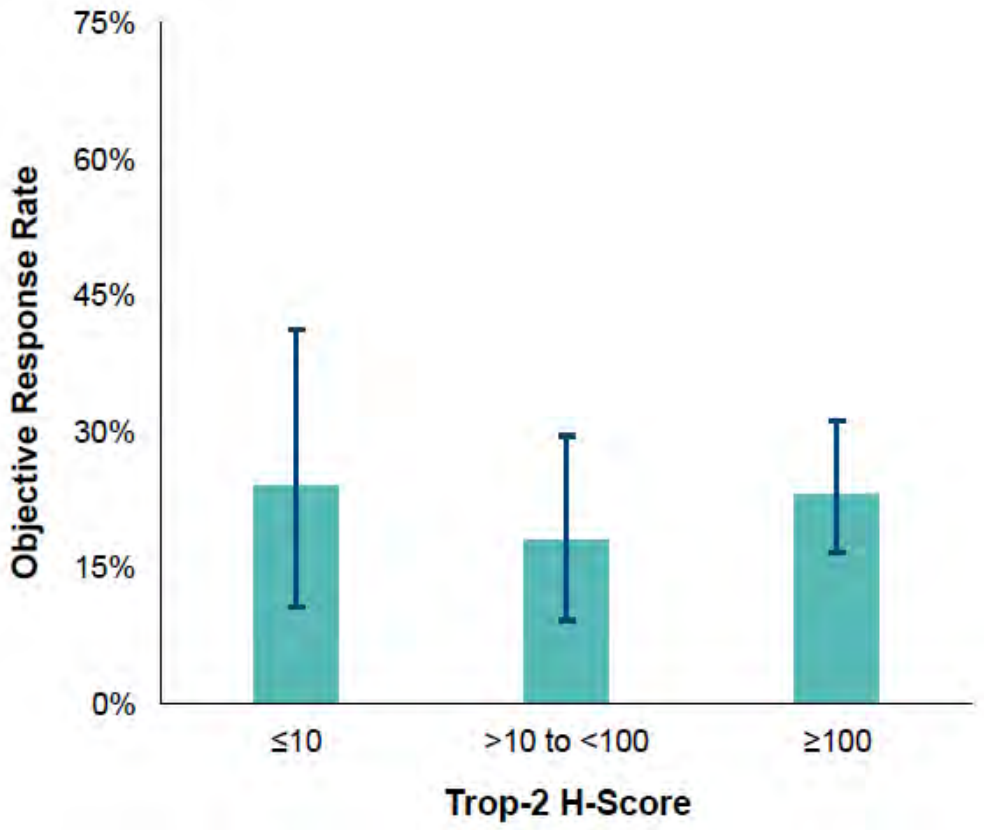
OS: SG vs TPC

- < 100: 14.6 vs 11.3 months; hazard ratio 0.75
- ≥ 100: 14.4 vs 11.2 months; hazard ratio 0.83

*Caution should be exercised in data interpretation given the small sample size in this TROP-2 subgroup.

Rugo HS, et al. Presented at: SABS; December 6-10, 2022; San Antonio, Texas. Presentation GS5-11.

TROPiCS-02: TROP-2 Expression Responses



TROP-2 Expression, H-Score	ORR n (%)	CBR n (%)	mDOR Months (95% CI)
≤ 10 (n = 34)	8 (24)	11 (32)	7.5 (2.5, NR)
> 10 to < 100 (n = 62)	11 (18)	17 (27)	7.4 (4.1, NR)
≥ 100 (n = 142)	33 (23)	55 (39)	8.5 (5.9, 16.9)

Response also observed in the small TROP-2 negative subgroup (H-score = 0, n=10)

Rugo HS, et al. Presented at: SABS; December 6-10, 2022; San Antonio, Texas. Presentation GS5-11.

TROPiCS-02: TROP-2 Expression Safety

n (%)	Sacituzumab Govitecan (n = 268)		TPC (n = 249)	
	H-Score < 100 (n = 96)	H-Score ≥ 100 (n = 140)	H-Score < 100 (n = 94)	H-Score ≥ 100 (n = 123)
Grade ≥ 3 TEAEs	76 (79)	103 (74)	58 (62)	78 (63)
TEAEs leading to treatment discontinuation	2 (2)	11 (8)	5 (5)	5 (4)
TEAEs leading to dose delay	68 (71)	93 (66)	43 (46)	52 (42)
TEAEs leading to dose reductions	32 (33)	51 (36)	37 (39)	35 (28)
TE SAEs	25 (26)	42 (30)	18 (19)	27 (22)
TEAEs leading to death	1 (1)	4 (3)	0	0
Treatment related	1 (1)	0	0	0
Select TEAEs (grade ≥ 3)				
Neutropenia	56 (58)	76 (54)	43 (46)	43 (35)
Febrile neutropenia	7 (7)	9 (6)	4 (4)	6 (5)
Diarrhea	10 (10)	13 (9)	1 (1)	1 (1)

SAE, serious adverse event; TE, treatment emergent.

Rugo HS, et al. Presented at: SABS; December 6-10, 2022; San Antonio, Texas. Presentation GS5-11.

MADRID 2023 ESMO congress

LBA11

Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer: Primary results from the randomised Phase 3 TROPION-Breast01 trial

Aditya Bardia,[1] Komal Jhaveri,[2] Seock-Ah Im,[3] Sonia Pernas,[4] Michelino De Laurentiis,[5] Shusen Wang,[6] Noelia Martínez Jañez,[7] Giuliano Borges,[8] David W. Cescon,[9] Masaya Hattori,[10] Yen-Shen Lu,[11] Erika Hamilton,[12] Qingyuan Zhang,[13] Junji Tsurutani,[14] Kevin Kalinsky,[15] Lu Xu,[16] Neelima Denduluri,[17] Hope S. Rugo,[18] Binghe Xu,[19]* **Barbara Pistilli**[20]*

*Contributed equally

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TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria

Patients with HR+/HER2– breast cancer*
(HER2– defined as IHC 0/1+/2+; ISH negative)

Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)

Experienced progression on ET and for whom ET was unsuitable

ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

ICC
Q3W as per protocol directions†
(eribulin mesylate, vinorelbine, capecitabine, or gemcitabine)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

- Lines of chemotherapy in unresectable/metastatic setting (1 vs 2)
- Geographic location (US/Canada/Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- Treatment continued until investigator-assessed PD (RECIST v1.1), unacceptable tolerability, or other discontinuation criteria
- At this data cut-off, the criteria for performing the primary PFS analysis were met (~419 events)

*Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W.
BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hazard ratio; ICC, investigator's choice of chemotherapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; Q3W, every 3 weeks; ROW, rest of world.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Demographics and Baseline Characteristics

		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other*	4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino†	40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy, n (%)	1 / 2‡	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)	Yes / No	299 (82) / 66 (18)	286 (78) / 81 (22)
Prior taxane and/or anthracycline, n (%)	Taxane alone	80 (22)	71 (19)
	Anthracycline alone	14 (4)	21 (6)
	Both	236 (65)	247 (67)
	Neither	35 (10)	28 (8)

