What's Happening in Breast Cancer

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LSU Health Sciences Center

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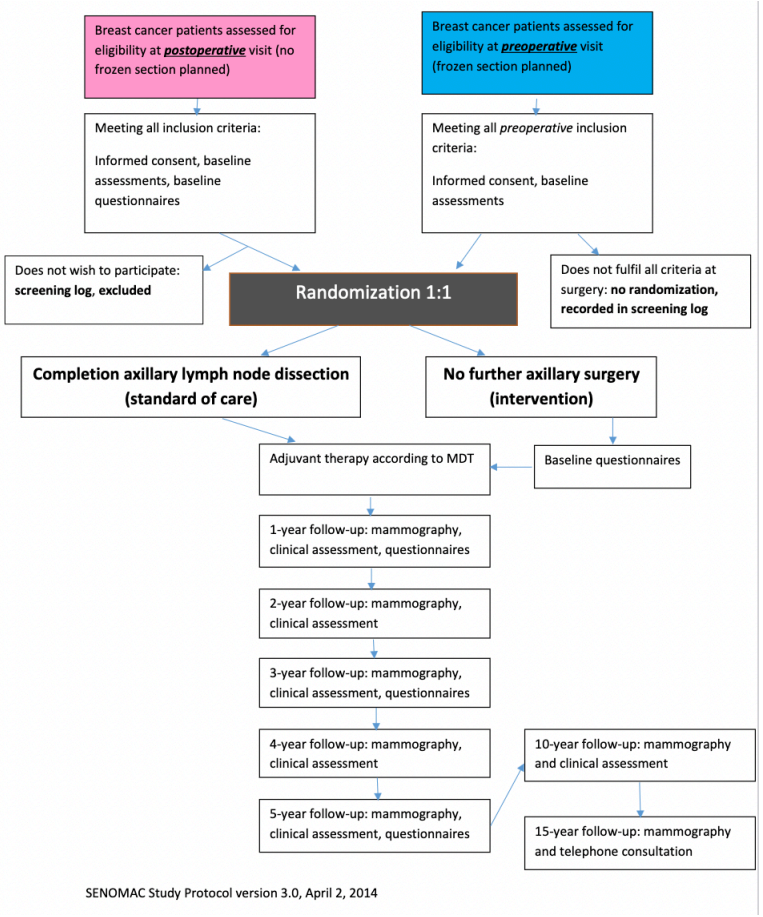
Objectives

- Review advances in breast cancer in 2023
  - Early breast cancer
  - Survivorship
  - Metastatic Breast Cancer
- On the horizon

Early Breast Cancer

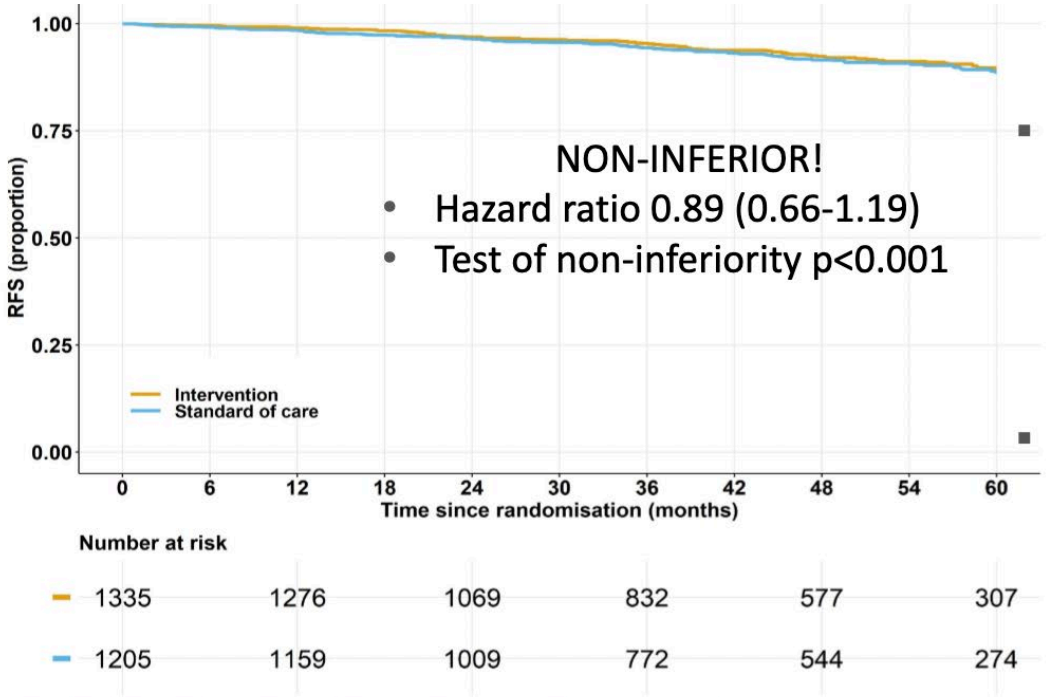
SENOMAC

- T1-3 primary IBC
- Clinically node negative
  - Mandatory preop US
- Male and female
- BCT and mastectomy
- Up to 2 SLND macromets
- No contraindication to XRT



Boniface et al, SABCS 2023

SENOMAC RFS



NON-INFERIOR!

- Hazard ratio 0.89 (0.66-1.19)
- Test of non-inferiority p<0.001

- 191 RFS events
  - **ALND** N=96 (8.0%)
  - **No ALND** N=95 (7.1%)
- Estimated 5-year RFS
  - **ALND** 88.7% (86.3-91.1)
  - **No ALND** 89.7% (87.5-91.9)

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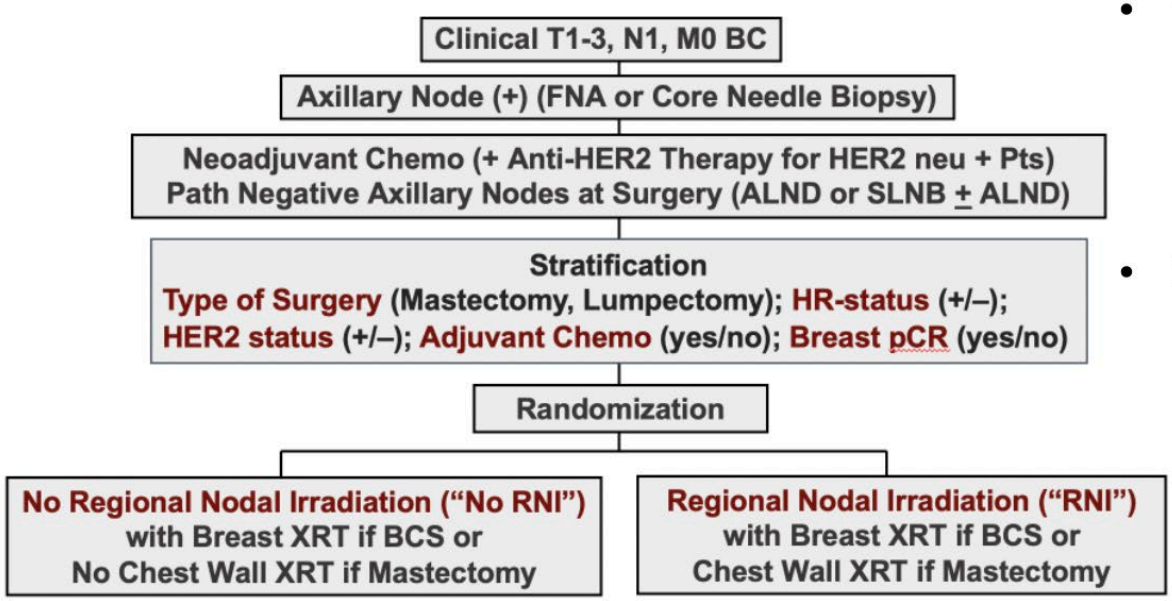
NSABP B51/RTOG 1304



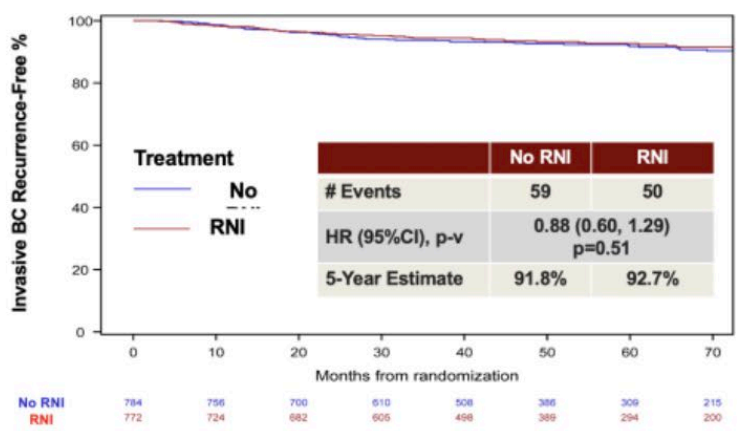
FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation

- 1556 patients
  - No RNI: 784
  - RNI: 772
- Median Follow-up: 59.5 mos

Mamounas et al, SABCS 2023

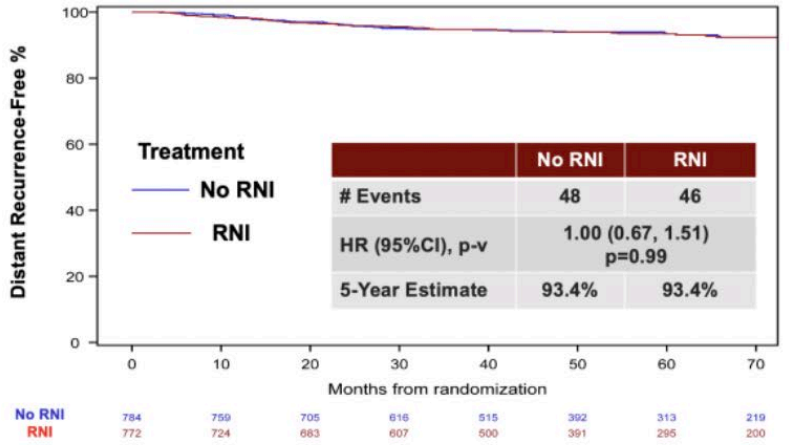
Primary Endpoint: Omission of RNI after pN1 to pN0 with NAC

Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

Distant Recurrence-free Interval (DRFI)



	No RNI	RNI
# Events	48	46
HR (95%CI), p-v	1.00 (0.67, 1.51) p=0.99	
5-Year Estimate	93.4%	93.4%

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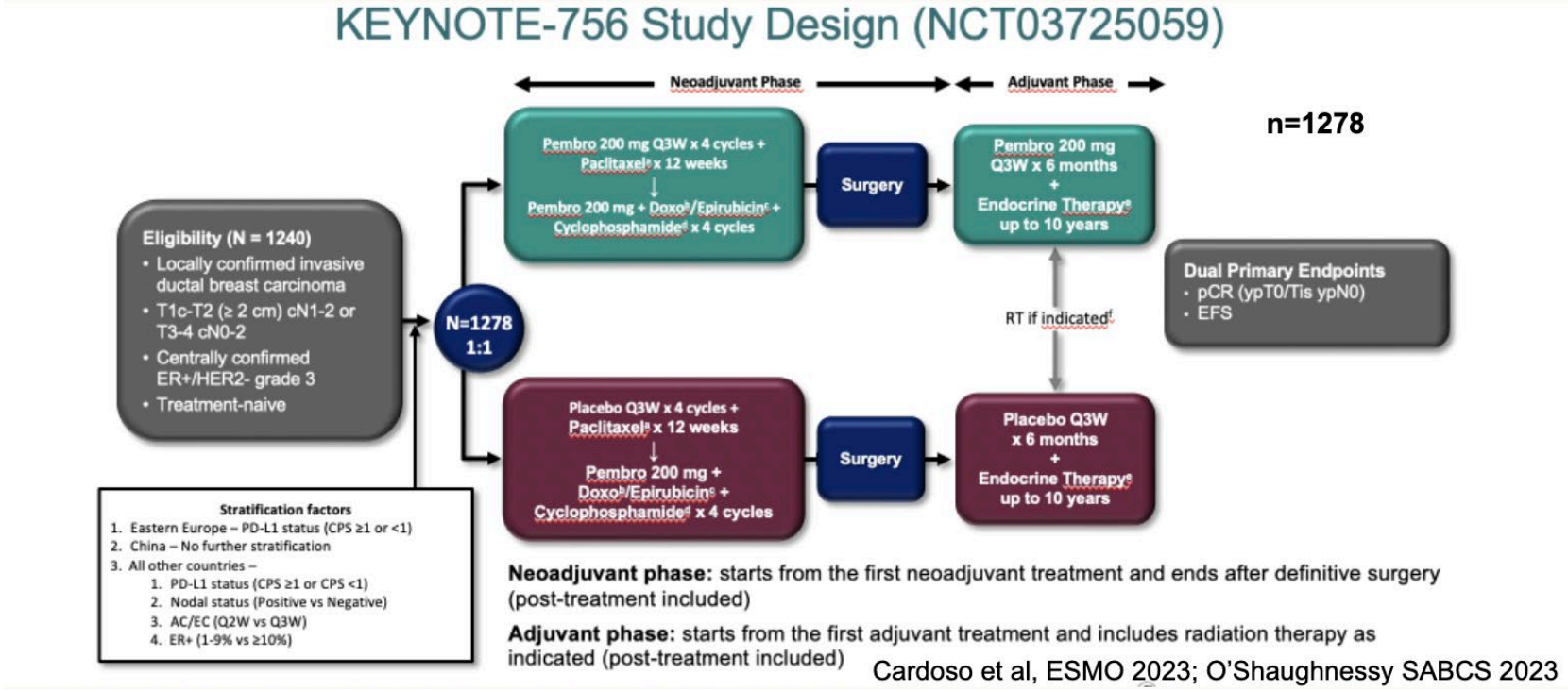
ICI in Early ER+ Breast Cancer



Cardoso et al, ESMO 2023; O'Shaughnessy SABCS 2023

CheckMate-7FL study design (NCT04109066)

n=510

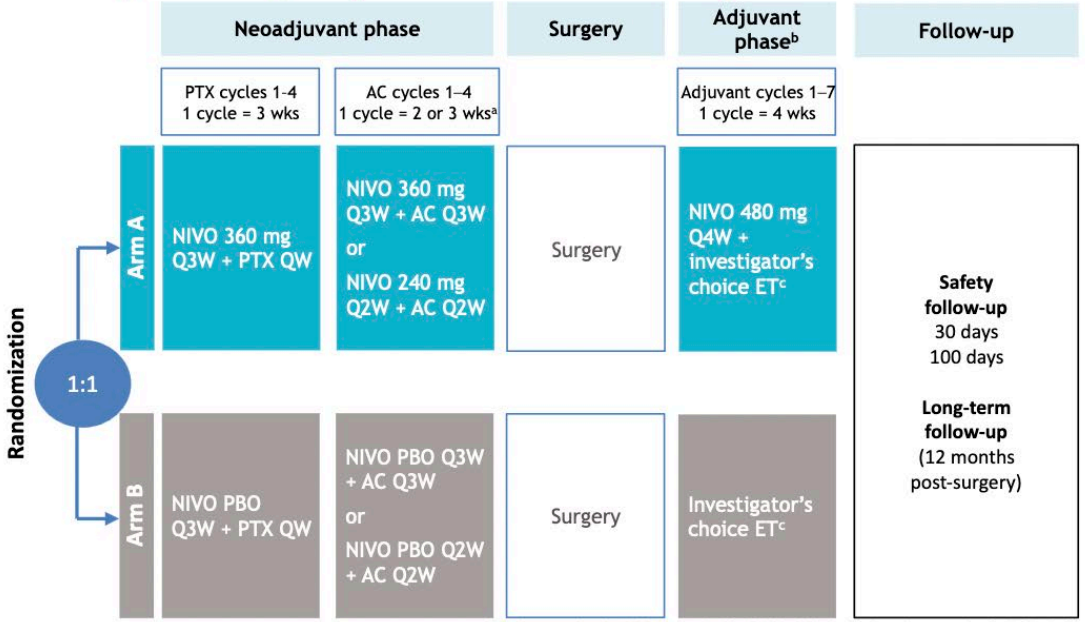
Screening

Key inclusion criteria

- Newly diagnosed ER+, HER2− BC
- Confirmed ER+ BC
- T1c-T2, cN0-cN2 or T3-T4, cN0-cN2
- Grade 3 or grade 2 with ER 1–10%
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

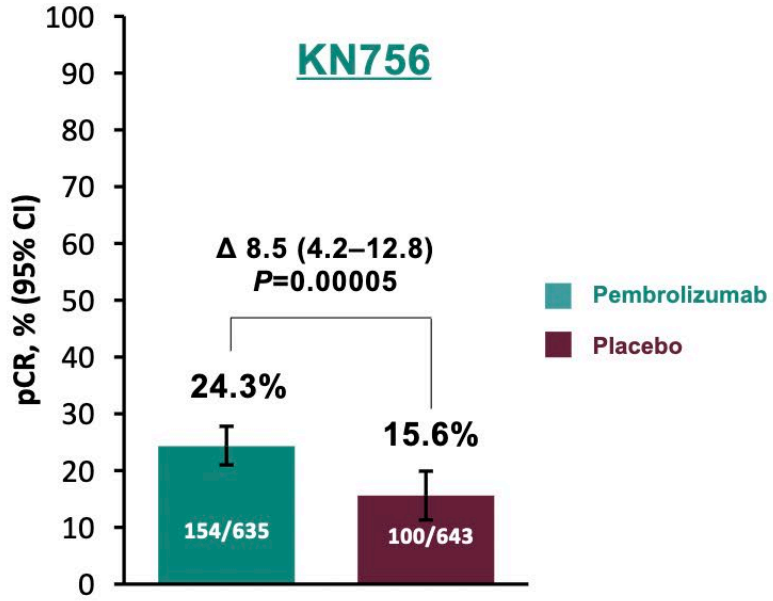
Stratification factors

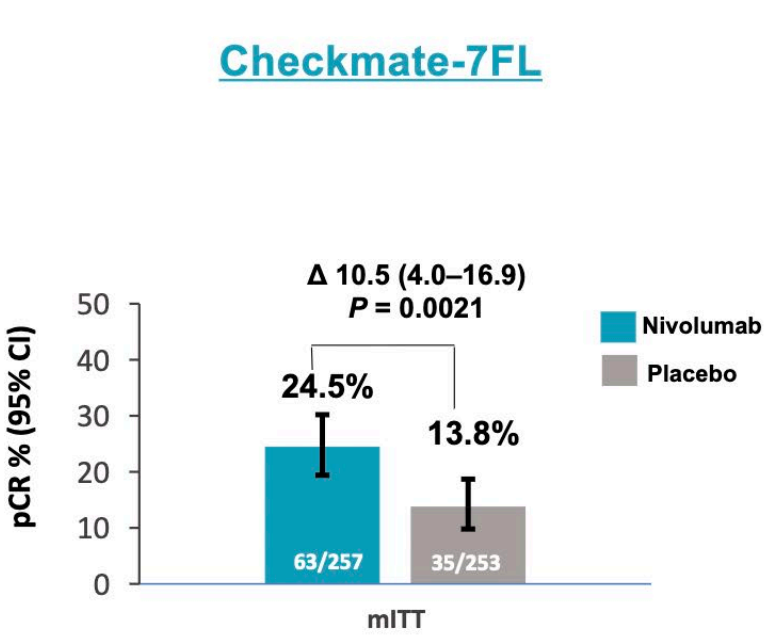
- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC (Q3W or Q2W)



