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Thriving Together

2025 CONFERENCE ON METASTATIC BREAST CANCER

Medical Updates in MBC: What You Need to Know

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Valley Health System | Mount Sinai

COMPREHENSIVE CANCER CARE

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Disclosures

- Advisory Board: Astra-Zeneca, Novartis, Abbvie, Pfizer
- Honorarium/Travel: OncLive, Total Health

Outline

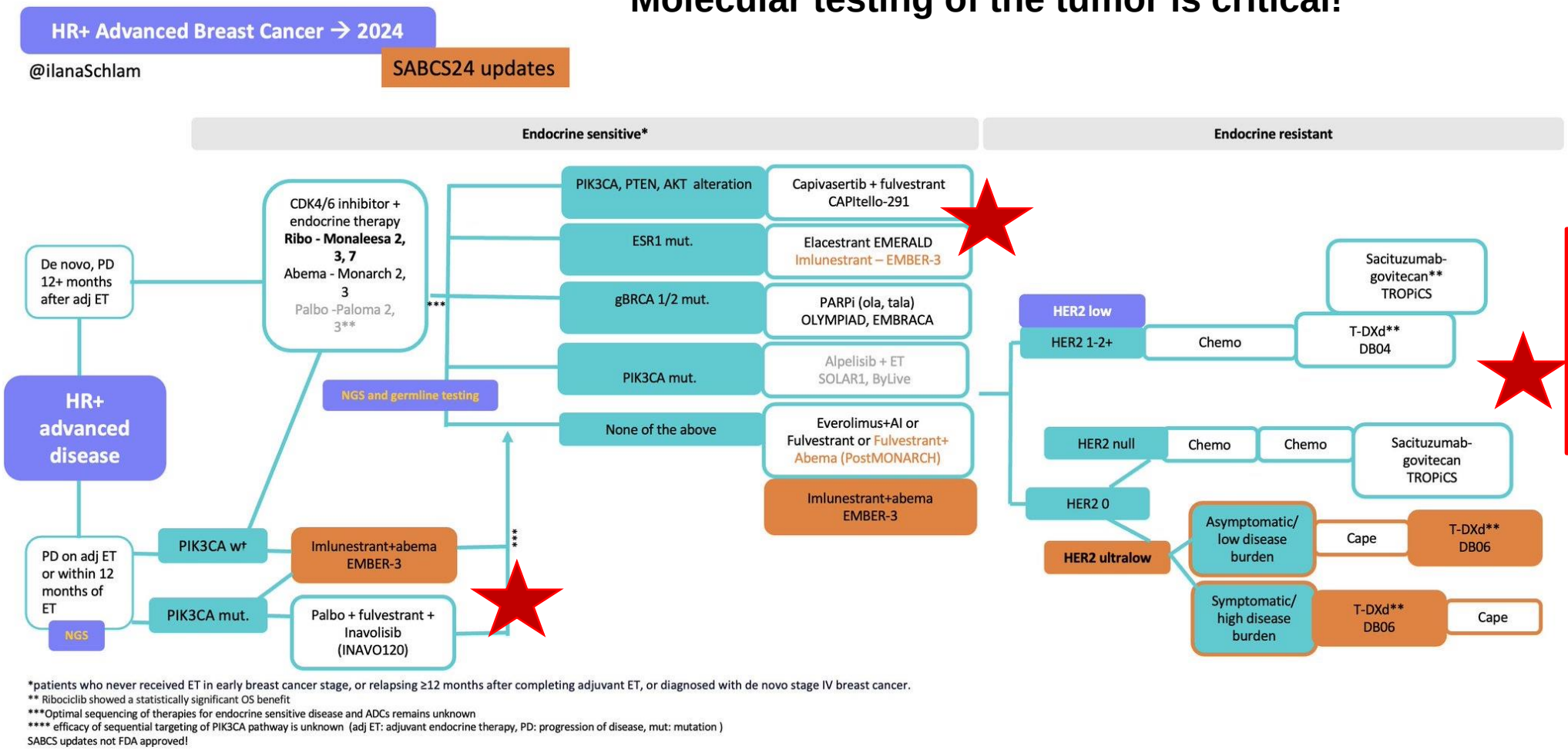
- Metastatic breast cancer (MBC) treatment is rapidly evolving, with significant advances in recent years. Today, we will discuss:
- Current treatment landscape in HR+, HER2+ and TNBC
- Medications including antibody-drug conjugates, PI3K inhibitors, novel endocrine therapies, immunotherapy, and more!