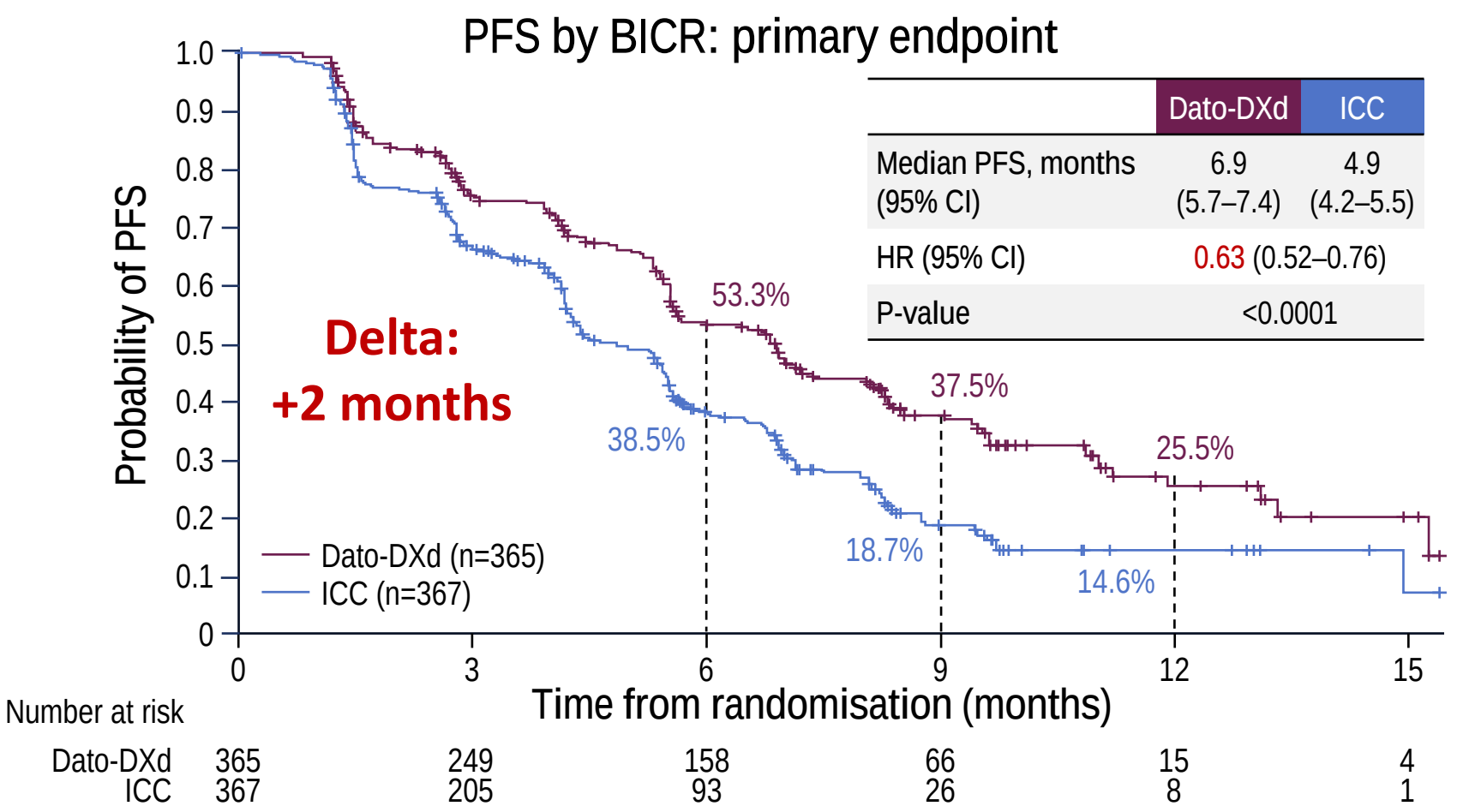
Data cut-off: 17 July 2023. *Including not reported. †Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group.
‡1 patient in the Dato-DXd group had 3 prior lines of chemotherapy; 1 patient in the ICC group had 4 prior lines.

Patient Disposition

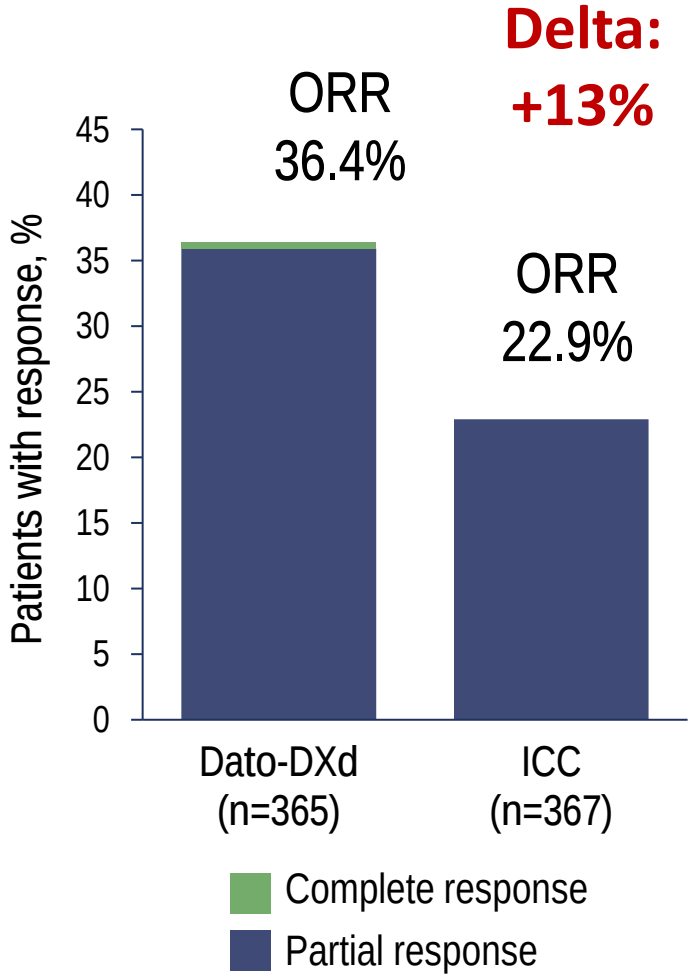
Disposition	Dato-DXd (n=360)	ICC (n=351)
Treatment status, n (%)		
Ongoing on study treatment	93 (26)	39 (11)
Discontinued from study treatment	267 (74)	312 (89)
Treatment duration, n (%)		
0–3 months	83 (23)	133 (38)
3–9 months	187 (52)	173 (49)
>9 months	90 (25)	45 (13)
Primary reason for treatment discontinuation, n (%)		
Adverse event	11 (3)	10 (3)
Progressive disease	229 (64)	240 (68)
Patient decision	13 (4)	32 (9)
Death	2 (1)	7 (2)
Other	12 (3)	23 (7)

- Median study follow-up: 10.8 months
- Investigator's choice of chemotherapy:
  - Eribulin mesylate: n=220
  - Vinorelbine: n=38
  - Capecitabine: n=76
  - Gemcitabine: n=33

Progression-Free Survival and Response Rate



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	



OS data were not mature: a trend favouring Dato-DXd was observed, HR 0.84 (95% CI 0.62–1.14)

TRAEs Occurring in ≥15% of Patients

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	**Grade ≥3**	Any Grade	**Grade ≥3**
Blood and lymphatic system disorders				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye disorders				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal disorders				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General disorders				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous disorders				
Alopecia	131 (36)	NA	72 (21)	NA

- Most frequent TRAEs with Dato-DXd were nausea and stomatitis
- Most common TRAEs with ICC were neutropenia and nausea
- Ocular events with Dato-DXd were low grade and most were dry eye (24%)

*Includes the preferred terms neutropenia and neutrophil count decreased.