Loi et al, LBA 20, ESMO 2023; Loi et al, SABCS 2023

pCR (ypT0/Tis ypN0)





Cardoso et. al. ESMO 2023

Slide courtesy of L Huppert

Loi et. al. ESMO 2023

KN756: Key subgroup and biomarker analyses

Clinical charact.	Impact of pembro on pCR rate
Stage II (n-807) III (n=471)	• Benefit regardless of stage - stage II (+Δ 9.1) and III (+Δ 8.0)
LN involvement pos (n=1152) neg (n=126)	• Benefit in LN pos (+Δ 9.3) • Benefit less in LN neg (+Δ3.8)
Chemo exposure full (n=634) partial (n=641)	• Benefit regardless of whether chemotherapy completed

Biomarker	Impact of pembro on pCR rate
PD-L1 22C3 CPS	• Benefit if CPS ≥1. Higher pCR rates & larger Δ with higher CPS • Benefit less clear CPS <1
ER status Stratified by CPS score	• CPS ≥1: Benefit for all ER%, with larger benefit if ER <10% • CPS <1: Benefit less clear ER ≥10%

Cardoso et. al. SABCS 2023

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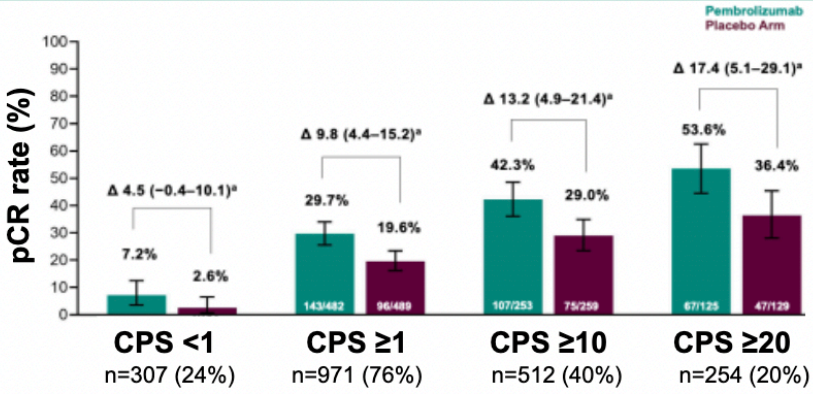
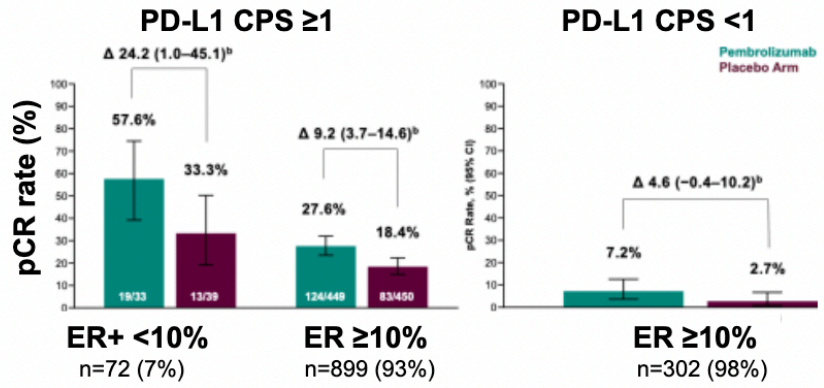
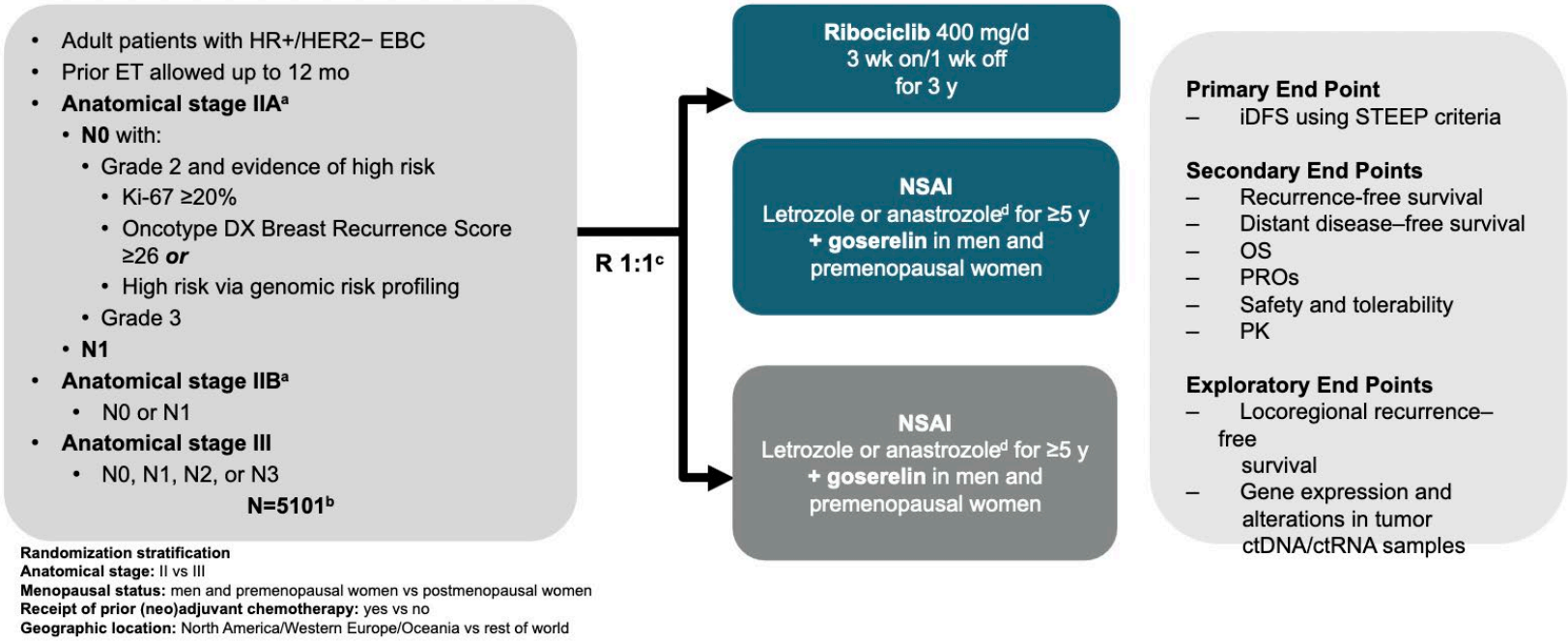
PD-L1 status (22C3 CPS)



ER status

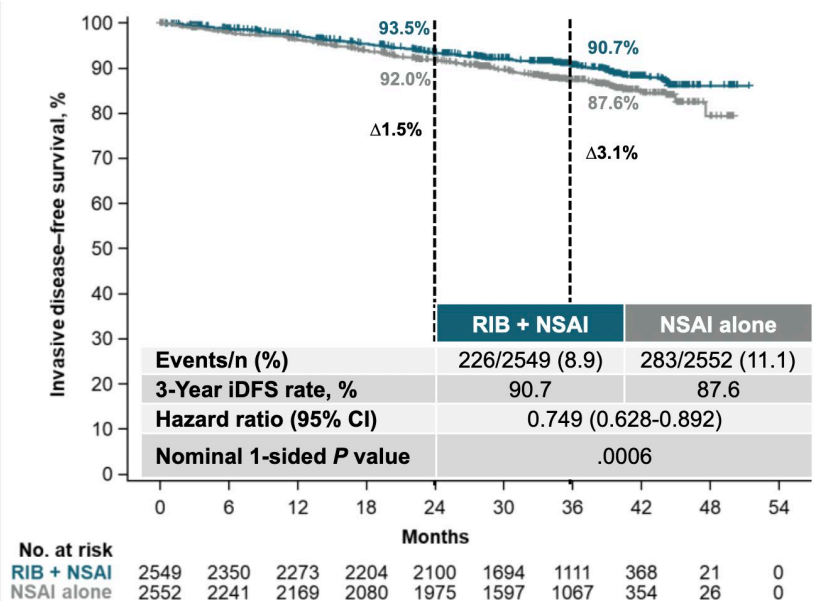


NATALEE



Slamon, et al ASCO 2023; Hortobagyi et al, SABCS 2023

IDFS

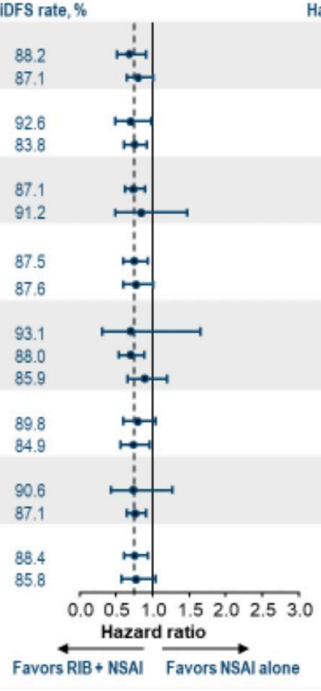


- Median follow-up 33.3 mos (max 51 mos)
- Absolute IDFS benefit with ribo + NSAI 3.1% at 3 years
- Risk of invasive disease reduced by 25.1% with ribo added

Slamon et al, ASCO 2023; Hortobagyi et al, SABCS 2023

IDFS Across Subgroups

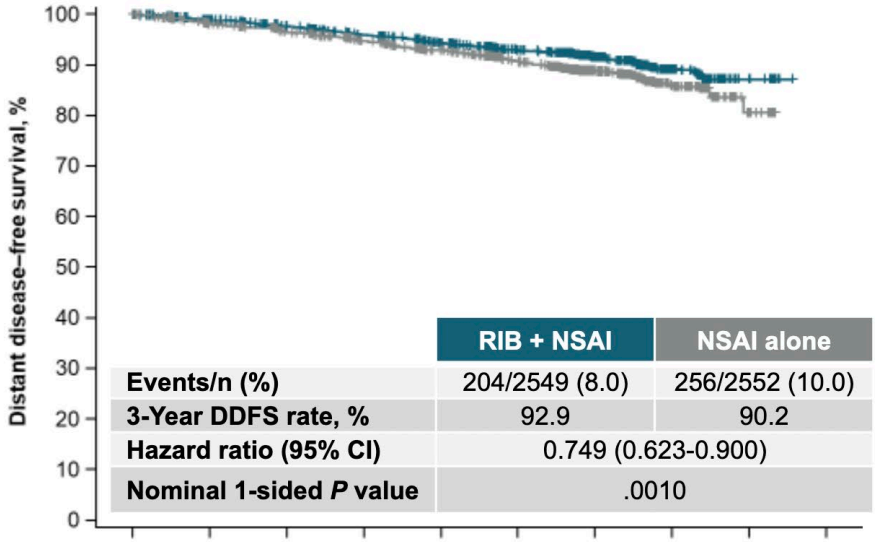
Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North America/Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histological grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status[a]						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status[b,c]						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040



AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging.
[c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Hortobagyi et al. SABCS 2023

DDFS



	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

No. at risk										
RIB + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI alone	2552	2245	2171	2091	1990	1609	1080	356	26	0

DDFS, distant disease–free survival.

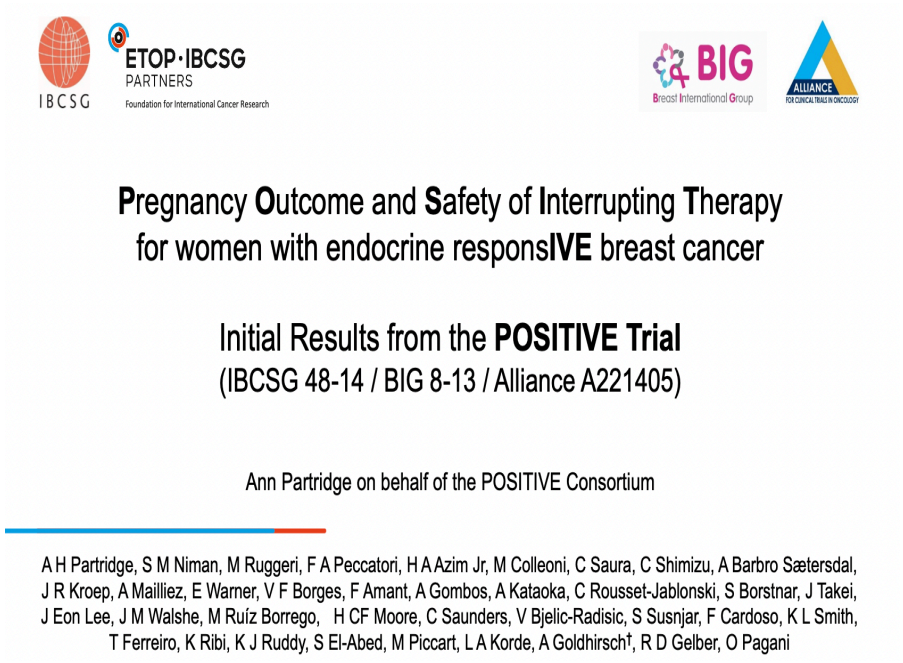
[a] DDFS is the time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary nonbreast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

- Absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years
- Risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis
- OS data require longer-term follow-up, as there were fewer than 4% of events in both treatment arms

Hortobagyi et al, SABCS 2023

Survivorship

POSITIVE Trial – SABCS 2022

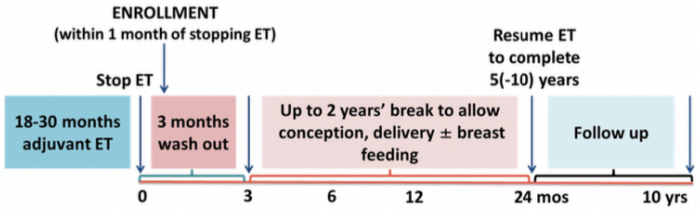


- Single arm
- First prospective study to assess pregnancy after BC and interruption of adjuvant ET to attempt pregnancy
- Primary:
  - BCFI
- Secondary:
  - Pregnancy, offspring outcomes, breastfeeding, ART use, adherence to ET, DRFI

TRIAL PROCEDURES

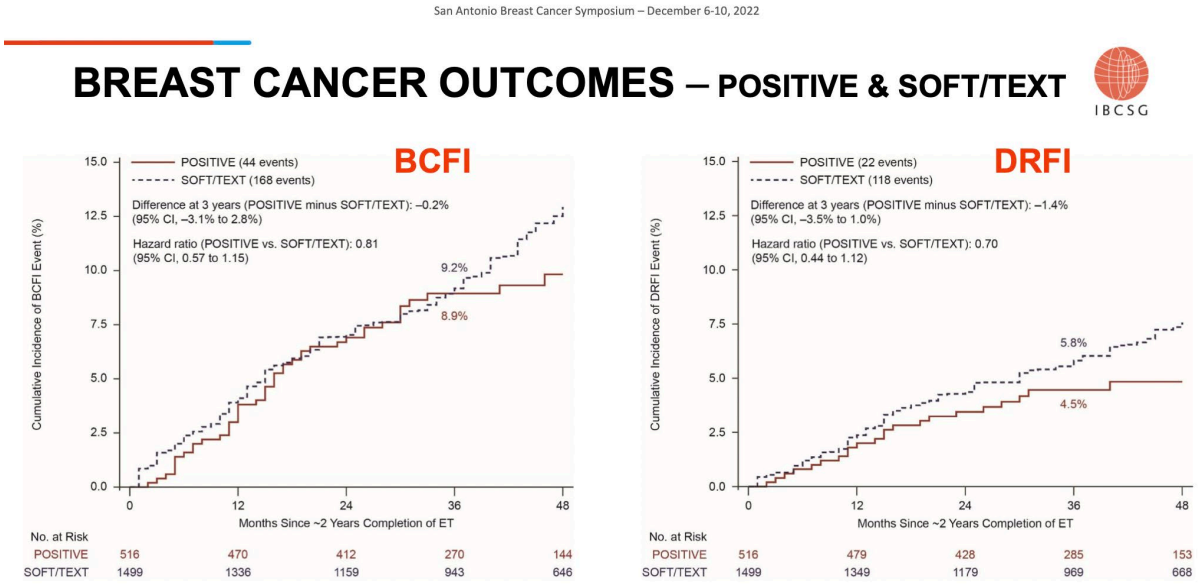
IBCSG

- Planned ET interruption (within 1 month of trial enrollment):
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including 3-months washout period
  - If no pregnancy by 1 year, fertility assessment strongly recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs
- Long-term follow-up



Partridge, et al SABCS 2022

SOFT/TEXT Data Used as External Control

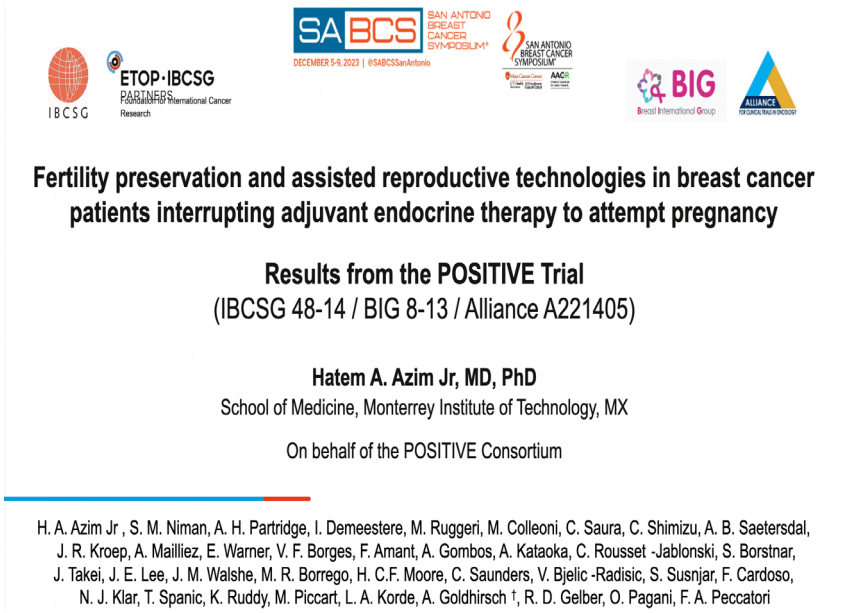


Partridge et al 2022

Conclusions

- Temporary interruption of ET did not impact short term outcomes (41mos)
- 74% of women had at least 1 pregnancy, most (70%) within 2 years
- Birth defects were low (2%) not clearly a/w treatment
- Longer follow-up planned

POSITIVE Trial – SABCS 2023



Fertility preservation and assisted reproductive technologies in breast cancer patients interrupting adjuvant endocrine therapy to attempt pregnancy

Results from the POSITIVE Trial
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Hatem A. Azim Jr, MD, PhD
School of Medicine, Monterrey Institute of Technology, MX

On behalf of the POSITIVE Consortium

H. A. Azim Jr , S. M. Niman, A. H. Partridge, I. Demeestere, M. Ruggeri, M. Colleoni, C. Saura, C. Shimizu, A. B. Saetersdal, J. R. Kroep, A. Mailliez, E. Warner, V. F. Borges, F. Amant, A. Gombos, A. Kataoka, C. Rousset -Jablonski, S. Borstnar, J. Takei, J. E. Lee, J. M. Walshe, M. R. Borrego, H. C.F. Moore, C. Saunders, V. Bjelic -Radisic, S. Susnjar, F. Cardoso, N. J. Klar, T. Spanic, K. Ruddy, M. Piccart, L. A. Korde, A. Goldhirsch †, R. D. Gelber, O. Pagani, F. A. Peccatori