What is Metastatic Breast Cancer (MBC)?

- Breast cancer that has spread outside of the breast and regional lymph nodes
- The term MBC is typically used to refer to a breast cancer that was initially diagnosed as early stage (stage I-III) and has now metastasized
- Breast cancer that is metastatic upon presentation is referred to as stage 4 or de novo MBC
- Metastatic recurrences are decreasing due to more effective systemic therapies and proportion of de novo cancers is increasing
    - Big difference is exposure to prior systemic therapy and recurrent disease represents growth of cells that were resistant to therapy
- Metastatic spread is different between ductal and lobular cancers (lobular cancers tend to spread more to peritoneum, ovaries and GI tract; lower risk of initial recurrence and higher risk of late recurrence)

Current Treatment Landscape for HR+/HER2- MBC

Molecular testing of the tumor is critical!



*patients who never received ET in early breast cancer stage, or relapsing ≥12 months after completing adjuvant ET, or diagnosed with de novo stage IV breast cancer.
** Ribociclib showed a statistically significant OS benefit
***Optimal sequencing of therapies for endocrine sensitive disease and ADCs remains unknown
**** efficacy of sequential targeting of PIK3CA pathway is unknown (adj ET: adjuvant endocrine therapy, PD: progression of disease, mut: mutation)
SABCS updates not FDA approved!

Datopotamab deruxtecan (Dato-DXd) approved as another ADC option in HR+/HER2- disease in 1/2025

Dr. Ilana Schlam @ilanaschlam, December 13, 2024, X.

PI3K Pathway in HR+ MBC

- This is a major signaling pathway that can lead to cell growth and tumor proliferation and play a role in endocrine resistance in breast cancer
- HR+ breast cancers can have PIK3CA mutations that can hyperactivate this pathway leading to uncontrolled growth
- Several drugs against the PI3K/AKT/mTOR pathway have been developed
- Three PI3K inhibitors approved for HR+ MBC: capivasertib (for PIK3CA/AKT/PTEN mutations), inavolisib and alpelisib and others in development

INAVO120 Trial: Inavolisib + Palbociclib + Fulvestrant in PIK3CA Mutated HR+/HER2- MBC

- High risk population of patients who experienced relapse during or within 12 months after completion of adjuvant endocrine therapy and had a known PIK3CA mutation
- PIK3CA mutations occur in ~35-40% of HR+ breast cancer, have been shown to have a worse prognosis, and are biomarkers of response to PI3K inhibitors
- This study tested inavolisib (PI3K inhibitor) plus fulvestrant-palbociclib versus placebo plus fulvestrant-palbociclib in patients with PIK3CA mutated HR+/HER2- locally advanced or metastatic breast cancer
- Inavolisib is an oral medication, 9mg once daily