Data cut-off: 17 July 2023.

Adverse Events of Special Interest and Overall Safety

All-cause events, n (%)	Dato-DXd (n=360)	ICC (n=351)
Oral mucositis/stomatitis*		
All grades	211 (59)	61 (17)
Grade 3†	25 (7)	9 (3)
Ocular events‡		
All grades	175 (49)	81 (23)
Grade 3†	3 (1)	0
Adjudicated drug-related ILD§		
All grades	9 (3)	0
Grade ≥3	2 (1)	0
Infusion-related reactions		
All grades	32 (9)	12 (3)
Grade 3†	1 (0.3)	0

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

Data cut-off: 17 July 2023.

MADRID 2023 ESMO congress

SKB264 (MK-2870) in previously treated hormone receptor-positive (HR+)/ HER2-negative metastatic breast cancer (mBC): results from a phase I/II, single-arm, basket trial

Quchang Ouyang[1], Yongmei Yin[2], Lihua Song[3], Min Yan[4], Xinhong Wu[5], Zhongsheng Tong[6], YunPeng Liu[7], Xian Wang[8], Xiaoping Jin[9],Yina Diao[9],Gesha Liu[9], Junyou Ge[9], Jin Li[10]

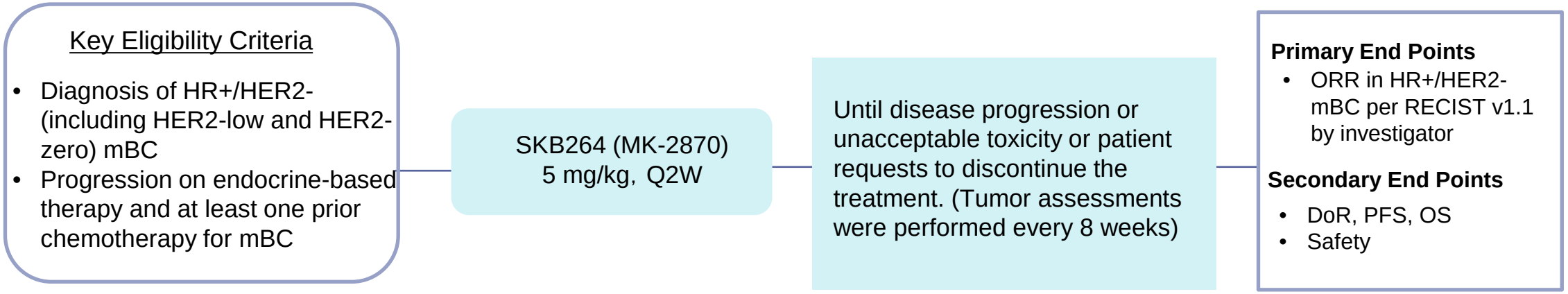
[1]Hunan Cancer Hospital, Changsha, China; [2]Jiangsu Province Hospital, Nanjing, China; [3]Shandong Cancer Hospital, Jinan, China; [4]Henan Cancer Hospital, Zhengzhou, China; [5]Hubei Cancer Hospital, Wuhan, China; [6]Tianjin Cancer Hospital, Tianjin, China; [7]The first Hospital of China Medical University, Shenyang, China; [8]Sir Run Run Shaw Hospital, Hangzhou, China [9]Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China; [10]Shanghai East Hospital, Shanghai, China

Presenter: Dr. Yongmei Yin

Sunday, October 22, 2023, 08:35-08:40
380MO

Study design

- KL264-01 is a phase I/II basket study in heavily pretreated patients with advanced solid tumors including HR+/HER2- mBC. As of data cut-off (April 12, 2023), 41 HR+/HER2- mBC patients were enrolled. Median follow-up was 8.2 months (mo).



1. Yongmei Yin, et al. *SABCS*. 2022
2. Rugo H S , Bardia A , Tolaney S M ,et al. *Future Oncology*. 2020(12):16.

Study design and pts characteristics

- KL264-01 is a phase I/II basket study in heavily pretreated patients with advanced solid tumors including HR+/HER2- mBC. As of data cut-off (April 12, 2023), 41 HR+/HER2- mBC patients were enrolled. Median follow-up was 8.2 months (mo).

Key Eligibility Criteria

- Diagnosis of HR+/HER2- (including HER2-low and HER2-zero) mBC
- Progression on endocrine-based therapy and at least one prior chemotherapy for mBC

Primary endocrine resistance: relapse while on the first 2 years of (neo)adjuvant endocrine therapy, or progression within first 6 months of first-line endocrine therapy in unresectable or metastatic setting

Until disease progression or toxicity or patient discontinue the mor assessments d every 8 weeks)

Primary End Points

- ORR in HR+/HER2- mBC per RECIST v1.1 by investigator

Secondary End Points

- DoR, PFS, OS
- Safety

Characteristics	Overall (N=38) [a]
Age (Median [range]), years	50 [34-66]
ECOG scores, n (%)	
0	15 (39.5)
1	23 (60.5)
Presence of visceral metastases, n (%)	38 (100)
Endocrine resistance[b], n (%)	
Primary	18 (47.4)
Secondary	20 (52.6)