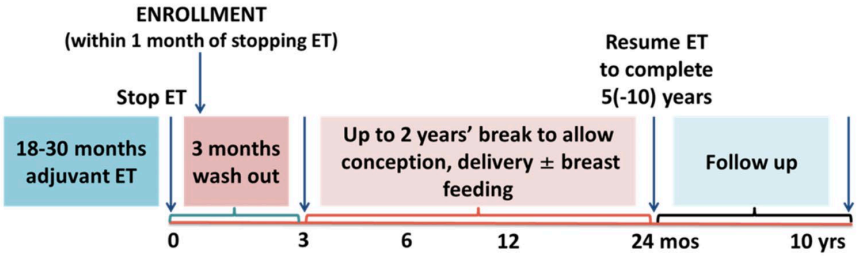
- Premenopausal
- ≤42yo
- At least 18 mos, no more than 30 mos ET
- No evidence of recurrence
- Reporting secondary outcomes
  - menstruation recovery
  - Use of ART

Azim et al SABCS 23

POSITIVE trial design

IBCSG

- Prospective, international, multicenter, investigator-initiated, single-arm trial



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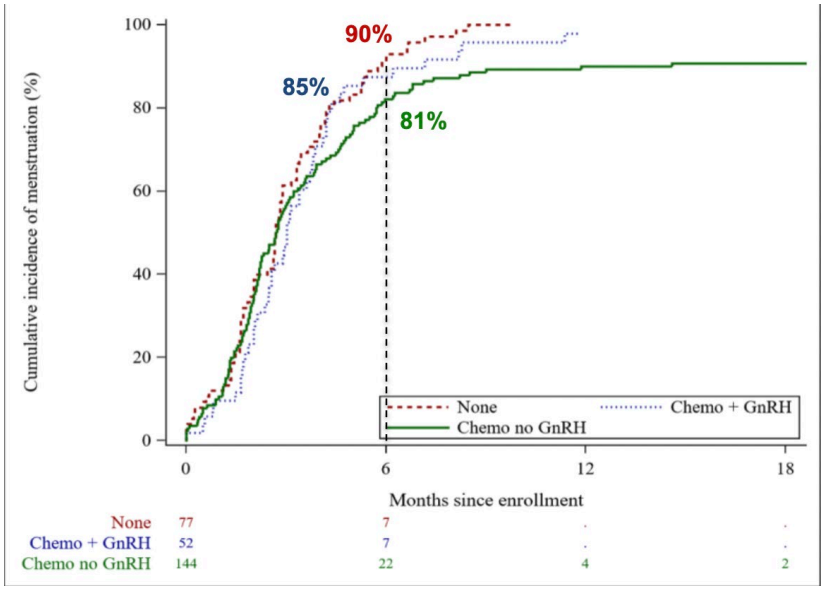
Menstruation Resumption



- All 516 pts in the 1st analysis stopped ET within 1 month of study entry
- 273 (53%) reported amenorrhea at enrollment
  - 255 (94%) recovered menses

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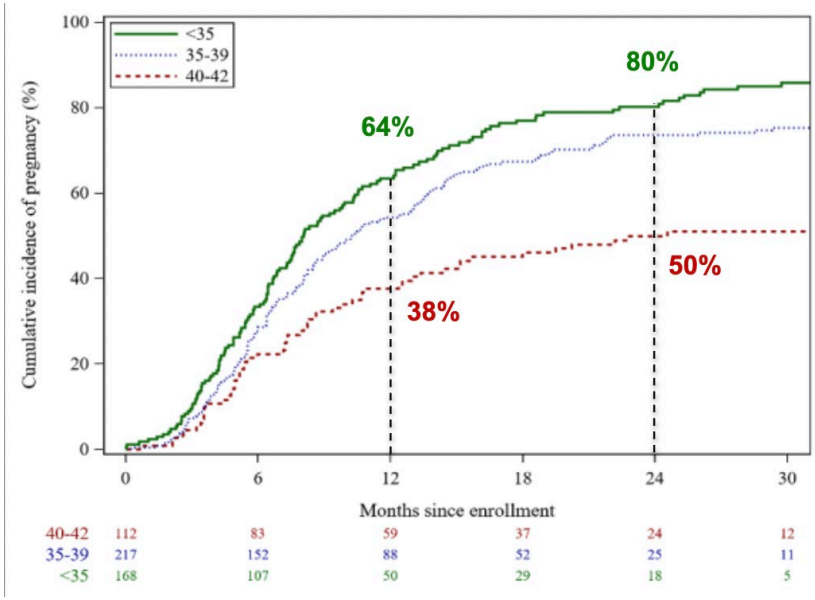
Time to Pregnancy



Multivariable Fine and Gray competing risk model	sHR (95% CI)
Chemo + GnRHa vs Chemo alone	1.29 (0.94 – 1.79)
None vs Chemo alone	1.05 (0.85 – 1.32)
35-39 vs <35	0.74 (0.59 – 0.93)
40-42 vs <35	0.40 (0.29 – 0.56)
SERM+OFS vs SERM only	0.94 (0.71 – 1.24)
AI+OFS vs SERM only	0.94 (0.67 – 1.33)
Prior birth: Yes vs No	0.94 (0.72 – 1.23)
Irregular vs Persistent amenorrhea	1.17 (0.85 – 1.63)
Normal vs Persistent amenorrhea	1.01 (0.78 – 1.32)

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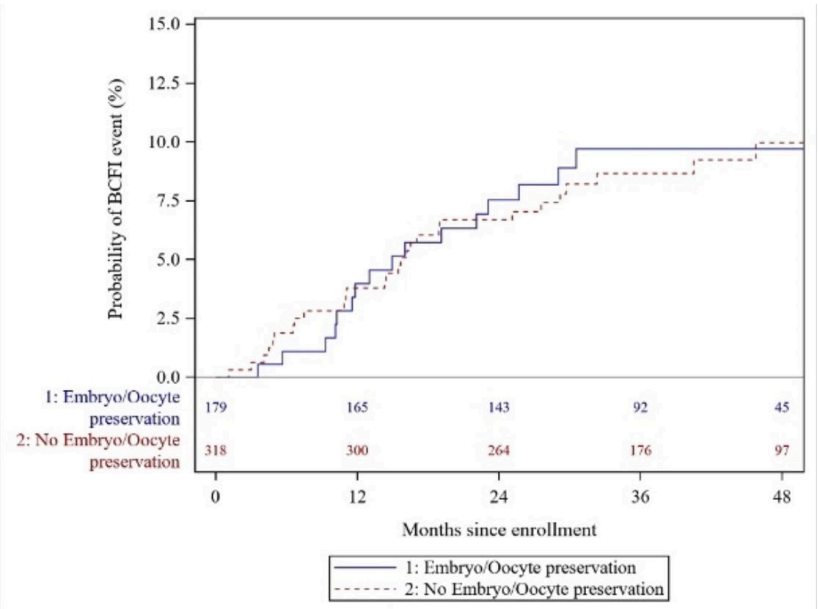
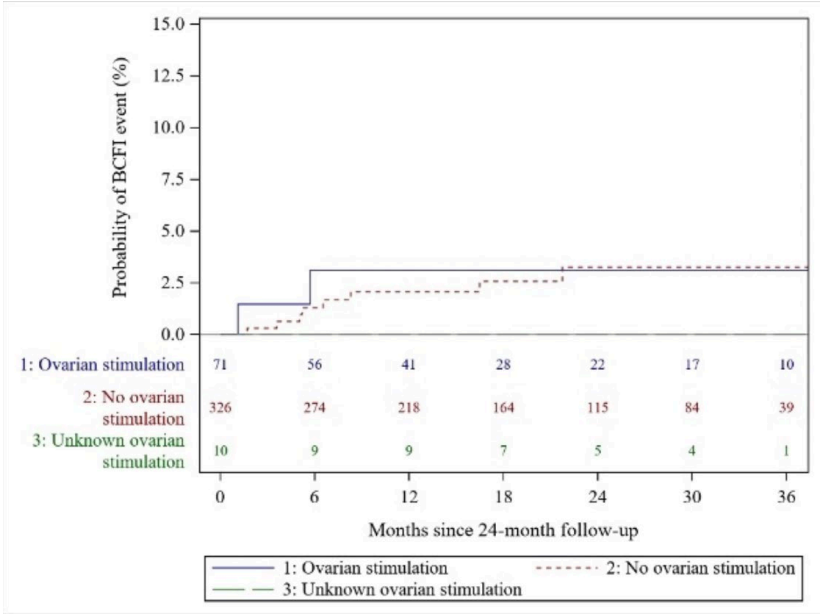
Ovarian Stimulation and Breast Cancer Outcomes



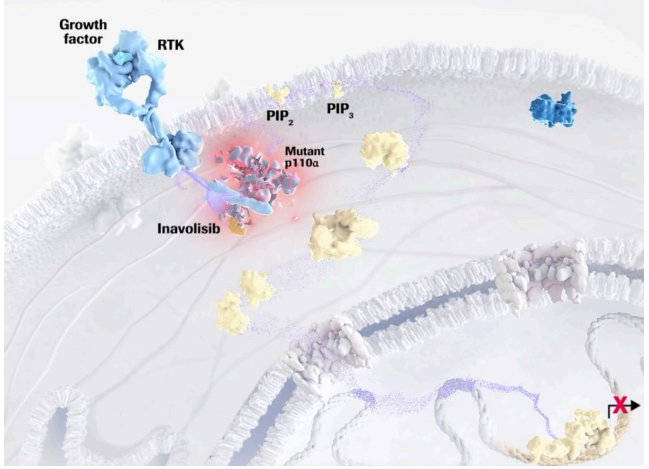


Azim et al SABCS 23

Conclusions

- Largest prospective study investigating fertility preservation and ART in patients with early HR+ breast cancer desiring pregnancy
- >90% of women presenting with amenorrhea resumed menses, usually within the first 6 mos
- Young age was the main factor a/w shorter time to pregnancy whereas type of ET was not
- Embryo/oocyte cryopreservation at diagnosis followed by embryo transfer after ET interruption had higher pregnancy rates but was not associated with worse prognosis
- No increase in breast cancer events observed in patients undergoing IVF on study albeit few events, longer follow-up needed

Metastatic Breast Cancer



INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

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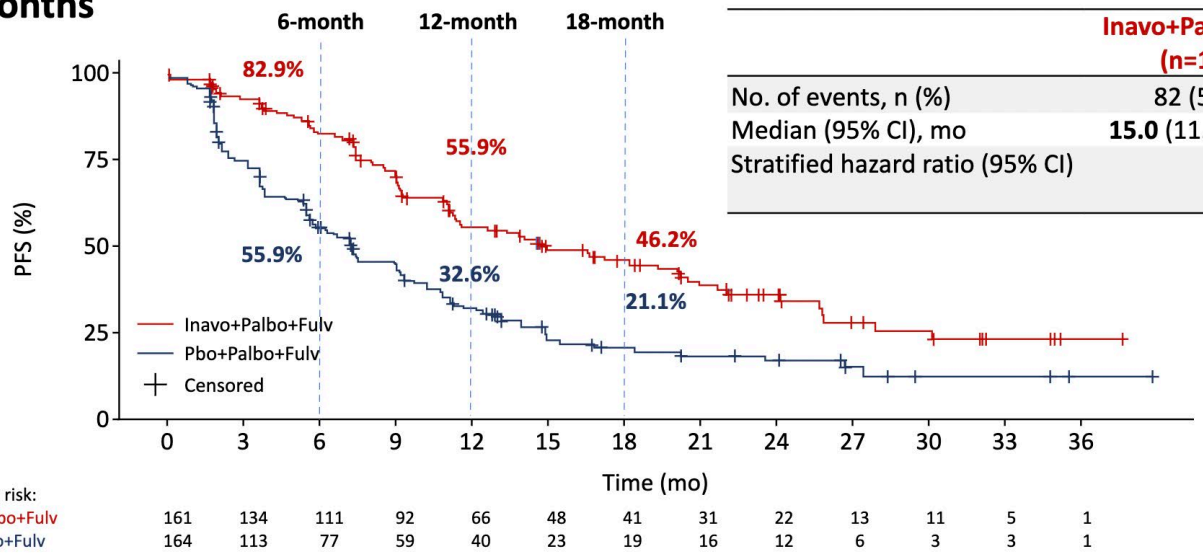
Primary Endpoint: PFS

Median follow-up: **21.3 months**



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	**15.0** (11.3, 20.5)	**7.3** (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

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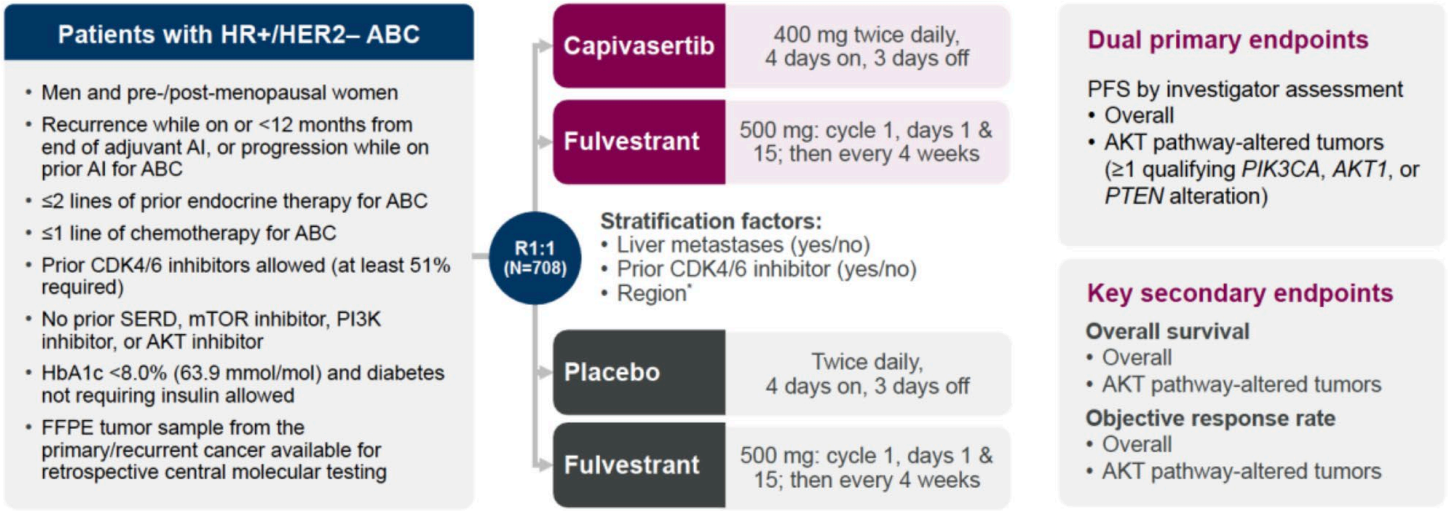
Capitello-291

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

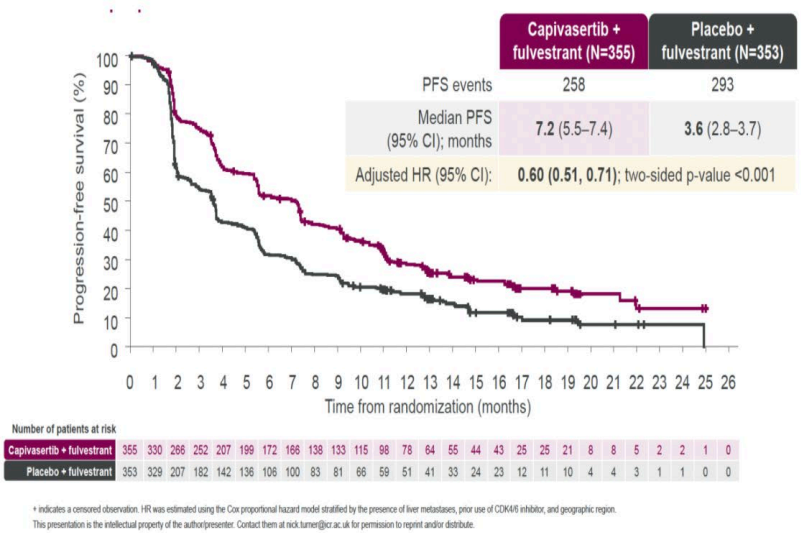


HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Turner SABCS 2022

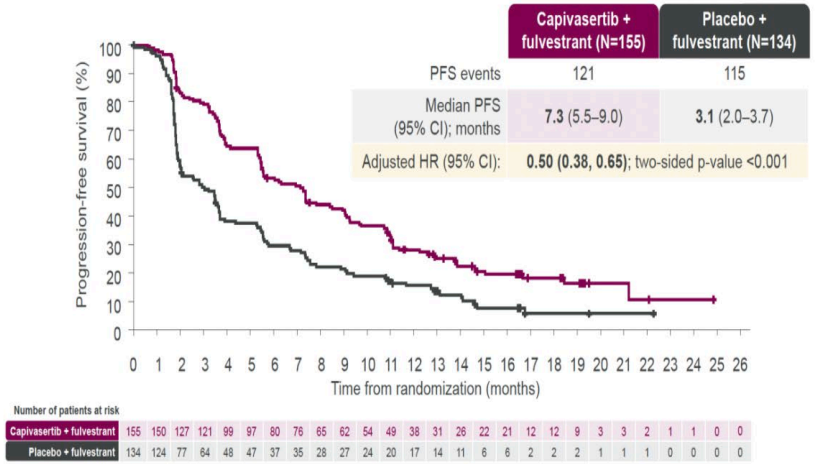
Dual Primary Endpoints

PFS in overall population



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

PFS in altered population



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

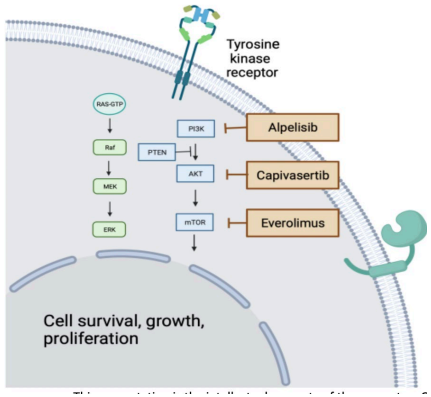
Turner, SABCS 2022

FDA approves capivasertib with fulvestrant for breast cancer

On November 16, 2023, the Food and Drug Administration approved capivasertib (Truqap, AstraZeneca Pharmaceuticals) with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Content current as of:
11/16/2023

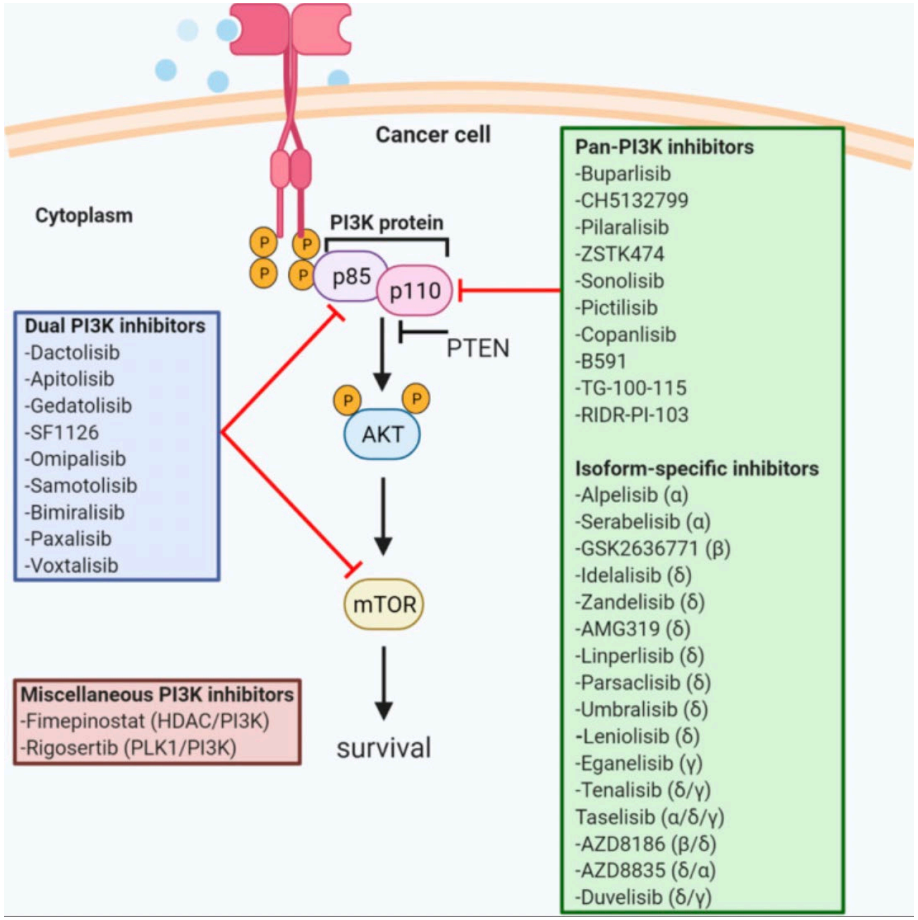
Current Approvals for MBC inhibiting PIK3CA/AKT/mTOR Pathway



	Everolimus (BOLERO-2)	Alpelisib (SOLAR-1)	Capivasertib (Capitello-291)
Mechanism of action	mTOR inhibitor	PI3Kα-specific inhibitor	AKT inhibitor
Design	Postmenopausal women (n=724), randomized 2:1 to exemestane + everolimus or placebo	n=572 (341 with PIK3CAm) randomized 1:1 to fulvestrant +alpelisib or placebo	n=708 (289 with AKT pathway alterations, 489 with prior iCDK4/6) randomized 1:1 to fulvestrant + capivasertib or placebo
Median PFS (months)	**10.6 vs 4.1 mo**	**PIK3CA WT: 7.4 vs. 5.6 mo** **PIK3CAm: 11 vs 5 mo**	**ITT 7.2 vs. 3.6 mo** **altered: 7.3 vs. 3.1**
HR (95%CI)	0.36 (0.27-0.47)	0.65 (0.5-0.85)	Altered 0.50 (0.38-0.65)
US FDA Approval	2012	2019 for patients with PIK3CA altered MBC HR+	2023 for patients with AKT, PTEN, PIK3CA altered HR+ breast cancer

Baselga J el ta, NEJM 2012; Andre F et al NEJM 2029; Turner N et al, NEJM 2023.

Emerging Therapies



Mishra, R et al. Int J Mol Sci 2021

npj | breast cancer

www.nature.com/npjbcancer

REVIEW ARTICLE OPEN

Check for updates

An emerging generation of endocrine therapies in breast cancer: a clinical perspective

Rima Patel[1]✉, Paula Klein[1], Amy Tiersten[1] and Joseph A. Sparano[1]

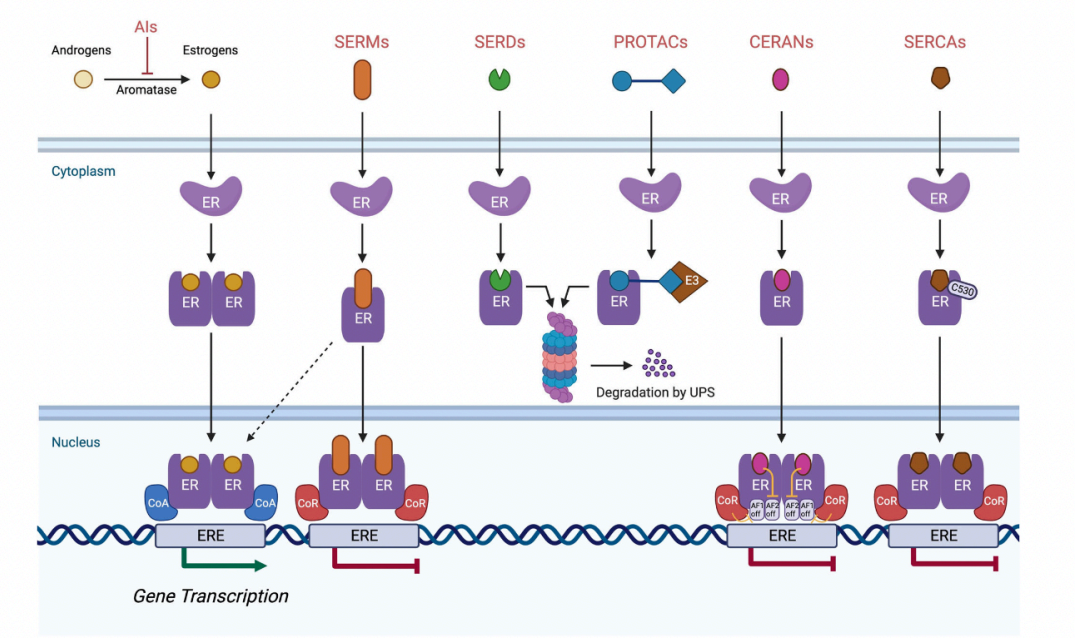


Fig. 1 Mechanisms of action of various classes of anti-estrogen therapies. The binding of estrogen to the ligand-binding domain of ER induces an activating conformational change enabling its dimerization and intranuclear localization. Activated ER can interact with estrogen-responsive elements (EREs), allowing for gene transcription, which leads to cell survival and proliferation. *Aromatase inhibitors (AIs)*. AIs, block estrogen production by inhibiting aromatase, which converts androgens to estrogens. *Selective estrogen receptor modulators (SERMs)*. SERMs competitively inhibit the binding of estrogen to ER. SERM-bound ER dimers interact with chromatin at EREs of the DNA. In the breast, they are associated with co-repressors (CoR) which inhibit ER transcriptional activity, but in other organ tissues such as bone and endometrium, they are associated with co-activators (CoA), allowing for gene transcription. *Selective estrogen receptor downregulators (SERDs)*. SERDs are pure ER antagonists. The SERD–ER complex is unable to translocate to the nucleus or undergo an open chromatin conformation that would allow transcription of ER-regulated genes. The SERD-ER complex subsequently undergoes proteosomal degradation. *Proteolysis targeting chimerics (PROTACs)*: PROTACs are bifunctional molecules that consist of a ligand that binds to a target protein (ER) and another ligand that binds to the E3 ubiquitin ligase. The interaction results in ubiquitination and degradation of the target protein through the ubiquitin-proteasome complex. *Complete estrogen receptor antagonists (CERANs)*. CERANs block both transcriptional activation domains (AF1 and AF2) of ER by recruiting nuclear receptor corepressors (N-CoR) to inactivate AF1 and directly inhibit AF2. *Selective estrogen receptor covalent antagonists (SERCAs)*. SERCAs covalently bind to a cysteine residue (C530) on ER, resulting in ER inactivation and inhibition of gene transcription.

Patel, R et al. NPJ 2023

Pipeline

TABLE 2. HIGHLIGHTS OF NEAR-TERM PIPELINE THERAPEUTICS FOR BREAST CANCER[10,19,a]

Drug name	Lead company	Target(s)	Current phase
Camizestrant	AstraZeneca	Estrogen receptor (Selective estrogen receptor degrader)	3
Trilaciclib (Cosela)	G1 Therapeutics, Inc	CDK4/6	3
Datopotamab deruxtecan	Daiichi Sankyo Co, Ltd	TROP-2	3
Elacestrant	Menarini Group	Estrogen receptor β Estrogen receptor α (Selective estrogen receptor degrader)	NDA (2/17/2023)
Enobosarm	Veru Inc	Androgen receptors	3
Giredestrant	Roche Holding AG	Estrogen receptor (Selective estrogen receptor degrader)	3
GLSI-100	Greenwich LifeSciences	HER2	3
Imlunestrant	Eli Lilly and Company	Estrogen receptor (Selective estrogen receptor degrader)	3
Nivolumab (Opdivo)	Bristol Myers Squibb	Immune system PD-1/PD-L1 and PD-L2	3
Oral paclitaxel and encequidar (Oraxol)	Athenex, Inc	Microtubules (tubulin) P-glycoprotein	3 (Cancer Research Laboratory 3/1/21)
Veliparib	AbbVie Inc	PARP	3
SYD985 (Vic-trastuzumab duo-carmazine)	Byondis BV	HER2 DNA DNA synthesis Antibody-drug conjugate	BLA (5/12/23)
Niraparib (Zejula)	GSK	PARP	3

BLA, biologics license application; NDA, new drug application.
[a]List is not all-inclusive.

Anderson, RK. Pharm Practice Focus: Onc 2022

Selective Estrogen Receptor Degraders (SERDs) in ER+/HER2- MBC

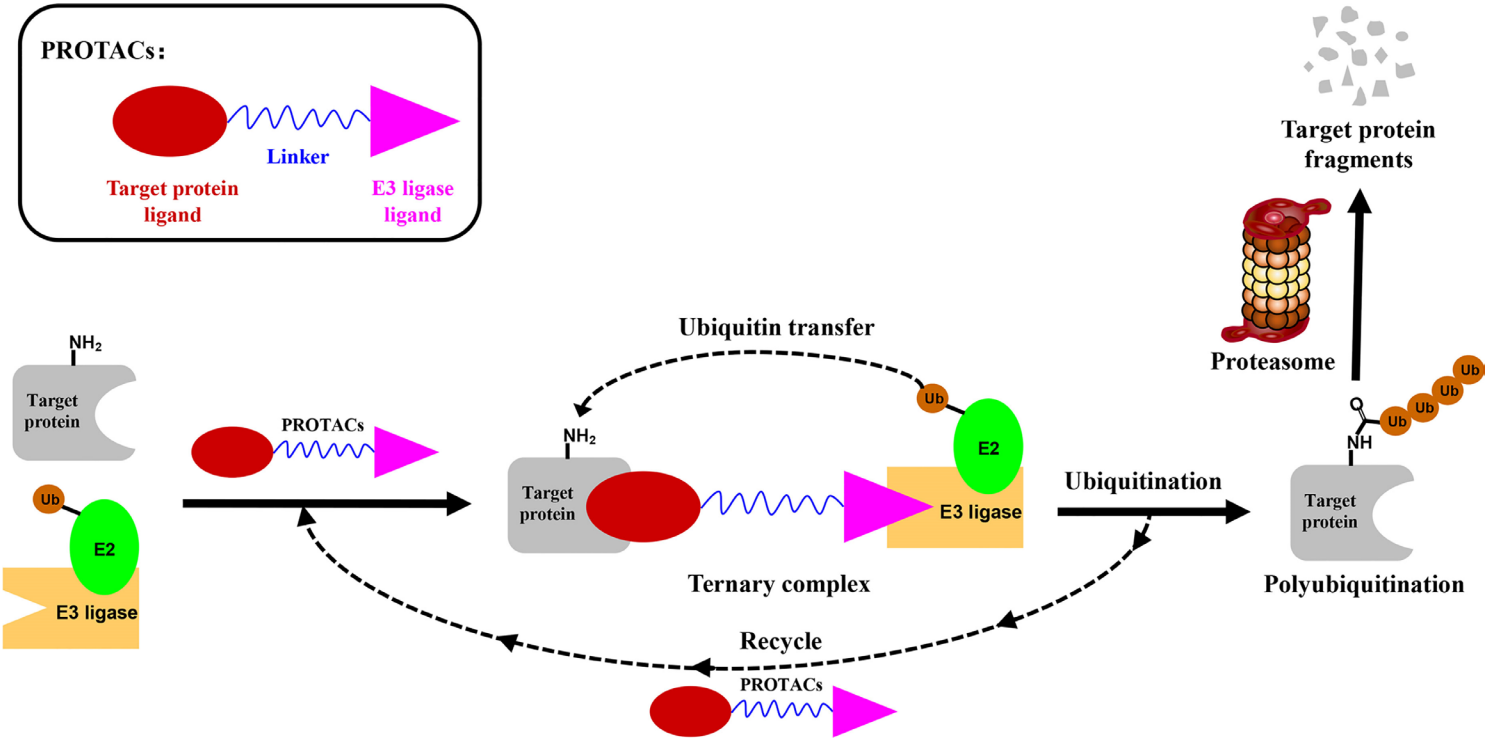
Parameter	EMERALD[1,2]	SERENA-2[3,4]	EMBER-3[5]	AMEERA-3[6,7]	acelERA[8,9]
Treatment	Elacestrant	Camizestrant	Imlunestrant ± abemaciclib	Amcenestrant	Giredestrant
Control arm	Fulvestrant/AIs	Fulvestrant	Fulvestrant/ exemestane	Fulvestrant/AIs/ tamoxifen	Fulvestrant/AIs
Phase (N)	Phase III (477)	Phase II (240)	Phase III (860)	Phase II (290)	Phase II (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 (51%)	Permitted	Permitted (79%)	Permitted (42%)
Allowed prior fulvestrant	YES	NO	NO	YES	YES
Allowed prior CT in MBC	YES	YES	NO	YES	YES
Data readout	Positive (registrational)	Positive (non-registrational)	Ongoing	Negative	Negative

1. Bidard. JCO. 2022;40:3246. 2. Elacestrant PI. 3. NCT04214288. 4. Oliveira. SABCS 2022. Abstr GS3-02. 5. NCT04975308.
6. NCT04059484. 7. Tolaney. JCO. 2023;41:4014. 8. NCT04576455. 9. Martin Jimenez. ESMO 2022. Abstr 211MO.

Key Trials With Oral SERDs

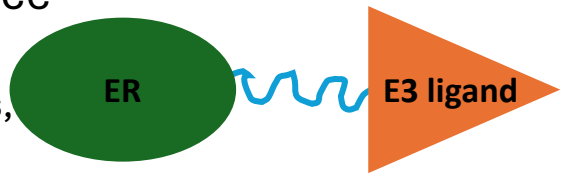
Trial Name	N	Arms	Setting	Trial Identifier
lidERA	4100	Giredestrant vs ET	Adjuvant	NCT04961996
EMBER-4	6000	Imlunestrant vs ET	Adjuvant	NCT05514054
CAMBRIA-2	5500	Camizestrant vs ET	Adjuvant	NCT05952557
SERENA-4	1342	Camizestrant + palbociclib vs anastrozole + palbociclib	1L	NCT04711252
persevERA	992	Giredestrant + palbociclib vs fulvestrant + palbociclib	1L	NCT04546009
pionERA	1050	Giredestrant + CDK4/6i vs fulvestrant + CDK4/6i	ET resistant after adjuvant ET; ESR1m	NCT06065748
SERENA-6	300	Camizestrant + CDK4/6i vs AI + CDK4/6i	Prior AI + CDK4/6i; ESR1m, switch to SERD	NCT04964934
EMBER-3	860	Imlunestrant ± abemaciclib vs ET	After prior AI ± CDK4/6i	NCT04975308
CAMBRIA-1	4300	Camizestrant vs ET	EBC after 2-5 yr adjuvant ET	NCT05774951

PROteolysis TArgeting Chimeras: PROTACs



Vepdegestrant (ARV-471) Background

- Vepdegestrant: selective, oral PROTAC protein degrader targeting wild-type and mutated ER[1,2]
- Vepdegestrant binds ER and an E3 ubiquitin ligase to induce ubiquitination and proteasomal degradation of ER[1,2]
  - SERDs induce ER immobilization and/or conformational changes, indirectly recruiting ubiquitin-proteasome system[3]
- Fulvestrant use challenged by IM administration, limited ER degradation (40%-50%) at optimal dose[4-6]
- In preclinical models, vepdegestrant associated with greater ER degradation and tumor growth inhibition vs fulvestrant[1,2]



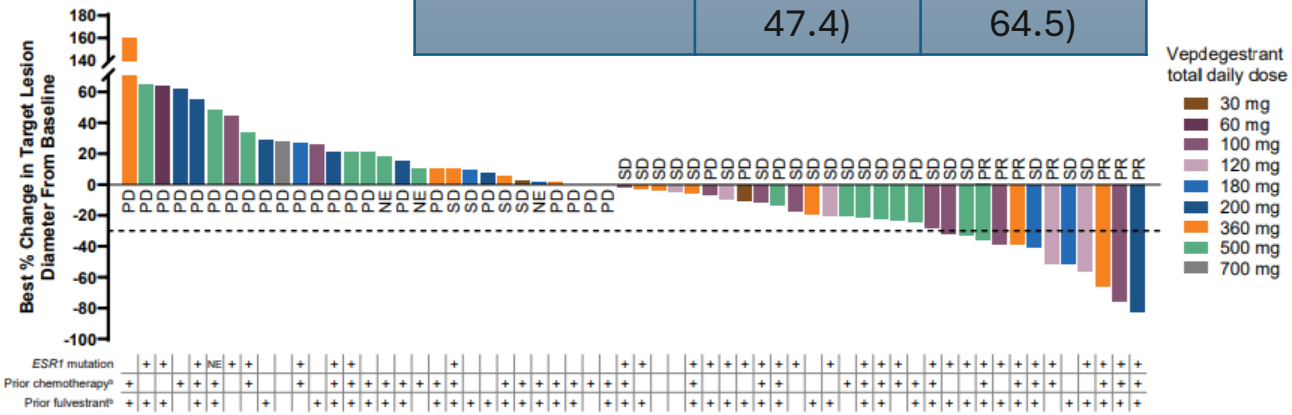
1. Hamilton. ESMO 2023. Abstr 390P. 2. Hurvitz. SABCS 2022. Abstr GS3-03. 3. Hanker. Cancer Cell. 2020;37:496. 4. Nathan. Oncol Ther. 2017;5:17. 5. Kuter. Breast Cancer Res Treat. 2012;133:237. 6. Robertson. Breast Cancer Res. 2013;15:R18.

VERITAC: Phase I Dose Expansion Efficacy and Safety

- Phase I trial expansion cohort (N = 83)
- Vepdegestrant: 30 mg →700 mg
  - No DLT
- Fatigue (26.5%) and nausea (24.1%) were the most common TRAEs
- No TRAE grade ≥4
- RP2D: 200 mg QD or 500 mg QD

Efficacy

Outcome	All Patients (n = 83)	ESR1m (n = 43)
CBR, n (%) (95% CI)	36.1 (25.9-47.4)	48.8 (33.3-64.5)



Hamilton. ESMO 2023. Abstr 390P. Hurvitz. SABCS 2022. Abstr GS3-03.