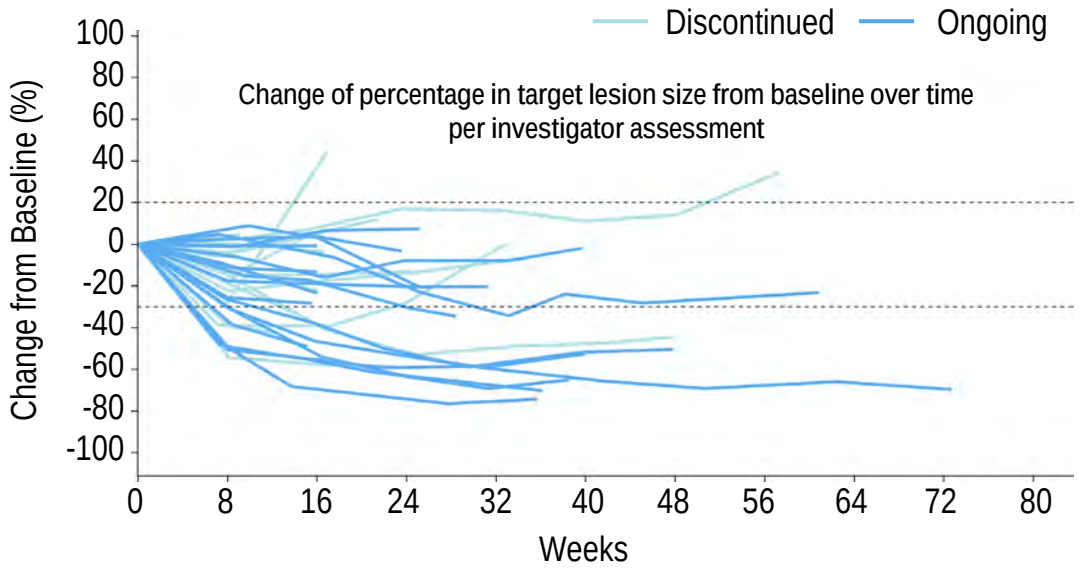
Prior therapies	Overall (N=38) [a]
Prior chemotherapy in (neo) adjuvant setting, n (%)	34 (89.5)
Line of chemotherapy in metastatic setting, n (%)	
Median (range)	2 (0-5)
1	7 (18.4)
2	17 (44.7)
≥3	13 (34.2)
Prior Taxane use, n (%)	38 (100)
Prior CDK4/6 inhibitor use, n (%)	25 (65.8)
≤12 mo	17 (44.7)
>12 mo	8 (21)

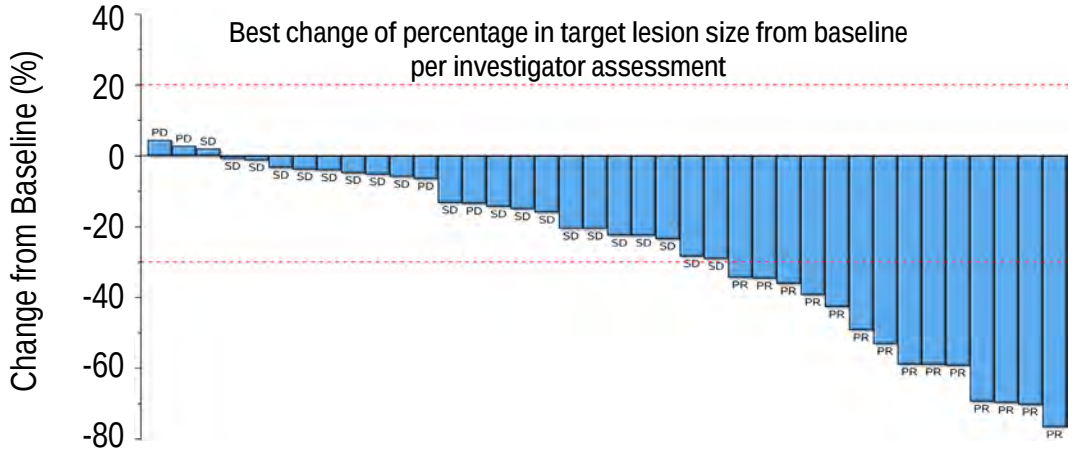
1. Yongmei Yin, et al. *SABCS*. 2022
2. Rugo H S , Bardia A , Tolaney S M ,et al. *Future Oncology*. 2020(12):16.

Efficacy of SKB264 (MK-2870) in HR+/HER2- BC

	All patients (N=38)[a]
ORR, n (%)	14 (36.8)
Confirmed PR	12
DCR, n (%)	34 (89.5)
DoR	
Median (Range), mo	7.4 (4.2~14.9+)
6-mon DoR rate, % (95% CI)	80.0 (40.9, 94.6)
PFS	
Median (95% CI), mo	11.1 (5.4, 13.1)
6-mon PFS rate, % (95% CI)	61.2 (41.3, 76.1)
OS	
Median (95% CI), mo	NE (10.71, NE)
9-mon OS rate (95% CI), %	81.4 (57.1, 92.7)

a. of 41 patients were enrolled, 38 patients were evaluable for response assessment (defined as ≥1 on-study scan).





Efficacy of SKB264 (MK-2870) in Key Sub-groups

	HER2 Expression		Endocrine resistance[a]		Prior CDK4/6i[c]	
	Low[b] (N=27)	Zero (N=11)	Primary (N=18)	Secondary (N=20)	Yes (N=25)	No (N=13)
ORR, %[d]	40.7	27.2	22.2	50.0	32.0	46.0
Median PFS, mo (95% CI)	11.0 (5.6, 13.1)	NE (3.8, NE)	5.6 (3.7, NE)	13.1 (5.8, NE)	11.0 (5.4, NE)	7.6 (2.1, NE)
6-month PFS rate, % (95% CI)	65.0 (41.5, 81.0)	54.6 (18.4, 80.5)	46.8 (20.6, 69.4)	74.8 (44.9, 90.0)	66.2 (38.7, 83.6)	52.8 (23.4, 75.5)

a. Primary endocrine resistance defined as relapse while on the first 2 years of (neo)adjuvant endocrine therapy, or progression within first 6 months of first-line endocrine therapy in unresectable or metastatic setting.[1] Secondary endocrine resistance defined as relapse while on adjuvant endocrine therapy but after the first 2 years, or progression ≥ 6 months after initiating endocrine therapy in unresectable or metastatic setting.[1]
b. HER2 low expression including IHC 1+ or IHC 2+ and FISH-.
c. 72% of patients with primary endocrine resistance had received a CDK4/6 inhibitor; 60% of patients with secondary endocrine resistance had received a CDK4/6 inhibitor.
d. ORR including confirmed or unconfirmed responses

1. Cardoso F, et al. *Ann Oncol.* 2018. Aug;29(8):1634–57.

Safety of SKB264 (MK-2870) in HR+/HER2 BC

Category	SKB264 5mg/kg Q2W (N=41), n (%)	
	All Grade	≥Grade 3
TRAEs	41(100)	20(48.8)
TRAEs leading to dose reduction	7 (17.1)	5 (12.2)
TRAEs leading to dose delay	8 (19.5)	7 (17.1)
TRAEs leading to death	0	0
TRAEs in ≥25% any grade or ≥5% Grade >=3		
WBC decreased	35 (85.4)	9 (22.0)
Neutrophil count decreased	33 (80.5)	15 (36.6)
Anemia	33 (80.5)	6 (14.6)
Stomatitis	19 (46.3)	1 (2.4)
ALT increased	18 (43.9)	0
AST increased	17 (41.5)	0
Platelet count decreased	14 (34.1)	4 (9.8)
Rash	14 (34.1)	0
Blood LDH increased	13 (31.7)	0
GGT increased	12 (29.3)	3 (7.3)
Oropharyngeal pain	12 (29.3)	0
Lymphocyte count decreased	11 (26.8)	2 (4.9)