VERITAC: Phase II Trial of Vepdegestrant—Cohort Expansion

- Phase II dose expansion cohort (data cutoff: June 6, 2022)

Confirmed ER+ and HER2- advanced breast cancer with measurable or nonmeasurable disease per RECIST criteria v1.1; ≥1 prior ET (≥1 regimen for ≥6 mo in the locally advanced or metastatic setting); ≥1 prior CDK4/6 inhibitor; ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting
(N = 71)

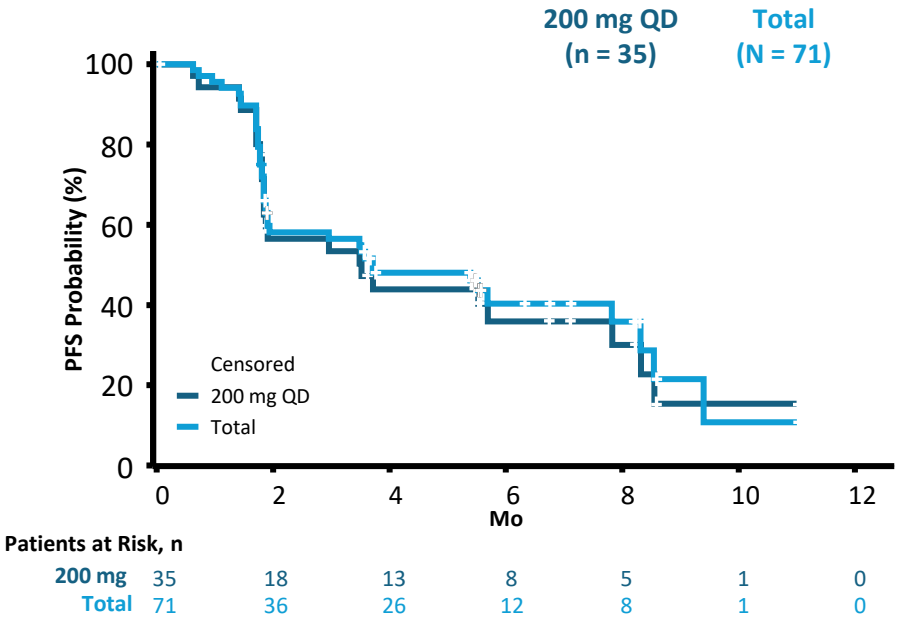
ARV-471
200 mg oral QD
(n = 35)

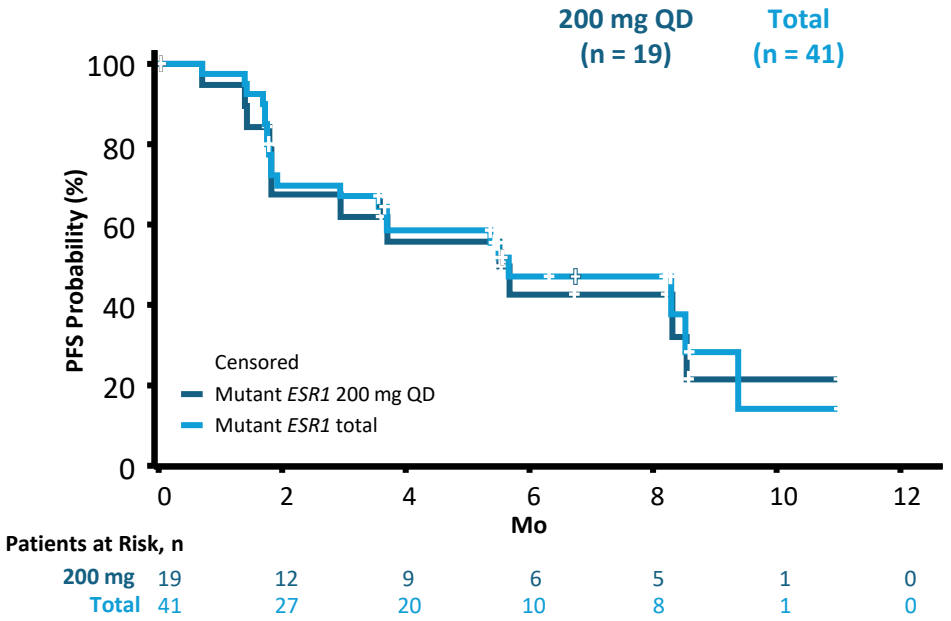
ARV-471
500 mg oral QD
(n = 36)

- **Primary endpoint:** CBR (rate of confirmed CR or PR or SD ≥24 wk)
- **Secondary endpoints:** ORR, DoR, PFS, and OS, safety, PK
- **Exploratory endpoints:** *ESR1* mutational status, ER protein levels

Hurvitz. SABCS 2022. Abstr GS3-03.

VERITAC: Progression-Free Survival



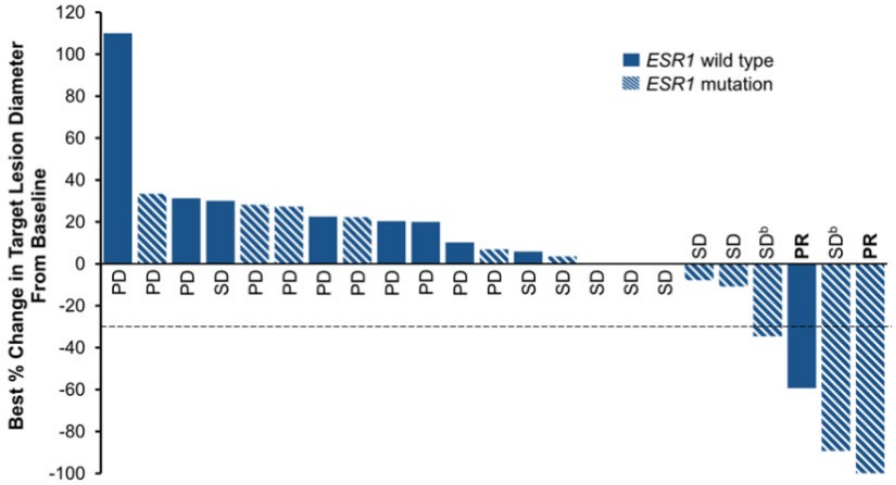


Hurvitz. SABCS 2022. Abstr GS3-03.

VERITAC: Updated Efficacy

- 200 mg dose (n = 35)

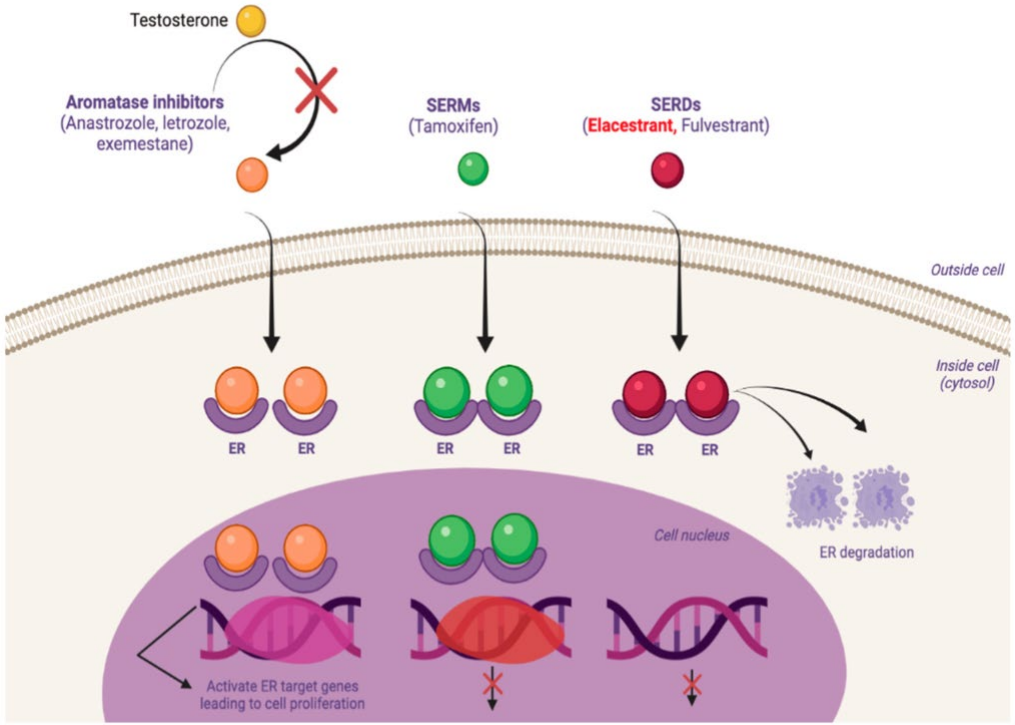
Efficacy Outcomes	ESR1m (n = 19)	Total (N = 35)
CBR, %	47.4	37.1
Median PFS, mo	7.5	3.5



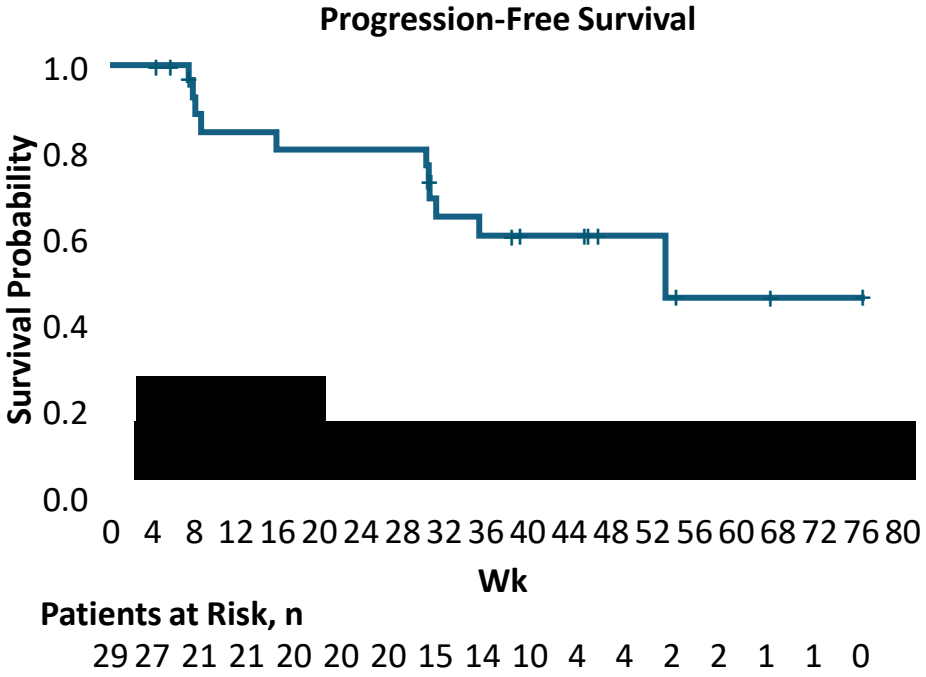
Hurvitz. SABCS 2023. Abstr PO3-05-08.

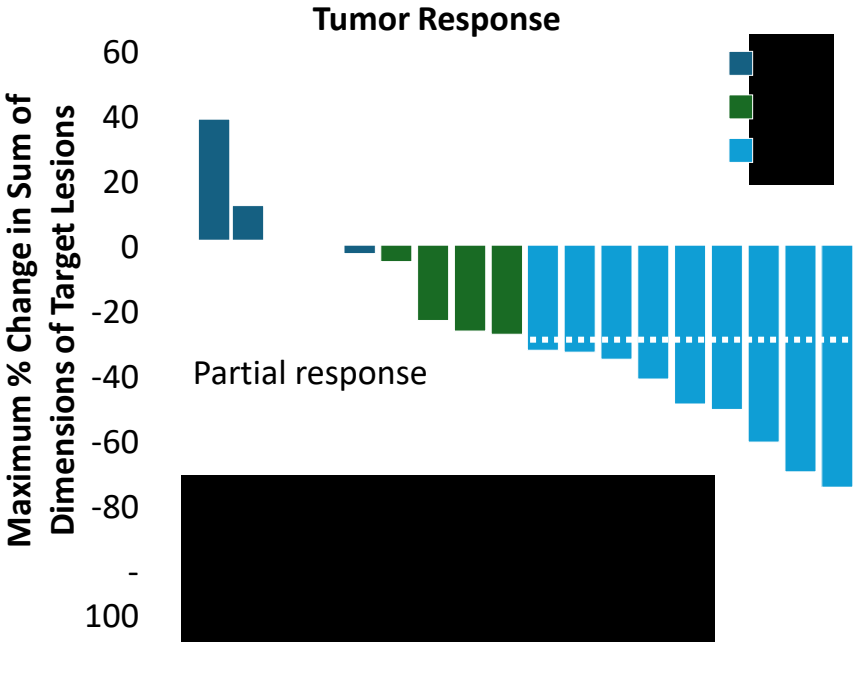
SERMS: Selective Estrogen Receptor Modulators

- SERMS block estrogen binding to ER bind thus blocking transcription
- Tamoxifen
- Bazedoxifene



Lasofoxifene + Abemaciclib in Previously Treated *ESR1*+ MBC (ELAINE II): Efficacy





- Most AEs grade 1/2: fatigue, nausea, diarrhea, cytopenias

Damodaran. ASCO 2022. Abstr 1022.

ELAINE II: Lasofoxifene + Abemaciclib in Previously Treated *ESR1*+ MBC

- Single-arm phase II trial of lasofoxifene (SERM) + CDK4/6 inhibition
  - Preclinical data in *ESR1*+ tumors: active as monotherapy or with a CDK4/6i vs fulvestrant

Women with *ESR1*+ (by ctDNA) locally advanced or MBC; PD after 1-2 lines ET; ≤1 line chemo allowed* (N = 29)

*Prior CDKi: 97%; prior chemo for MBC: 48%.

Lasofoxifene 5 mg/day + **Abemaciclib** 150 mg BID

For 2 yr or until PD or unacceptable toxicity

- **Primary endpoint:** safety/tolerability
- **Secondary endpoints:** PFS, CBR, ORR, DoR, TTR

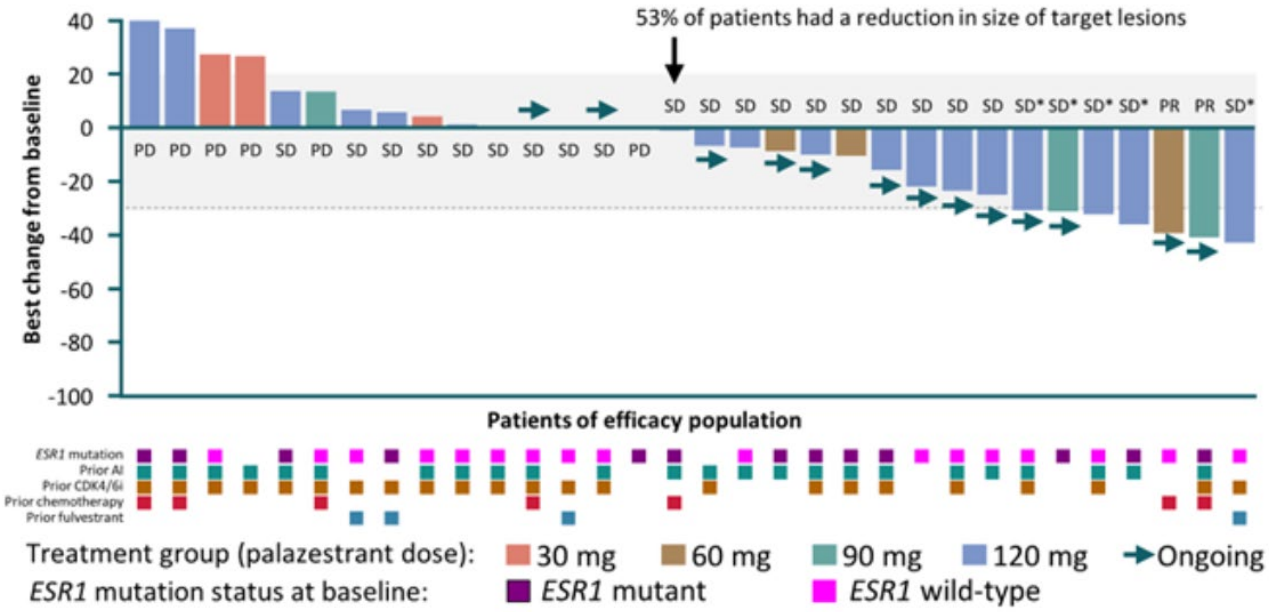
Damodaran. ASCO 2022. Abstr 1022. NCT04432454.

CERANs - Palazestrant (OP-1250)

- CERANs are **c**omplete **ER an**tagonists
- Palazestrant is both a CERAN and a SERD that binds and fully blocks transcriptional activity of wild-type and *ESR1m* ER
- RP2D: 120 mg QD

Hamilton. AACR NCI EORTC Mol Targets and Cancer Therapeutics Symposium. 2022. Abstr 101. Parisian. SABCS 2022. Abstr P2-24-07. Hodges-Gallagher. SABCS 2019. Abstr P5-05-02. Lin. ESMO 2023. Abstr 382MO.

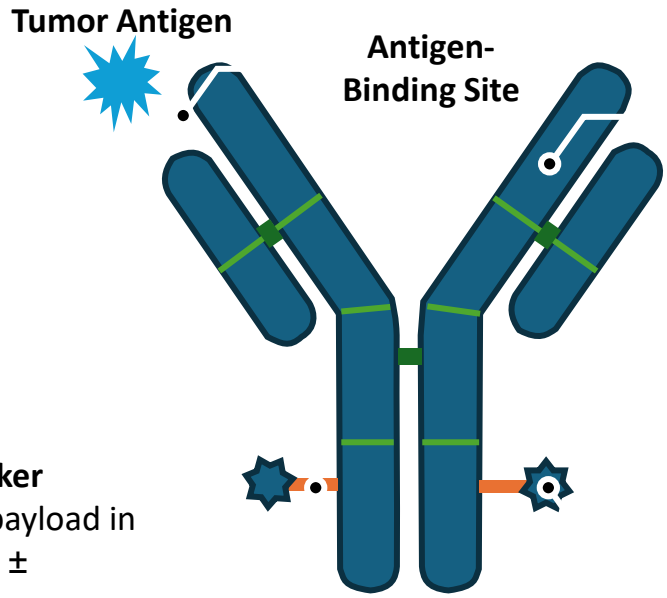
Palazestrant + Palbociclib: Efficacy



Chan. SABCS 2023. Abstr PS15-04.