- The most common ≥ Grade 3 TRAEs (≥ 5%) was neutrophil count decreased, WBC decreased, anemia, platelet count decreased, GGT increased
- No neuropathy or drug-related ILD/pneumonitis was reported.
- No TRAEs led to treatment discontinuation or death
- Most of the hematology toxicity occurred within the first 2 months of treatment and recovered after treatment with G-CSF or erythropoietin without blood transfusions

ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	Ph3 RCT (TROPION-Breast01)	Single arm Ph1-2
Age, median (range), years	57 (29-86)	56 (29–86)	50 (34-66)
ECOG PS 0, %	43%	54%	40%
Prior lines of chemotherapy, median	**3**	**1**	**2**
Prior CDK4/6 inhibitor, %	98%	82%	66%
Prior taxane and/or anthracycline, %	64%	65%	100%

ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	Ph3 RCT (TROPION-Breast01)	Single arm Ph1-2
Age, median (range), years	57 (29-86)	56 (29–86)	50 (34-66)
ECOG PS 0, %	43%	54%	40%
Prior lines of chemotherapy, median	**3**	**1**	**2**
Prior CDK4/6 inhibitor, %	98%	82%	66%
Prior taxane and/or anthracycline, %	64%	65%	100%
ORR, %	**21%**	**36%**	**37%**
Median PFS, months - HR	**5.5 vs. 4.0** HR: 0.65 (95% CI 0.53-0.81)	**6.9 vs. 4.9** HR: 0.63 (95% CI 0.52–0.76)	11.1
Median OS, months - HR	14.5 vs. 11.2 HR 0.79 (0.65-0.95)	**Not mature** HR 0.84 (95% CI 0.62–1.14)	NR
Median FUP, months	12.7	10.8	8.2
Treatment discontinuation due to TRAE, %	**6%**	**3%**	**0%**
Oral mucositis/stomatitis - all grades | G3, %	NA	59% | 7%	46% | 2%
Drug-related ILD - all grades | G3, %	NA	3% | 1%	0% | 0%

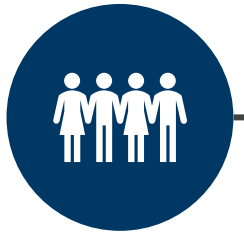
Investigating T-DXd in combination with endocrine therapies in patients with HER2-low HR+ advanced/mBC

DESTINY-Breast08: A Phase 1b, multicenter, open-label, two-part, modular study (NCT04556773)

Population for T-DXd-ET combination arms

- Locally assessed HER2-low (IHC 1+, IHC 2+/ISH−) HR+ advanced/mBC
- ≤1 prior treatment line of ET ± a targeted therapy (such as CDK4/6, mTOR, or PI3K inhibitors) for mBC allowed
- No prior chemotherapy in the metastatic setting allowed
- At least one measurable lesion per RECIST 1.1
- ECOG PS 0–1

Allocation



HR+/HR−
T-DXd + capecitabine, n=20

HR−
T-DXd + capivasertib, n=40

HR+
T-DXd + ANA, n=21
(T-DXd 5.4 mg/kg IV Q3W + anastrozole 1 mg daily*)

HR+
T-DXd + FUL, n=20
(T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg IM Q4W, with a 500 mg loading dose on Cycle 1, Day 15*)

Endpoints for the dose-expansion phase

- **Primary:** Safety and tolerability, including AEs, AESIs, and SAEs
- **Secondary:** ORR, PFS, DOR (all evaluated by investigator per RECIST 1.1), and OS

Part 1 dose-finding and Part 2 dose-expansion; results reported here are from the dose-expansion phase

*Patients received the RP2D from the study's dose-finding phase

AE, adverse event; AESI, adverse event of special interest; ANA, anastrozole; CDK4/6, cyclin-dependent kinases 4 and 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; IM, intramuscular; ISH, in situ hybridization; IV, intravenous; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; QXW, every X weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

André F, et al. Poster presented at ASCO 2022 (Abstract 3025)

Baseline characteristics and patient disposition

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median age, years (range)	55.0 (29.0–75.0)	65.5 (31.0–73.0)
Female, n (%)	21 (100.0)	20 (100.0)
Race, n (%)		
Asian	11 (52.4)	12 (60.0)
White	10 (47.6)	7 (35.0)
Black or African	0	1 (5.0)
HER2 status, n (%)		
IHC 1+	16 (76.2)	13 (65.0)
IHC 2+/ISH−	5 (23.8)	7 (35.0)
HR status, n (%)		
ER+ and PR+	14 (66.7)	10 (50.0)
ER+ and PR−	7 (33.3)	9 (45.0)
ER+ and PR missing	0	1 (5.0)
ECOG PS, n (%)		
0	12 (57.1)	17 (85.0)
1	8 (38.1)	3 (15.0)
2	1 (4.8)	0
Received no prior line of treatment for mBC, n (%)	7 (33.3)*	6 (30.0)†
Received a prior line as first line for mBC, n (%)	14 (66.7)‡	14 (70.0)§

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median duration of follow up, months (range)	20.2 (4.9–24.8)	15.2 (2.2–22.6)
Treatment ongoing	6 (28.6)	7 (35.0)
Patients who discontinued both IPs	15 (71.4)	13 (65.0)
Patients who discontinued T-DXd	15 (71.4)	16 (80.0)
AE	4 (19.0)	5 (25.0)
Subject decision	0 (0)	4 (20.0)
Objective disease progression	8 (38.1)	5 (25.0)
Subjective disease progression	3 (14.3)	2 (10.0)
Patients who discontinued ET	15 (71.4)	13 (65.0)

All patients received study drug

As of August 16, 2023, **6 patients** (28.6%) **in the T-DXd + ANA arm** and **7 patients** (35.0%) **in the T-DXd + FUL arm** were **ongoing study treatment**

Disease progression was the leading reason for treatment discontinuation in both arms

nd three had de-novo mBC. ‡All patients received hormonal therapy with a targeted therapy. §11 patients received hormonal therapy with a targeted therapy, and three received hormonal therapy alone