ADCs

Antibody–Drug Conjugates in Breast Cancer



mAb
Targets tumor-specific or tumor-associated antigens

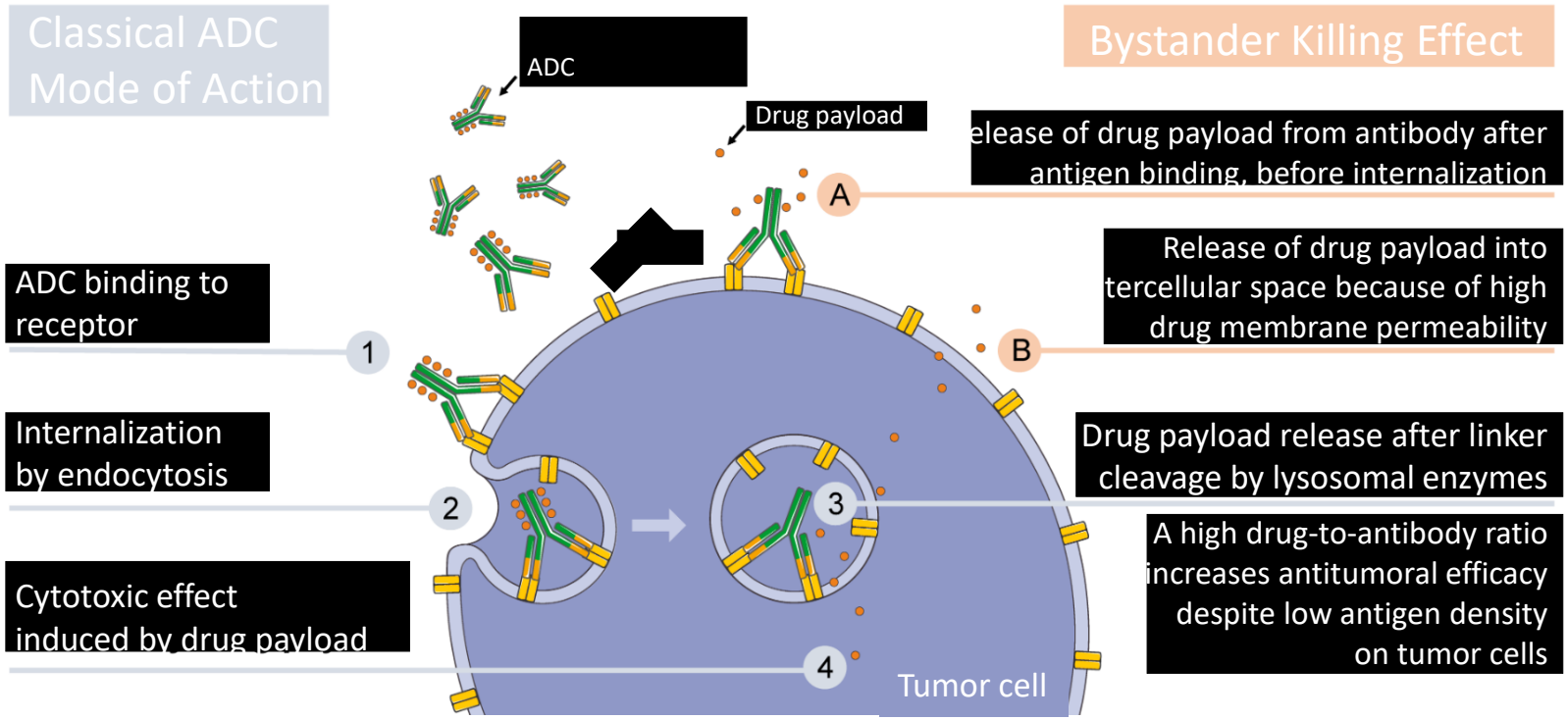
Stable Linker
Releases payload in tumor cell ± surrounding microenvironment

Potent Cytotoxic Payload Amount of payload varies among ADCs

- ADCs are now approved by FDA in multiple breast cancer subtypes and in early and advanced settings

Koster. Explor Target Antitumor Ther. 2022;3:27. Thomas. Lancet Oncol. 2016;17:e254. Ahmed. MedComm—Oncology. 2022;1:e19. Figure adapted from last citation used under terms and conditions of the Creative Commons Attribution 4.0 International license (CC BY 4.0: https://creativecommons.org/licenses/by/4.0/).

Mechanism of Action of ADCs

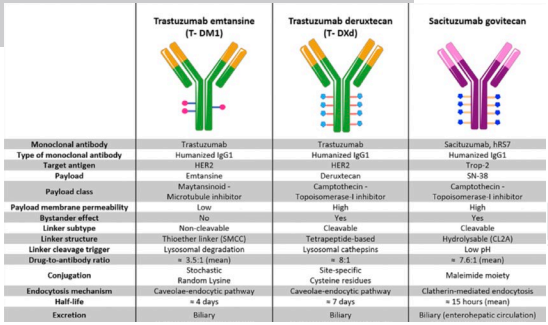


- Some ADCs require internalization for payload cleavage, but others can be hydrolyzed extracellularly

Key HER2-Targeting ADCs in HER2-Altered MBC

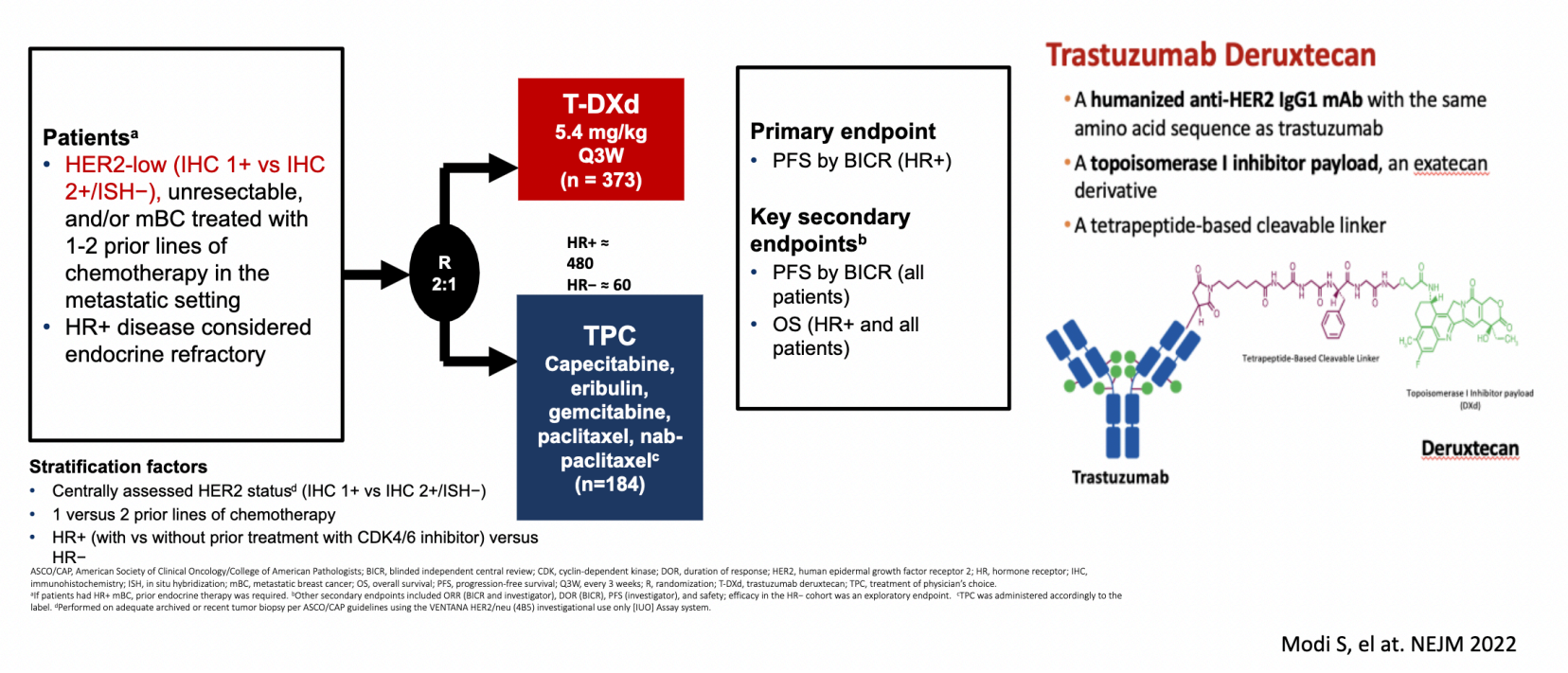
UPDATED

Characteristic	T-DM1	T-DXd	[Vic]-Trastuzumab Duocarmazine (SYD985)
Payload MoA	Microtubule inhibitor	Topoisomerase I inhibitor	DNA alkylator
Drug-to-Ab ratio	~3.5	~8	2.8
Tumor-selective cleavable linker	No	Yes	Yes
Bystander effect	No	Yes	Yes
FDA status	Approved for: ▪ **HER2+ MBC** with prior trastuzumab and taxane after either receiving prior tx for metastatic disease or having disease recurrence during/within 6 mo of completing adjuvant tx ▪ Adjuvant tx of **HER2+ EBC** with residual invasive disease after neoadjuvant taxane and trastuzumab-based tx	Approved for: ▪ **HER2+ unresectable/metastatic BC** previously treated with anti-HER2 tx in metastatic setting or in (neo)adjuvant setting with disease recurrence during/within 6 mo of completing tx ▪ **HER2-low* unresectable/metastatic BC** with prior CT in metastatic setting or disease recurrence during/within 6 mo of completing adjuvant CT	May 16, 2023: FDA suspended decision on approval for **HER2+ ABC** and issued Complete Response Letter, requesting additional information from sponsor



Trail. Pharmacol Ther. 2018;181:126. Trastuzumab emtansine PI. Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Ogitani. Cancer Sci. 2016;107:1039. Trastuzumab deruxtecan PI. Menderes. Clin Cancer Res. 2017;23:5836.

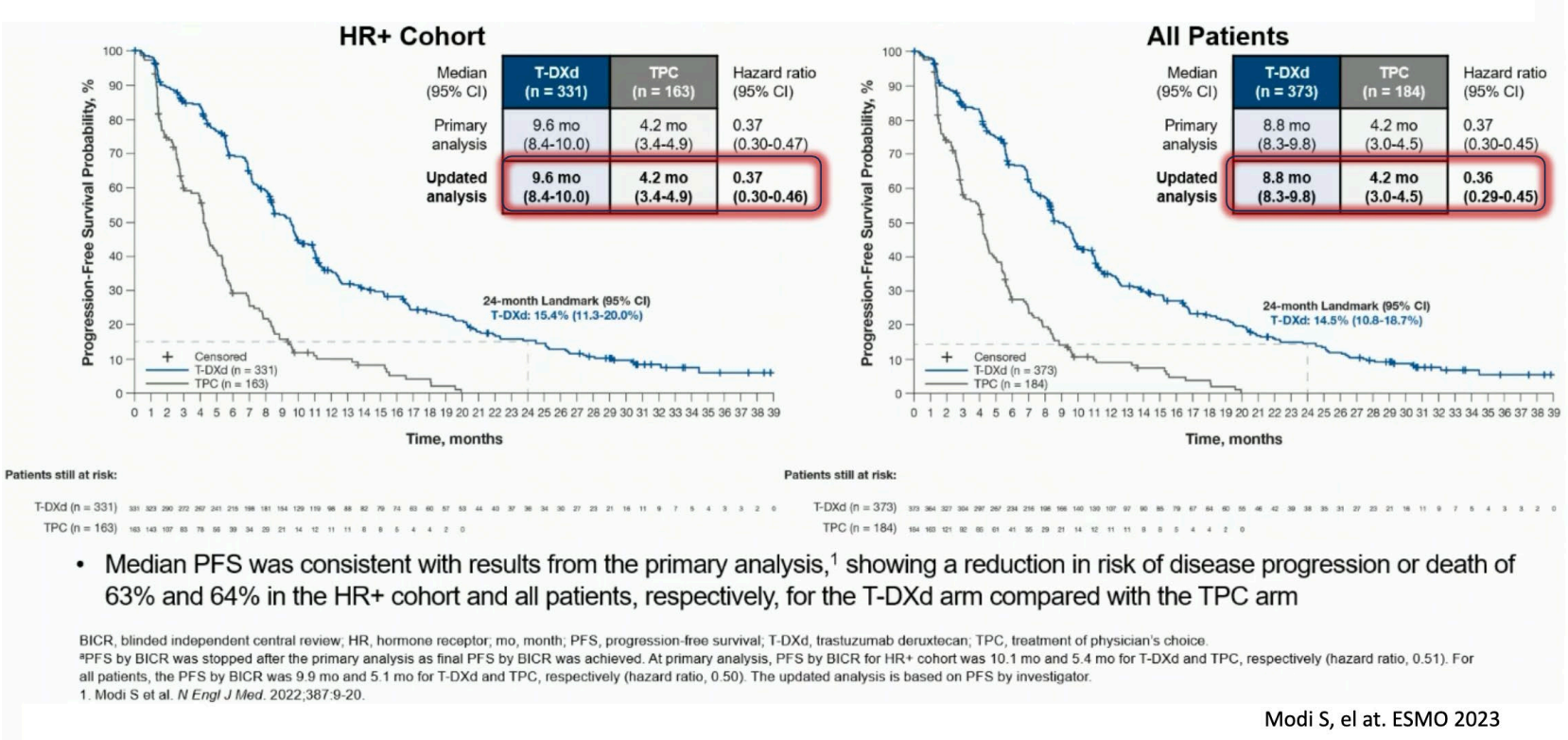
DB 04 – Updated Safety and Efficacy Data



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Modi S, el at. NEJM 2022

Updated PFS



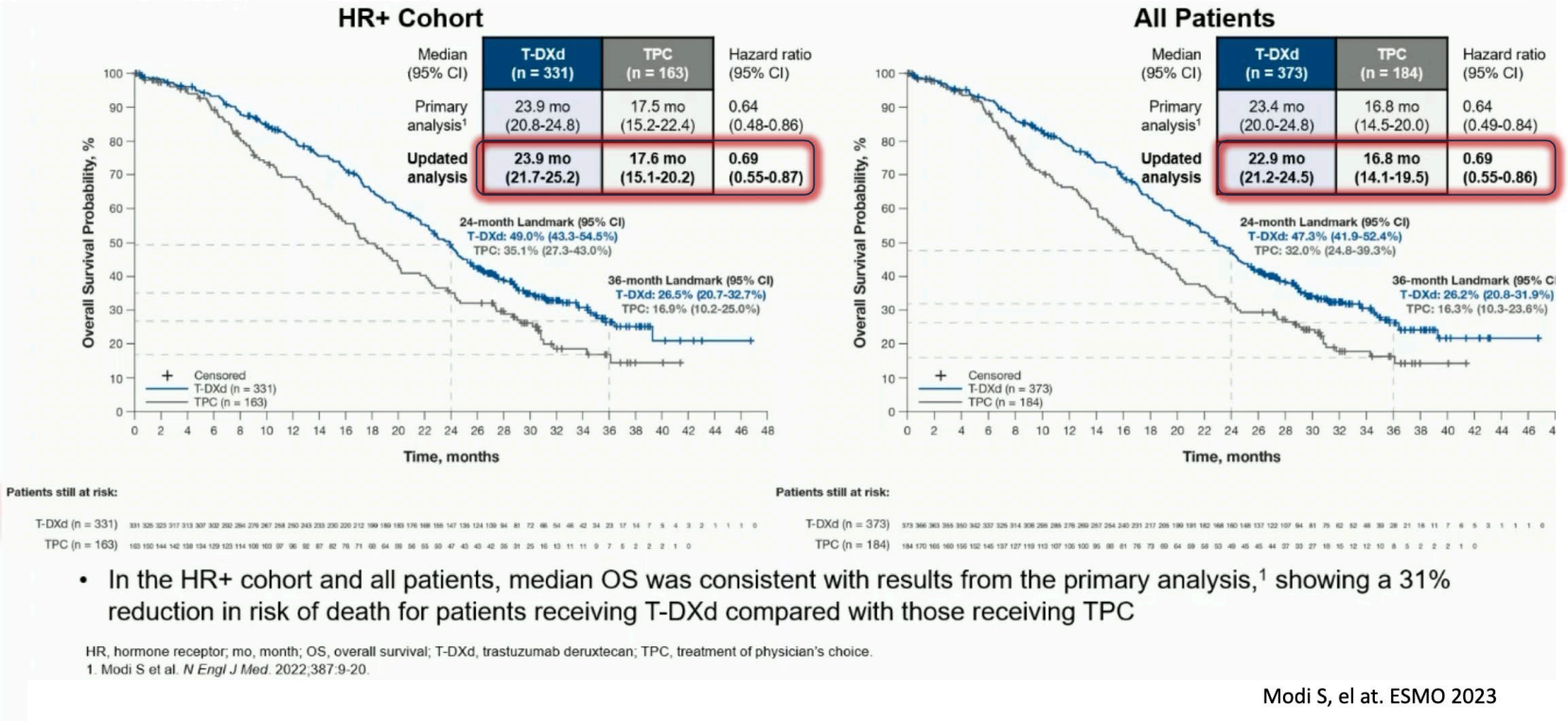
- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

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

Modi S, el at. ESMO 2023

Updated OS



- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

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.

Modi S, el at. ESMO 2023

Phase III DESTINY-Breast03: Updated Results With T-DXd vs T-DM1 in Previously Treated HER2+ MBC

Stratified by HR status, prior pertuzumab, history of visceral disease

Patients with unresectable or metastatic HER2+ breast cancer; previous trastuzumab + taxane tx in metastatic setting or (neo)adjuvant with recurrence ≤6 mo of tx; clinically stable, previously treated brain mets permitted; ECOG PS 0/1
(N = 524)

T-DXd
5.4 mg/kg IV Q3W
(n = 261)

T-DM1
3.6 mg/kg IV Q3W
(n = 263)

Primary endpoint: PFS by BICR

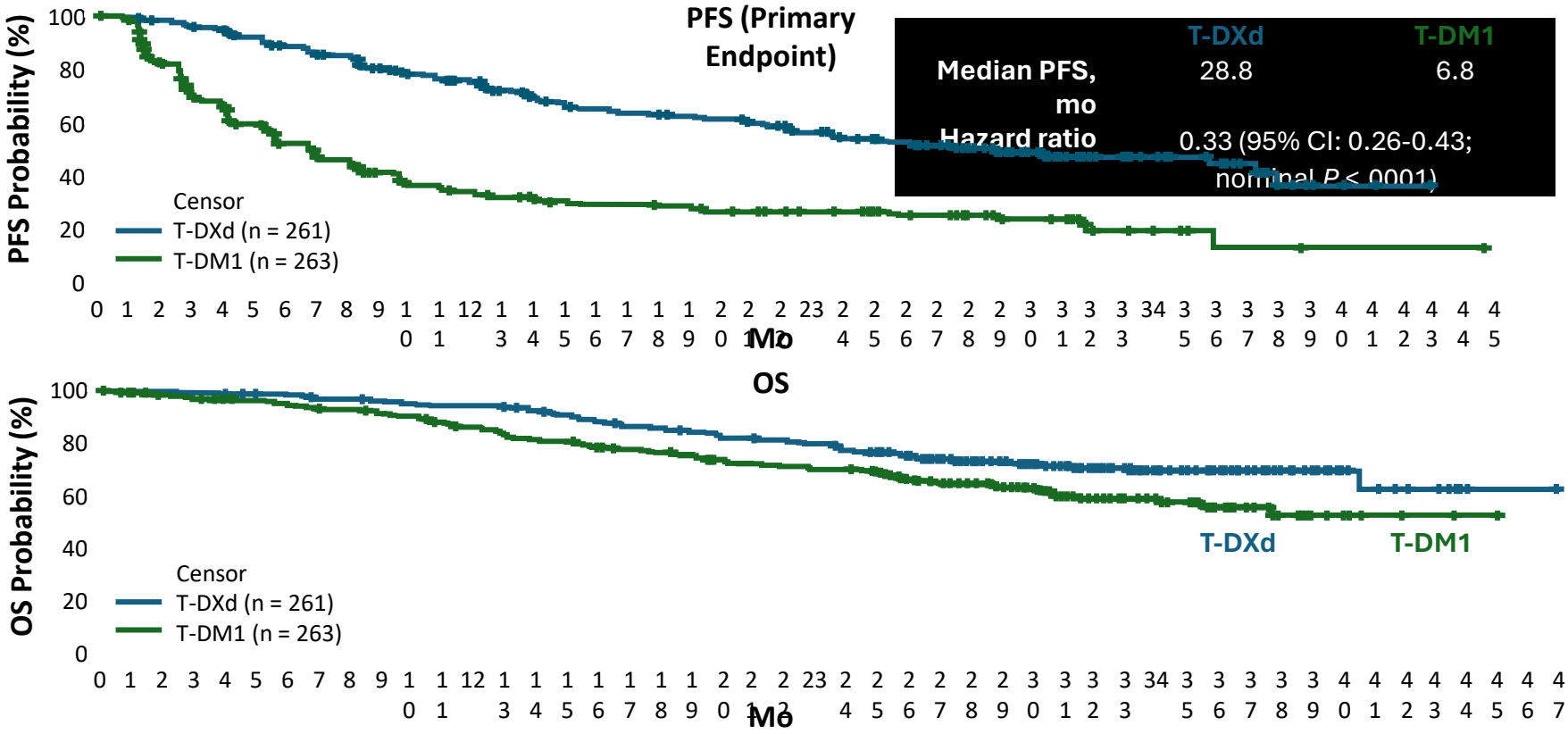
Key secondary endpoint: OS

Other secondary endpoints: ORR by BICR and investigator, DoR by BICR, PFS by investigator

- Median follow-up: 28.4 mo (T-DXd) and 26.5 mo (T-DM1)
- Median of 2 prior lines of therapy
  - 36% had ≥3 prior lines of therapy

Hurvitz. Lancet. 2023;401:105.

DESTINY-Breast03: Updated PFS and OS



Hurvitz. Lancet. 2023;401:105.

Phase III TULIP: [vic]-Trastuzumab Duocarmazine vs CT in Previously Treated HER2+ Advanced Breast Cancer

- [vic]-trastuzumab duocarmazine (SYD985) under FDA review for HER2+ ABC (PDUFA: May 12, 2023)

Stratification by region (European Union + Singapore vs North America), prior therapies for MBC (1-2 vs >2), prior pertuzumab (Y/N)

Patients with locally advanced or metastatic HER2+ breast cancer with ≥2 prior therapies for metastatic disease or T-DM1 for metastatic disease; treated brain metastases allowed
(N = 437)

2:1

[vic]-Trastuzumab Duocarmazine 1.2 mg/kg IV Q3W
(n = 291)

Physician's Choice of CT*
(n = 146)

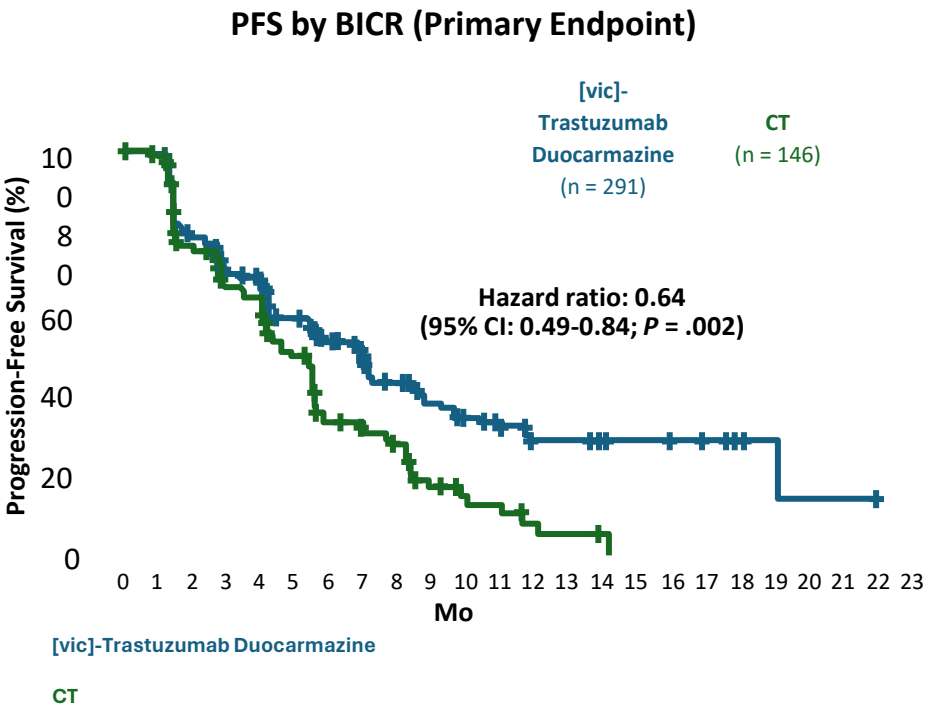
Until PD or unacceptable toxicity

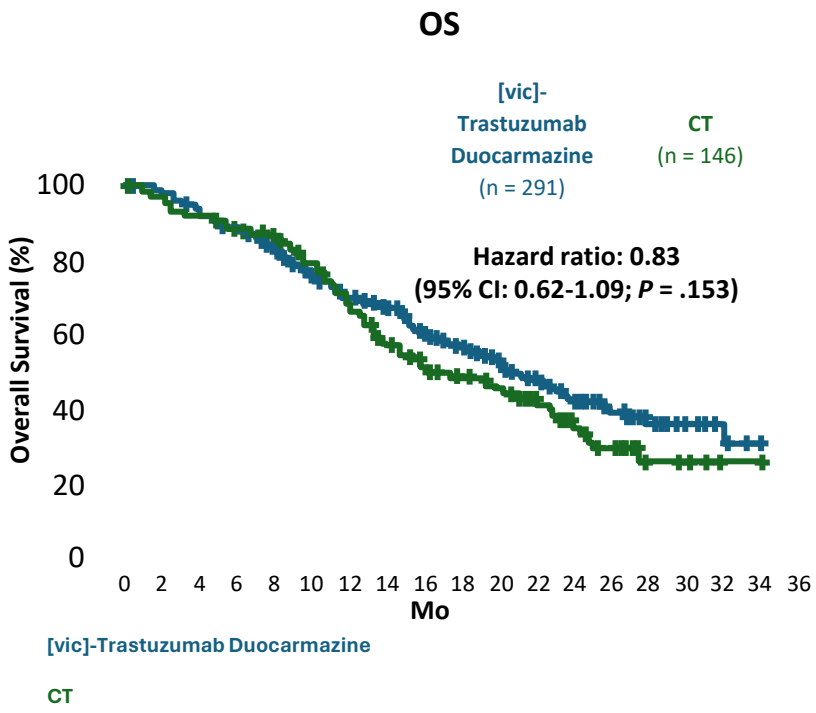
*Lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + vinorelbine, or trastuzumab + eribulin.

- Primary endpoint: PFS by BICR
- Secondary endpoints: PFS (investigator), OS, ORR, HRQoL

Manich. ESMO 2021. Abstr LBA15. NCT03262935.

TULIP: PFS and OS With [vic]-Trastuzumab Duocarmazine vs Physician's Choice of CT

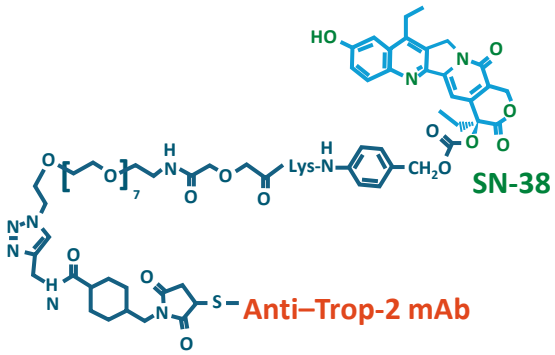




Manich. ESMO 2021. Abstr LBA15.

Sacituzumab Govitecan: Trop-2–Targeted ADC

- Trop-2 is expressed in all breast cancer subtypes and is associated with poor prognosis

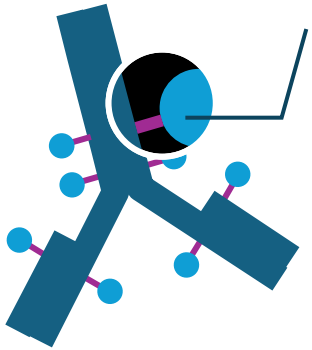


Humanized Anti–Trop-2 Antibody

- Targets Trop-2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload

- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor

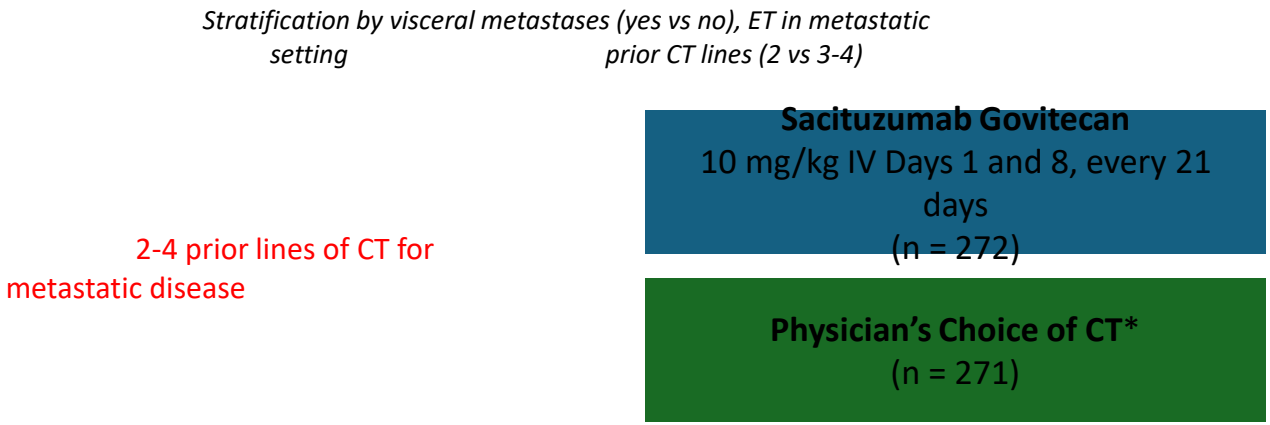


Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Goldenberg. Oncotarget. 2015;6:22496. Khoury. ASCO 2019. Abstr e14651.
Ambrogi. PLoS One. 2014;9:e96993. Vidula. ASCO 2017. Abstr 1075.
Sacituzumab govitecan PI. Tagawa. ASCO 2019. Abstr TPS3153.
Bardia. JCO. 2017;35:2141. Goldenberg. MAbs. 2019;11:987.
Sharkey. Clin Cancer Res. 2015;21:5131.

Phase III TROPiCS-02: Sacituzumab Govitecan vs TPC for HR+/HER2- Advanced Breast Cancer

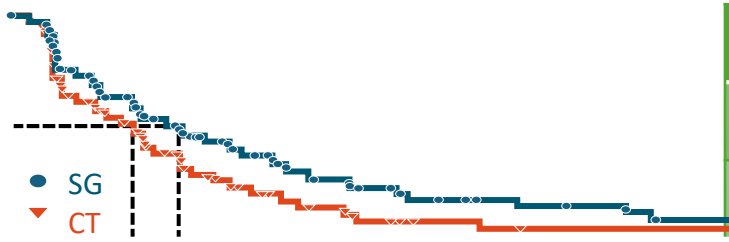


- February 3, 2023: Positive data from TROPiCS-02 led to FDA approving new indication for sacituzumab govitecan
  - For adults with unresectable locally advanced/metastatic HR+/HER2- (IHC 0, 1+, or 2+/ISH-) BC previously treated with ET and ≥2 additional systemic therapies in metastatic setting

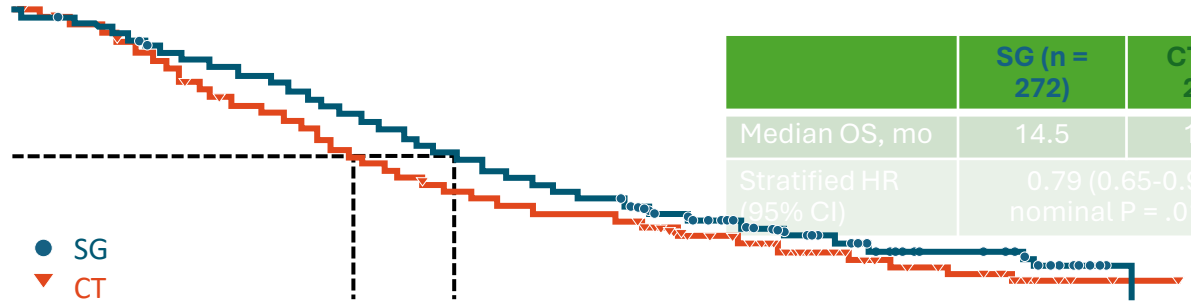
Tolaney. ASCO 2023. Abstr 1003. Rugo. JCO. 2022;40:3365. Sacituzumab govitecan PI.

TROPiCS-02: PFS and OS From Final OS Analysis After Median Follow-up of 12.75 Mo

UPDATED



	SG (n = 272)	CT (n = 271)
Median PFS, mo	5.5	4.0
Stratified HR (95% CI)	0.65 (0.53-0.81; nominal P = .0001)	

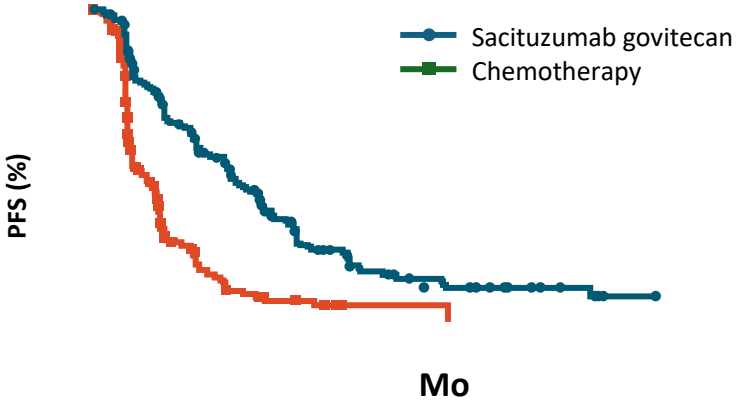


	SG (n = 272)	CT (n = 271)
Median OS, mo	14.5	11.2
Stratified HR (95% CI)	0.79 (0.65-0.95; nominal P = .0133)	

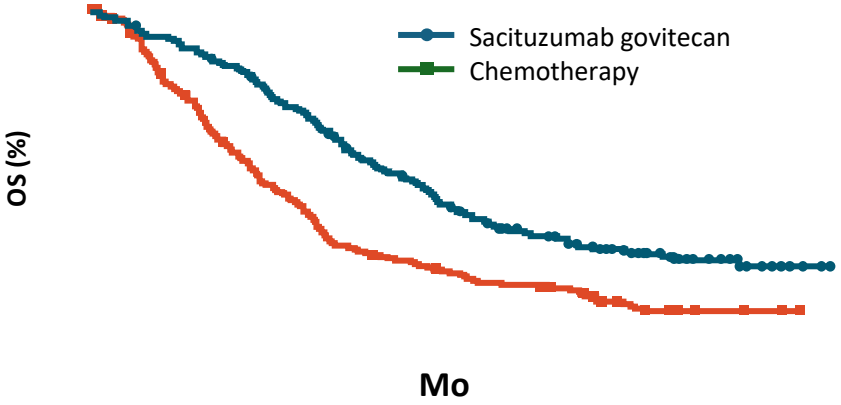
Tolaney. ASCO 2023. Abstr 1003.

ASCENT: PFS and OS Among Patients Without Brain Metastases (Final Analysis)

	SG (n = 235)	CT (n = 233)
Events	167	150
Median PFS, mo	5.6	1.7
HR	0.39 (95% CI: 0.31-0.49; *P* <.0001)	



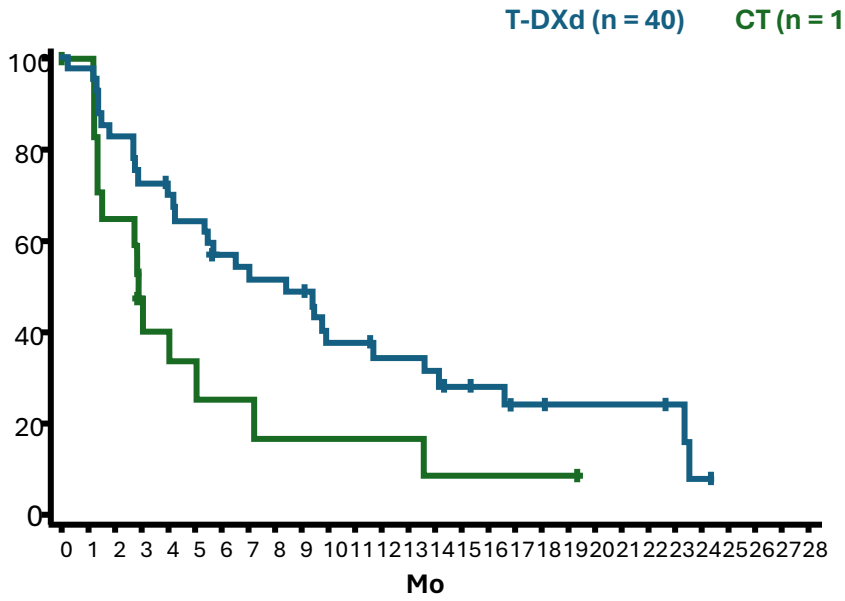
	SG (n = 235)	CT (n = 233)
Events	173	199
Median OS, mo	12.1	6.7
HR	0.48 (95% CI: 0.39-0.59; *P* <.0001)	

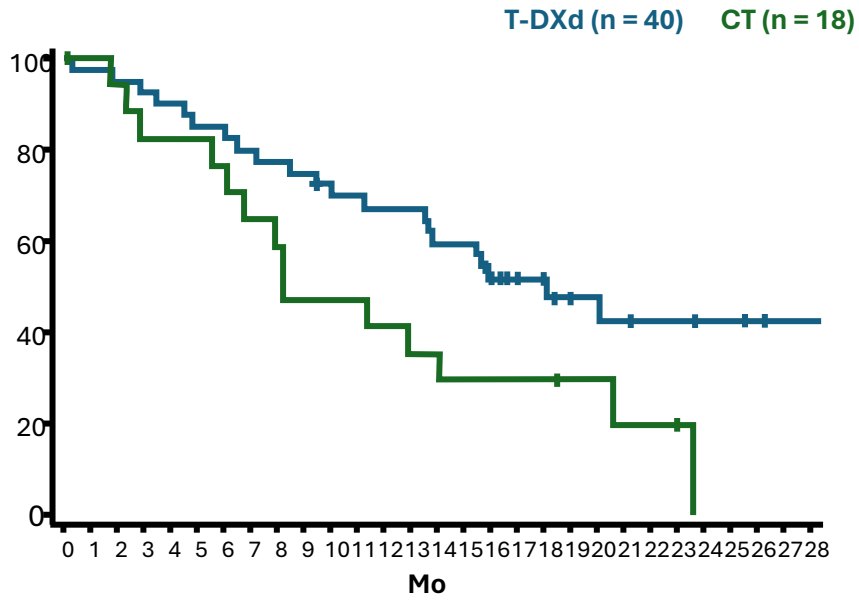


- Survival outcomes numerically better with SG vs CT in patients with high/medium Trop-2 expression, but small numbers with low Trop-2 expression limited ability to draw conclusions

Bardia. ASCO 2022. Abstr 1071. Bardia. Ann Oncol. 2021;32:1148.