ER, estrogen receptor; IP, investigational product; PR, progesterone receptor

Safety overview

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)	T-DXd + ET combinations (N=41)
Any-grade AEs	20 (95.2)	20 (100)	**40 (97.6)**
Any-grade AEs occurring in ≥30% of patients in either arm			
Nausea	14 (66.7)	19 (95.0)	**33 (80.5)**
Alopecia	9 (42.9)	10 (50.0)	**19 (46.3)**
Fatigue	9 (42.9)	3 (15.0)	**12 (29.3)**
Anemia	7 (33.3)	5 (25.0)	**12 (29.3)**
COVID-19	7 (33.3)	5 (25.0)	**12 (29.3)**
Decreased appetite	7 (33.3)	11 (55.0)	**18 (43.9)**
Decreased weight	7 (33.3)	4 (20.0)	**11 (26.8)**
Increased AST	7 (33.3)	4 (20.0)	**11 (26.8)**
Neutropenia*	6 (28.6)	7 (35.0)	**13 (31.7)**
Vomiting	6 (28.6)	7 (35.0)	**13 (31.7)**
Any AEs ≥Grade 3	10 (47.6)	11 (55.0)	**21 (51.2)**
Any AEs ≥Grade 3 possibly related to either drug	7 (33.3)	10 (50.0)	**17 (41.5)**
AEs leading to dose interruptions/delays of T-DXd	12 (57.1)	8 (40.0)	**20 (48.8)**
AEs leading to dose reduction of T-DXd	6 (28.6)	4 (20.0)	**10 (24.4)**
AEs leading to discontinuation of T-DXd	4 (19.0)	6 (30.0)	**10 (24.4)**
Any SAEs	4 (19.0)	4 (20.0)	**8 (19.5)**
AEs leading to death†	1 (4.8)	0	**1 (2.4)**
AESIs			

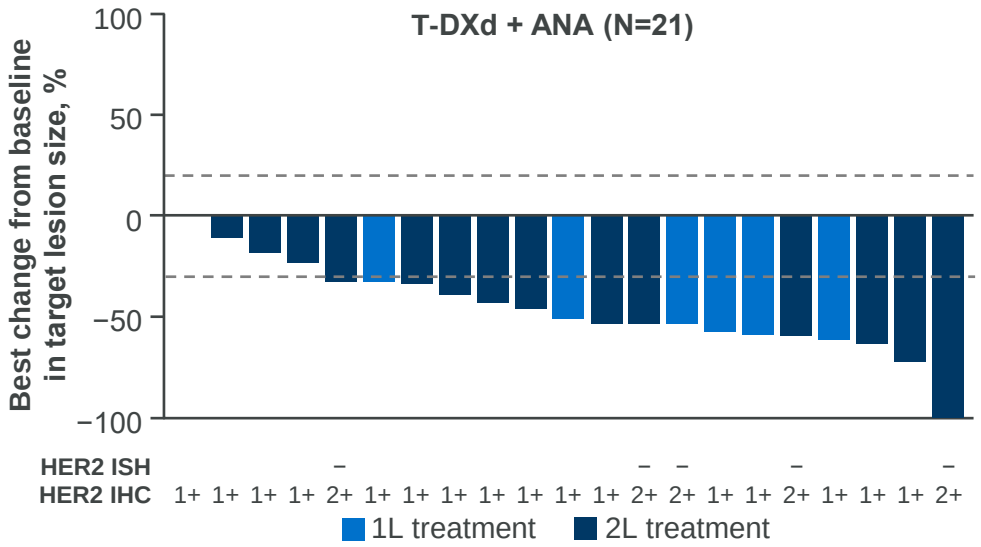
- In the T-DXd + ANA arm, median actual treatment duration was 10.4 months (range 2.8–22.2) for T-DXd and 11.0 months (range 1.4–22.4) for ANA §
- In the T-DXd + FUL arm, median actual treatment duration was 6.3 months (range 1.4–21.9) for T-DXd and 8.3 months (range 1.8–22.5) for FUL §

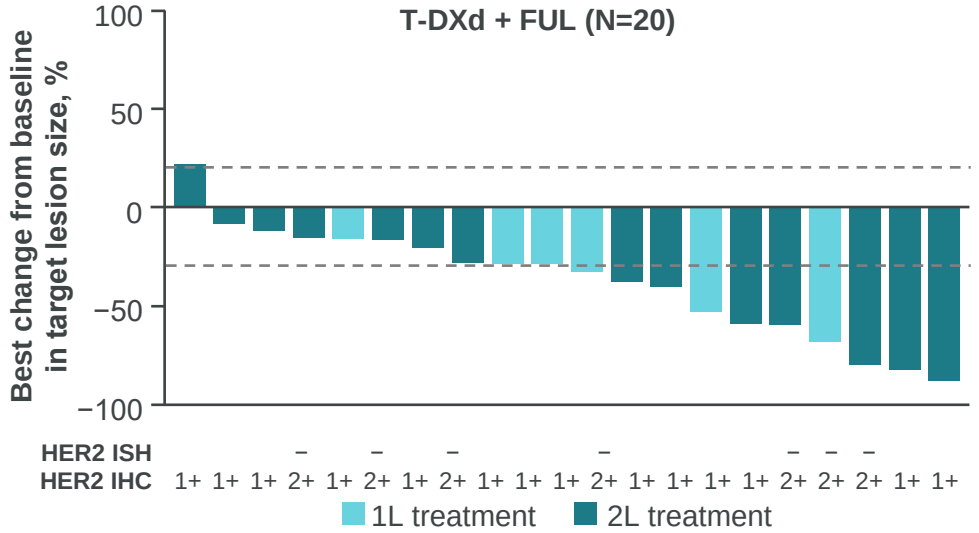
*Grouped term including neutropenia and decreased neutrophil count events. †Reported by investigator as related to disease and drug-induced pneumonitis, however, the ILD was not considered to be drug-induced by adjudication. ‡Both cases Grade 2 and resolved at DCO. §Total treatment duration, excluding drug interruptions and delays
AST, aspartate aminotransferase; DCO, data cutoff; ILD, interstitial lung disease

Efficacy overview

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	**71.4 (47.8, 88.7)**	**40.0 (19.1, 64.0)**
Unconfirmed ORR, % (95% CI)	**76.2 (52.8, 91.8)**	**50.0 (27.2, 72.8)**
Median DOR, months (95% CI)*	**9.8 (6.7, NE)**	**NE (4.1, NE)**
Total PFS events, n (%)	**14 (66.7)**	**7 (35.0)**
Median PFS, months (95% CI)*	**13.4 (8.5, 19.4)**	**NE (5.6, NE)**
PFS rate at 6 months, % (95% CI)	80.7 (56.3, 92.3)	75.3 (46.4, 90.0)
PFS rate at 12 months, % (95% CI)	50.4 (27.5, 69.5)	52.7 (25.0, 74.4)

- **Efficacy results need to be interpreted with caution owing to the small datasets**
  - **Of note, 15% of patients in the T-DXd + FUL arm withdrew consent and discontinued study treatment before disease progression**





*NE signifies that median DOR/PFS was not reached for these patients at the time of DCO
Median DOR calculated using Kaplan-Meier technique. Target lesion size is the sum of diameters of target lesions, assessed by investigator per RECIST 1.1.
Best change in target lesion is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively. PFS was assessed by investigator per RECIST 1.1
1L, first line; 2L, second line; CI, confidence interval

My thoughts about ADCs in HR+/HER2- mBC

- Longer T-DXd exposure **does not increase toxicity**!

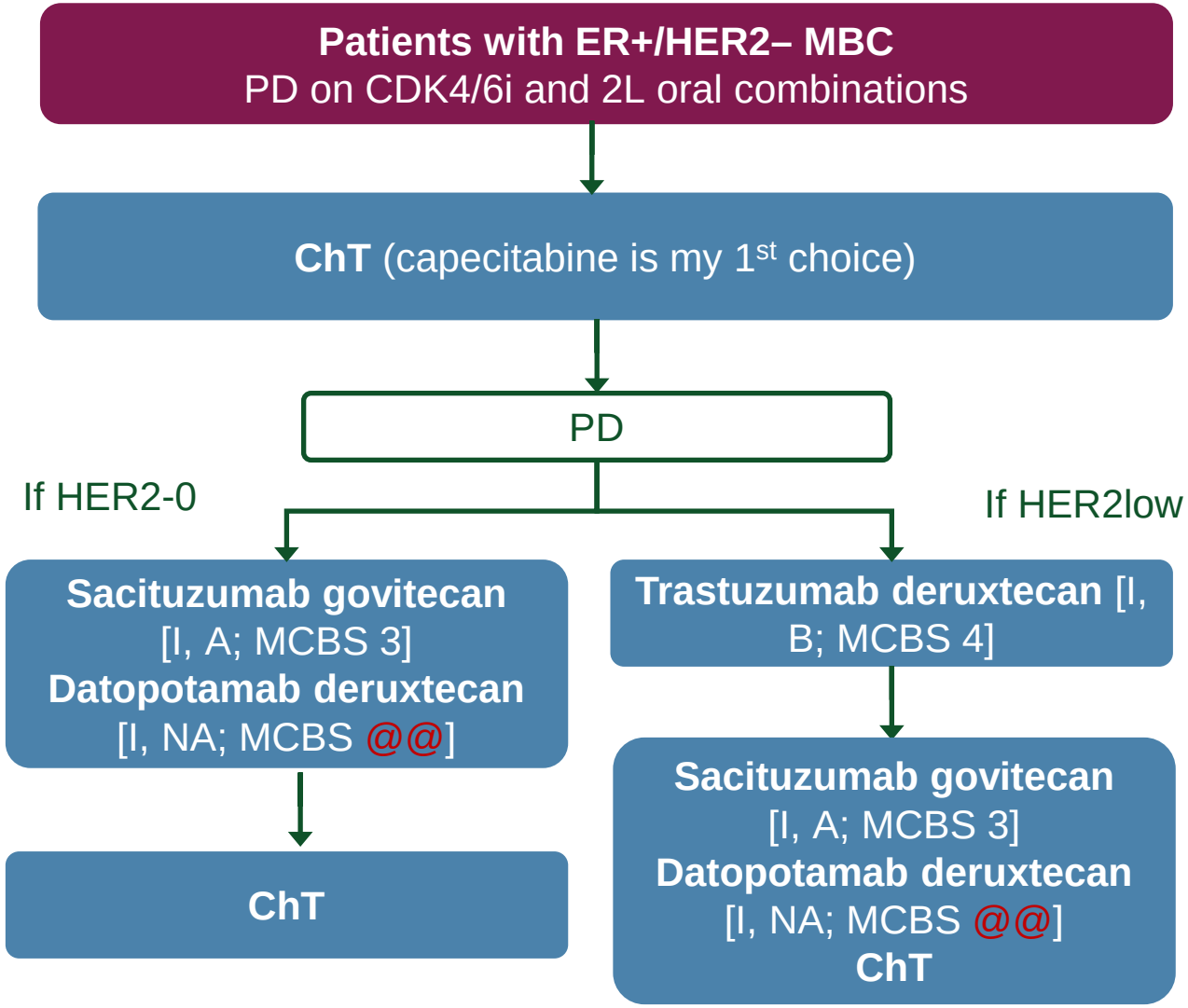
- ADCs anti-Trop2 demonstrated to improve clinical outcomes after 3 lines of CT (**Sacituzumab govitecan**) and in less pre-treated patients, i.e. **after 1 line of CT** (**Datopotamab deruxtecan**)

- In pts with HR+/HER2low mBC **after 1 line of CT**:
  - T-DXd provides a **higher magnitude of clinical benefit** than Dato-DXd, in terms of PFS (PFS **delta**: 4 vs. 2 months) and ORR (ORR **delta**: 36% vs. 13%) across similar patient population
  - **T-DXd** remains the **standard of care** in HR+/HER2low mBC **after 1 line of CT**

- **After T-DXd or in HER2-zero disease**, anti-Trop2 ADCs are my first choice:
  - Which is the best option after T-DXd between Dato-DXd (**same payload**) or Sacituzumab govitecan (**different payload but same mechanism of action, anti-TOPO1**)?
  - What about sequencing Dato-DXd and Sacituzumab (**different linker, DAR and payload**), with or without other therapies in between?

Giuseppe Curigliano, MD PhD

My thoughts about ADCs in HR+/HER2- mBC



Giuseppe Curigliano, MD PhD

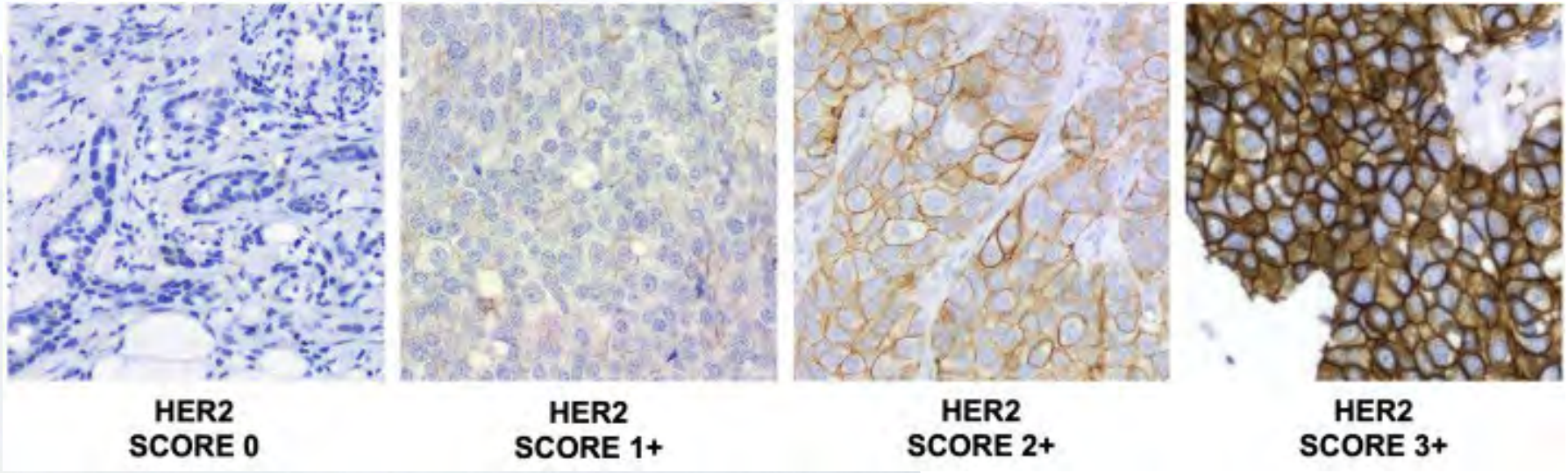
NEXT STEPS?