DESTINY-Breast04: Exploratory Analysis of PFS and OS With T-DXd vs CT in HR-/HER2-Low MBC





- Preliminary evidence of T-DXd efficacy in HR-/HER2-low MBC suggested by this exploratory analysis with small sample size (n = 58)

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;387:9.

Phase I TROPION-PanTumor01: Datopotamab Deruxtecan in Trop-2–Unselected TNBC and HR+/HER2- ABC Cohorts

- **Dato-DXd:** novel ADC targeting Trop-2 with topoisomerase I inhibitor payload; can elicit bystander antitumor effects

Parameter	Dato-DXd 6 mg/kg IV Q3W	
	TNBC (n = 44*)	HR+/HER2- ABC (n = 41)
Median study duration, mo	19.3	13.7
Median no. prior regimens for metastatic disease	3	5
Median OS, mo	13.5	NR
Median PFS, mo	4.4	8.3
ORR per BICR, %	32	27
Median DoR, mo	16.8	NE

*2 patients treated with dato-DXd at 8 mg/kg IV Q3W.

- Responses observed among patients with TNBC previously treated with sacituzumab govitecan
- 1 case of grade 3 drug-related ILD in HR+/HER2- ABC cohort
- Most common TEAEs
  - Stomatitis: 73%-83% (grade ≥3: 10%-11%)
  - Nausea: 56%-66%
  - Alopecia: 36%-37%
  - Fatigue: 34%-46%
- Neutropenia and diarrhea occurred in ≤20%

Bardia. SABCS 2022. Abstr P6-10-03. Meric-Bernstam. SABCS 2022. Abstr PD13-08. Krop. SABCS 2021. Abstr GS1-05

Phase II Trial of HER3-Targeted Patritumab Deruxtecan in HER2- MBC

UPDATED

- HER3 is expressed in 30.3%-75.1% of breast cancers; overexpression is associated with poor prognosis
- **Patritumab deruxtecan:** HER3-targeted ADC with topoisomerase I inhibitor payload capable of bystander antitumor effects
- Multipart phase II trial evaluated patritumab deruxtecan 5.6 mg/kg IV Q3W in 60 patients with HER2- MBC

Parameter	HER3 Membrane Expression			Clinical Subtype	
	≥75% (n = 30)	25%-74% (n = 13)	<25% (n = 4)	HR+ (n = 29)	TNBC (n = 19)
ORR, %	33.3	46.2	50.0	41.4	21.1
DoR ≥6 mo, %	40.0	33.3	100	--	--

Patritumab deruxtecan active regardless of HER3 expression

Ocana. J Natl Cancer Inst. 2013;105:266. Krop. ASCO 2022. Abstr 1002. Corti. Cancers (Basel). 2021;13:2898. Li. Oncotarget. 2017;8:67140. Hamilton. ASCO 2023. Abstr 1004.

Select Ongoing Phase III Trials of ADCs in BC

	Phase III Trial	Treatment Arm(s)	Population	Primary Completion
Early	ASCENT-05/OptimICE-RD (NCT05633654)	**Sacituzumab govitecan** + pembrolizumab vs pembrolizumab ± capecitabine	Residual invasive TNBC after neoadjuvant tx and surgery (N = 1514)	July 2027
Early	DESTINY-Breast05 (NCT04622319)	**T-DXd** vs **T-DM1**	High-risk HER2+ BC with residual invasive disease after neoadjuvant tx (N = 1600)	December 31, 2025
Early	SASCIA (NCT04595565)	**Sacituzumab govitecan** vs TPC	HER2- BC with residual disease after neoadjuvant CT (N = 1200)	December 1, 2026
Early	TROPION-Breast03 (NCT05629585)	**Dato-DXd** ± durvalumab vs capecitabine and/or pembrolizumab	Residual invasive TNBC at resection after neoadjuvant tx (N = 1075)	September 20, 2027
1L	ASCENT-03 (NCT05382299)	**Sacituzumab govitecan** vs TPC	Metastatic TNBC (N = 540)	May 2027
1L	ASCENT-04 (NCT05382286)	**Sacituzumab govitecan** pembrolizumab vs TPC + pembrolizumab	Inoperable/metastatic TNBC (N = 440)	February 2027
1L	DESTINY-Breast09 (NCT04784715)	**T-DXd** ± pertuzumab vs taxane/trastuzumab/pertuzumab	HER2+ MBC (N = 1134)	December 30, 2024
1L	TROPION-Breast02 (NCT05374512)	**Dato-DXd** vs TPC	Inoperable/metastatic TNBC ineligible for PD-1/PD-L1 tx (N = 600)	December 3, 2025
1L+	DESTINY-Breast06 (NCT04494425)	**T-DXd** vs TPC	HR+/HER2-low or HER2 IHC >0 <1+ MBC (N = 850)	July 31, 2023
2L/3L	TROPION-Breast01 (NCT05104866)	**Dato-DXd** vs TPC	Inoperable/metastatic HR+/HER2- (N = 725)	August 15, 2025

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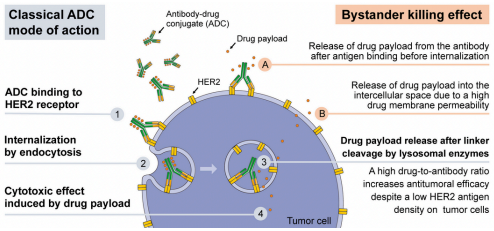
Review

Antibody–Drug Conjugates in Breast Cancer: Current Status and Future Directions

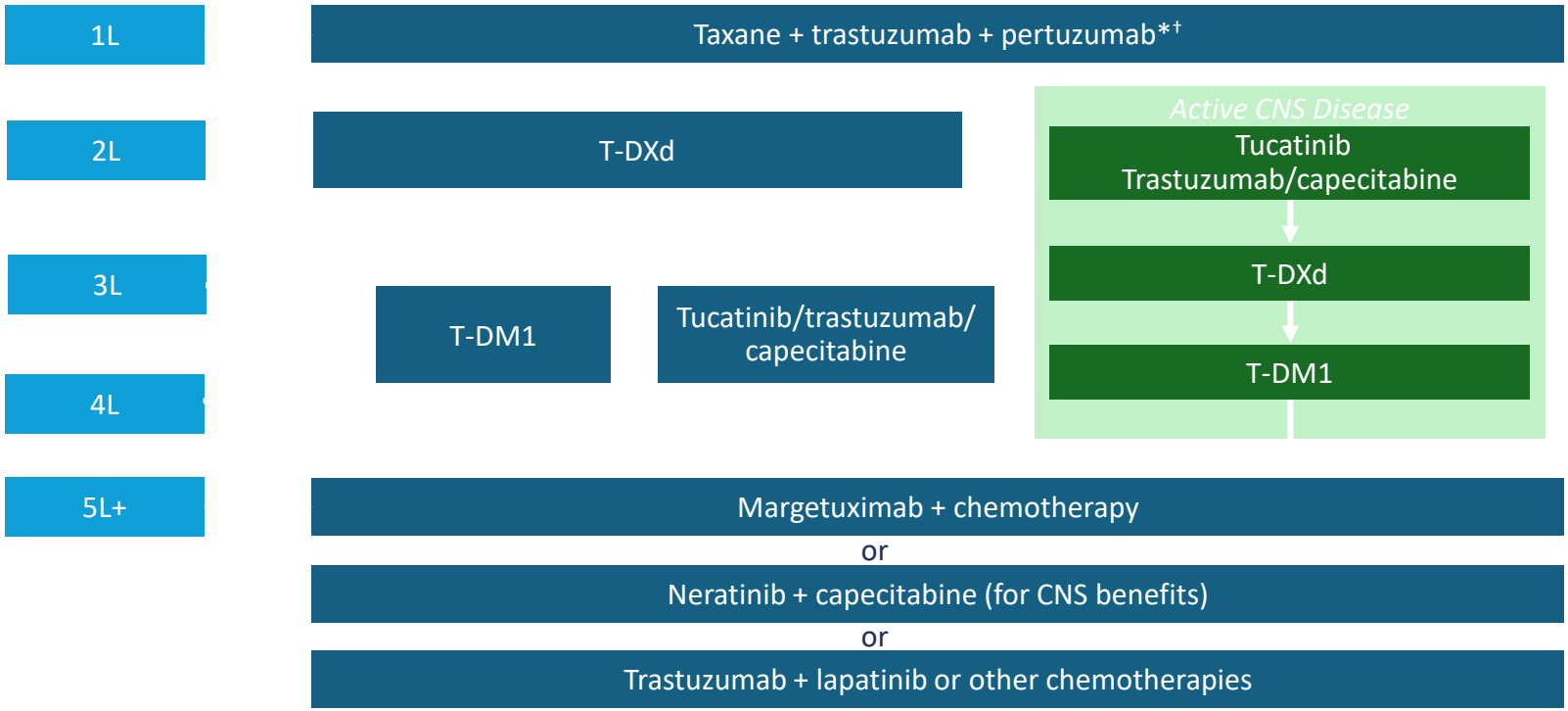
Cynthia Mark [1], Jin Sun Lee [1], Xiaojiang Cui [2] and Yuan Yuan [1,*]

ADC	ADC Target	Trials	Phase	Combination Therapy	Patient Population	Key Objective	NCT No.
Trastuzumab Emtansine (T-DM1)	HER2	KATE2	II	T-DM1+ atezolizumab	2L HER2+ MBC	PFS	NCT02924883
		CompassHER2 RD	III	T-DM1 + tucatinib	HER2+ stage II–III with residual disease after neoadjuvant treatment	iDFS	NCT04457596
Trastuzumab deruxtecan (T-DXd)	HER2	DESTINY Breast-08	IB/II	Capivasertib, Anastrozole, fulvestrant	1–2L HER-2 low MBC	AEs	NCT04556773
		TALENT	II	Anastrozole	Neoadjuvant HER2-low HR+	pCR	NCT04553770
		DASH	I	AZD6738	HER2+ advanced solid tumor	RP2D	NCT04704661
			I	Nivolumab	Advanced breast or urothelial Ca	DLT, ORR	NCT03523572
			IB	Pembrolizumab	Advanced breast cancer or NSCLC	DLT, ORR	NCT04042701
		DESTINY Breast-07	I/II	Durvalumab or pertuzumab, or paclitaxel +/− durvalumab or tucatinib	HER2+ MBC	AEs	NCT04538742
Disitamab vedotin (RC48-ADC)	HER2	ROSY	III	Endocrine therapy	1st line endocrine resistant HER2-low MBC	PFS	NCT05904964
			I	Penpulimab (AK105)	Neoadjuvant HER2-low BC	pCR	NCT05726175
ARX-788	HER2		II	Pyrotinib (HER2 TKI)	Neoadjuvant stage II–III HER2+ BC	RCB	NCT04983121
		ISPY-2.2	II	Cemiplimab	Neoadjuvant stage I–III HER2+ BC	pCR	NCT01042379

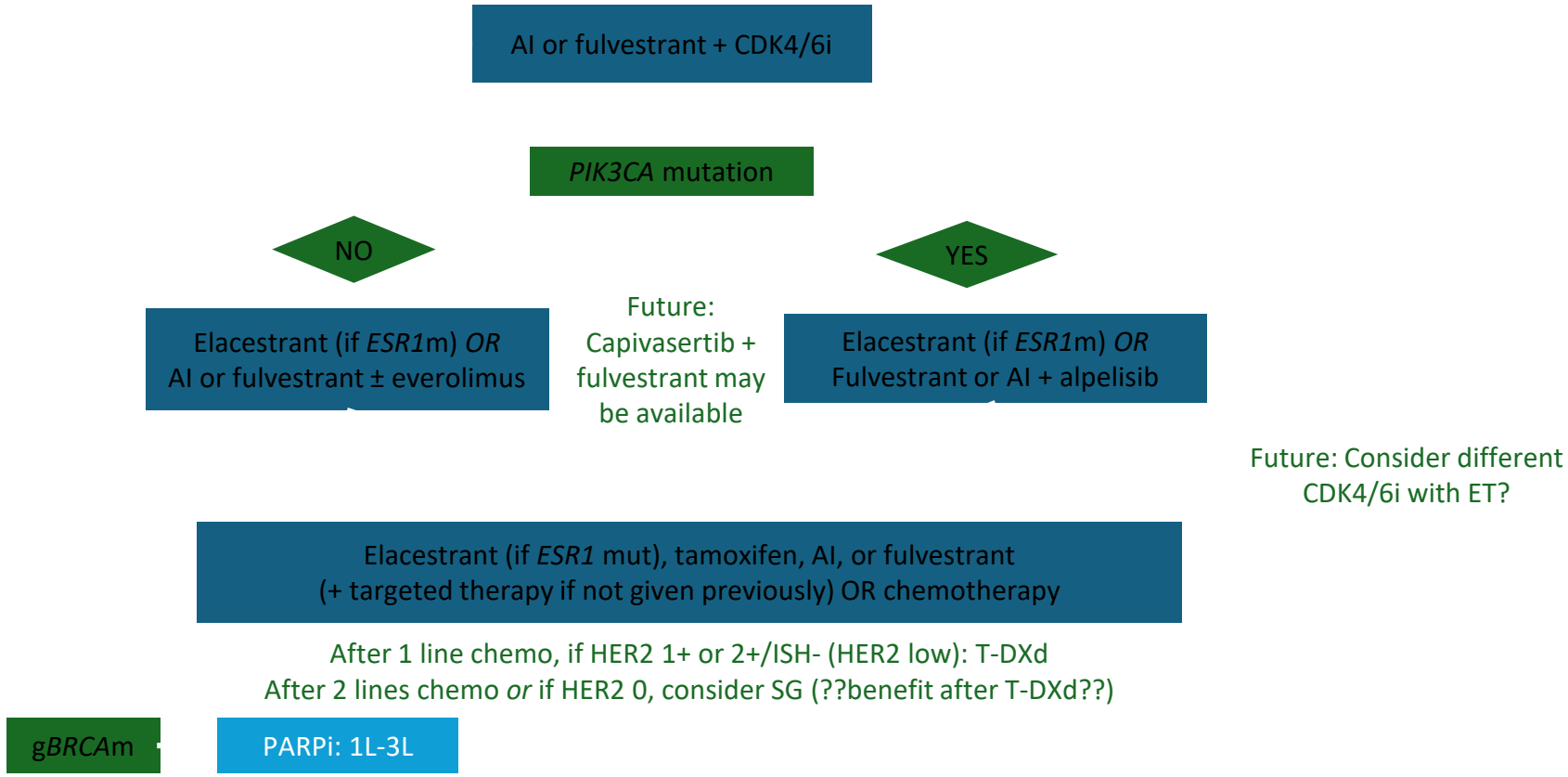
ADC	ADC Target	Trials	Phase	Combination Therapy	Patient Population	Key Objective	NCT No.
Sacituzumab Govitecan	TROP-2	ASCENT05	III	Pembrolizumab	Post-neoadjuvant stage I–III TNBC with residual disease	iDFS	NCT05633654
		ASCENT04	III	Pembrolizumab	1st line PD-L1+ metastatic TNBC	PFS	NCT05382286
		ASSET	I	Alpelisib	2°L HER2+ MBC	RP2D	NCT05143229
			I/II	Talazoparib	Metastatic TNBC	DLT	NCT04039230
			I	GS9716 (Mcl-1 antagonist)	Advanced solid tumors including MBC	DLT	NCT05006794
Dato-DXd	TROP-2	TROPION Breast 03	III	Durvalumab	Post-neoadjuvant stage I–III TNBC with residual disease	iDFS	NCT05629585
		ISPY-2.2	II	Durvalumab	Neoadjuvant stage I-III TNBC	pCR	NCT01042379
		PETRA	I/II	AZD5305 (PARPi)	Advanced solid tumor including breast cancer	DTL	NCT04644068
Ladiratuzumab vedotin (SGN-LIV1A)	LIV-1	MORPHEUS-panBC	II	Atezolizumab	Metastatic or Locally Advanced Breast Cancer	ORR	NCT03424005
		SGNLVA-002 Or KEYNOTE 721	I/II	Pembrolizumab	Advanced TNBC	ORR	NCT03310957
Patritumab Deruxtecan	HER3	VALENTINE	II	Endocrine therapy	Neoadjuvant high risk HR+/HER2− Early Stage BC	pCR	NCT05569811



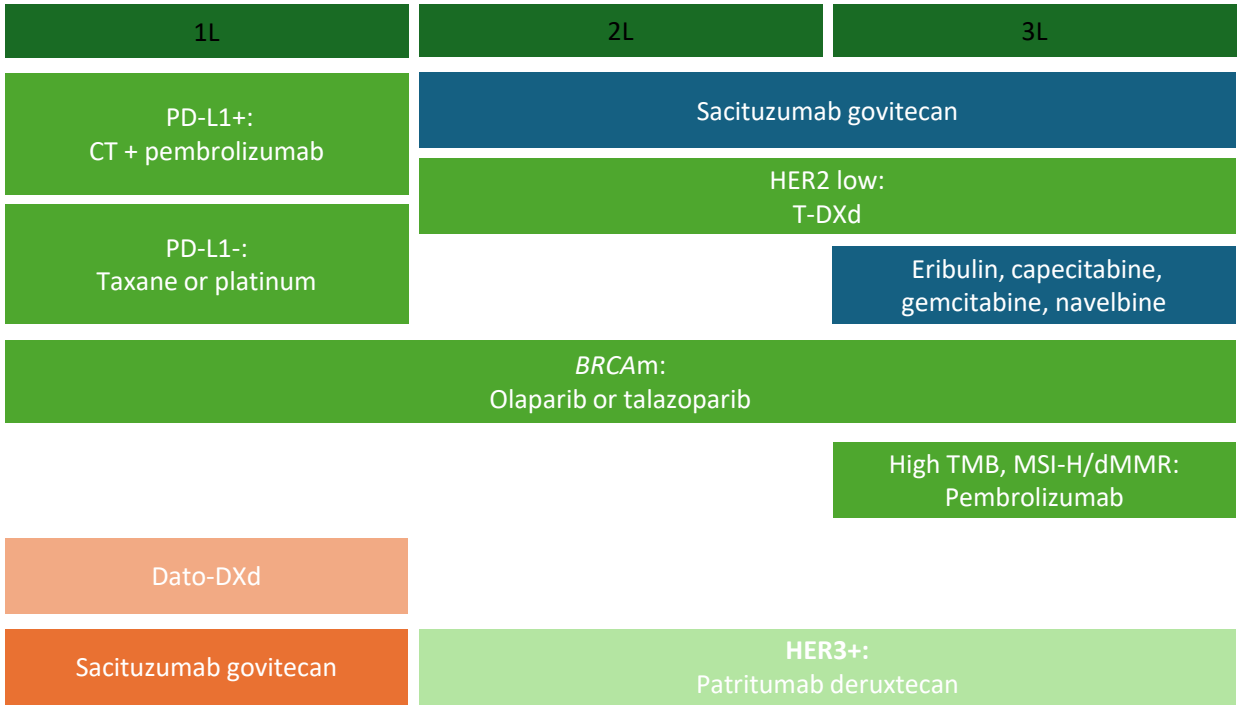
Where ADCs Fit Into Treatment of HER2+ MBC



Where ADCs Fit Into Treatment of HR+/HER2- MBC



Where ADCs Fit Into Treatment of Metastatic TNBC



Objectives

- Review advances in breast cancer in 2023
  - Early breast caner
  - Survivorship
  - Metastatic Breast Cancer
- On the horizon


THANK YOU