3) Move from a **binary** HER2 paradigm toward a **spectrum of expression**

Quantitative HER2 assays
(qIHC, RT-qPCR…)

↓

0-3+ SCORING →
CONTINUOUS SCORING! (0-100%)



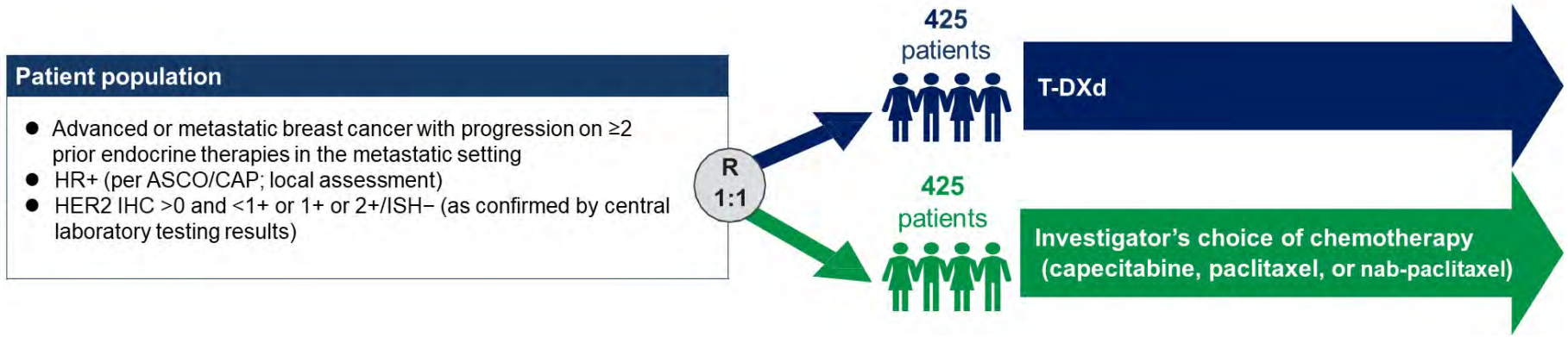
Adapted from Marchiò C et al. Semin Can Biol 2020

DESTINY 6

Study Design

N=850

(HER2 IHC 1+ or 2+/ISH−, n≈700; IHC >0 and <1+, n≈150)

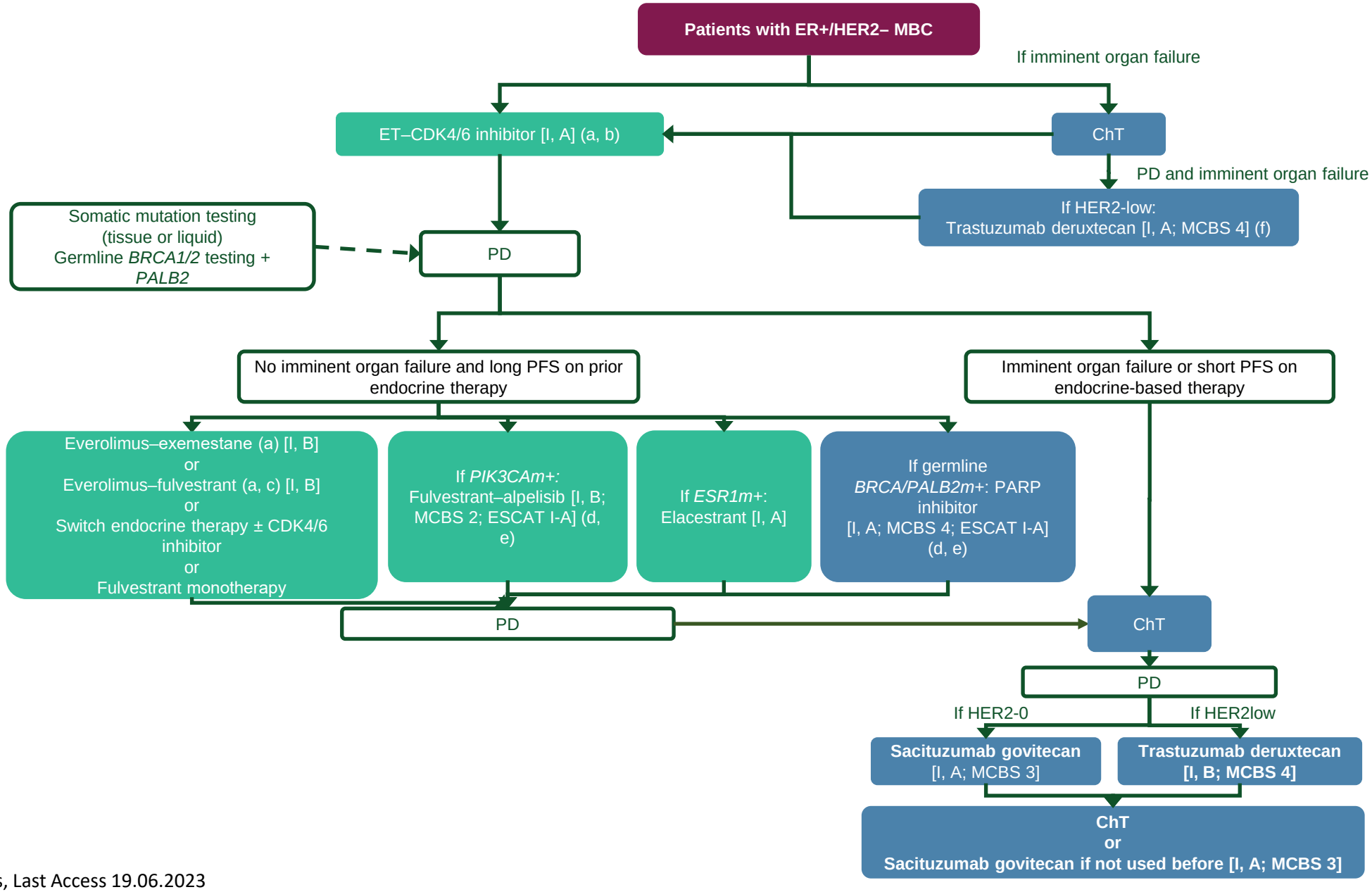


Stratified by: HER2 status (IHC 2+/ISH− vs IHC 1+ vs IHC >0 and <1+); prior CDK4/6 inhibitor (yes or no); prior taxane in a nonmetastatic setting (yes or no).

Non-approved medication information in Japan is contained in this slide.

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth receptor 2; HR, hormone receptor; IHC, immunohistochemistry; R, randomization; T-DXd, trastuzumab deruxtecan

ESMO Living Guidelines



ESMO Living Guidelines, Last Access 19.06.2023

Non-approved medication information in Japan is contained in this slide.