Turner NC et al. *N Engl J* Med 2024; 391:1584-96

INAVO 120 Outcomes

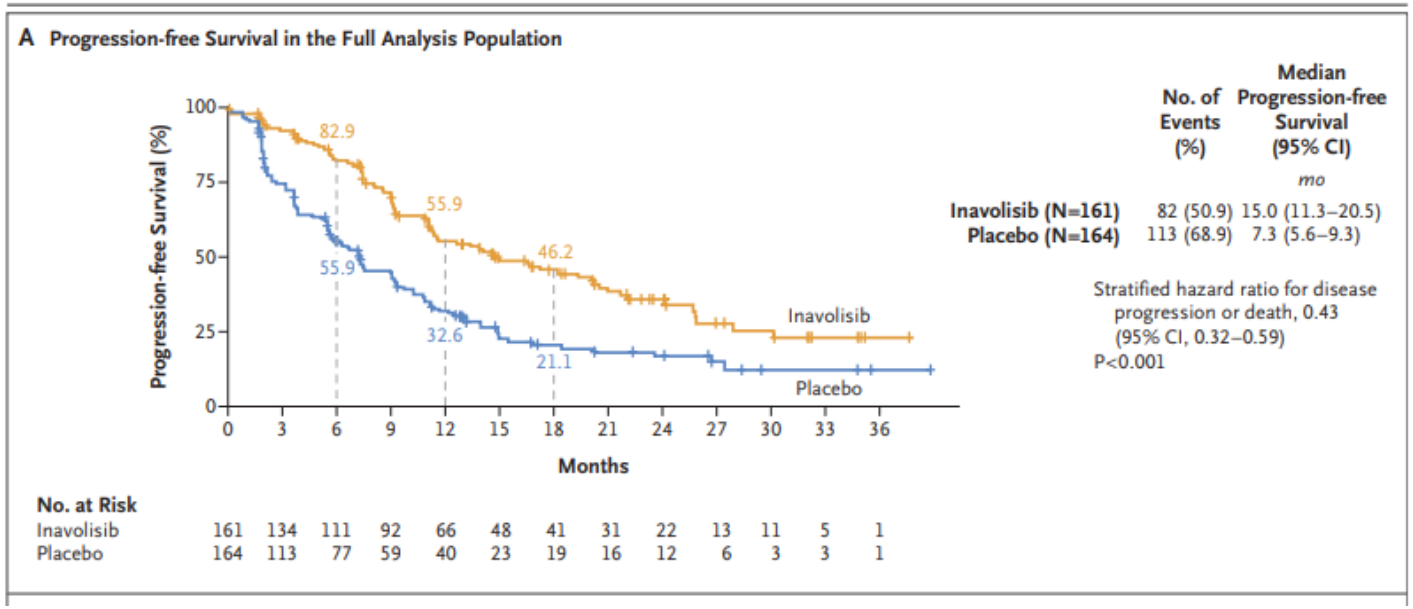


Table 2. Adverse Events.*

Adverse Event	Inavolisib (N=162)		Placebo (N=162)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Neutropenia	144 (88.9)	130 (80.2)	147 (90.7)	127 (78.4)
Thrombocytopenia	78 (48.1)	23 (14.2)	73 (45.1)	7 (4.3)
Stomatitis and mucosal inflammation	83 (51.2)	9 (5.6)	43 (26.5)	0
Anemia	60 (37.0)	10 (6.2)	59 (36.4)	3 (1.9)
Hyperglycemia	95 (58.6)	9 (5.6)	14 (8.6)	0
Diarrhea	78 (48.1)	6 (3.7)	26 (16.0)	0
Nausea	45 (27.8)	1 (0.6)	27 (16.7)	0
Rash	41 (25.3)	0	28 (17.3)	0
Decreased appetite	38 (23.5)	0	14 (8.6)	0
Fatigue	38 (23.5)	0	21 (13.0)	2 (1.2)
Covid-19	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)
Headache	34 (21.0)	0	22 (13.6)	0
Leukopenia	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)
Ocular toxic effects	36 (22.2)	0	21 (13.0)	0

Approved by FDA in October 2024. PIK3CA testing can be done on tissue biopsy or liquid biopsy (blood test).

Recent press release announced an overall survival benefit but full results to be presented at an upcoming meeting.

Duration of response: 18.4 months for inavolisib vs 9.6 months for placebo

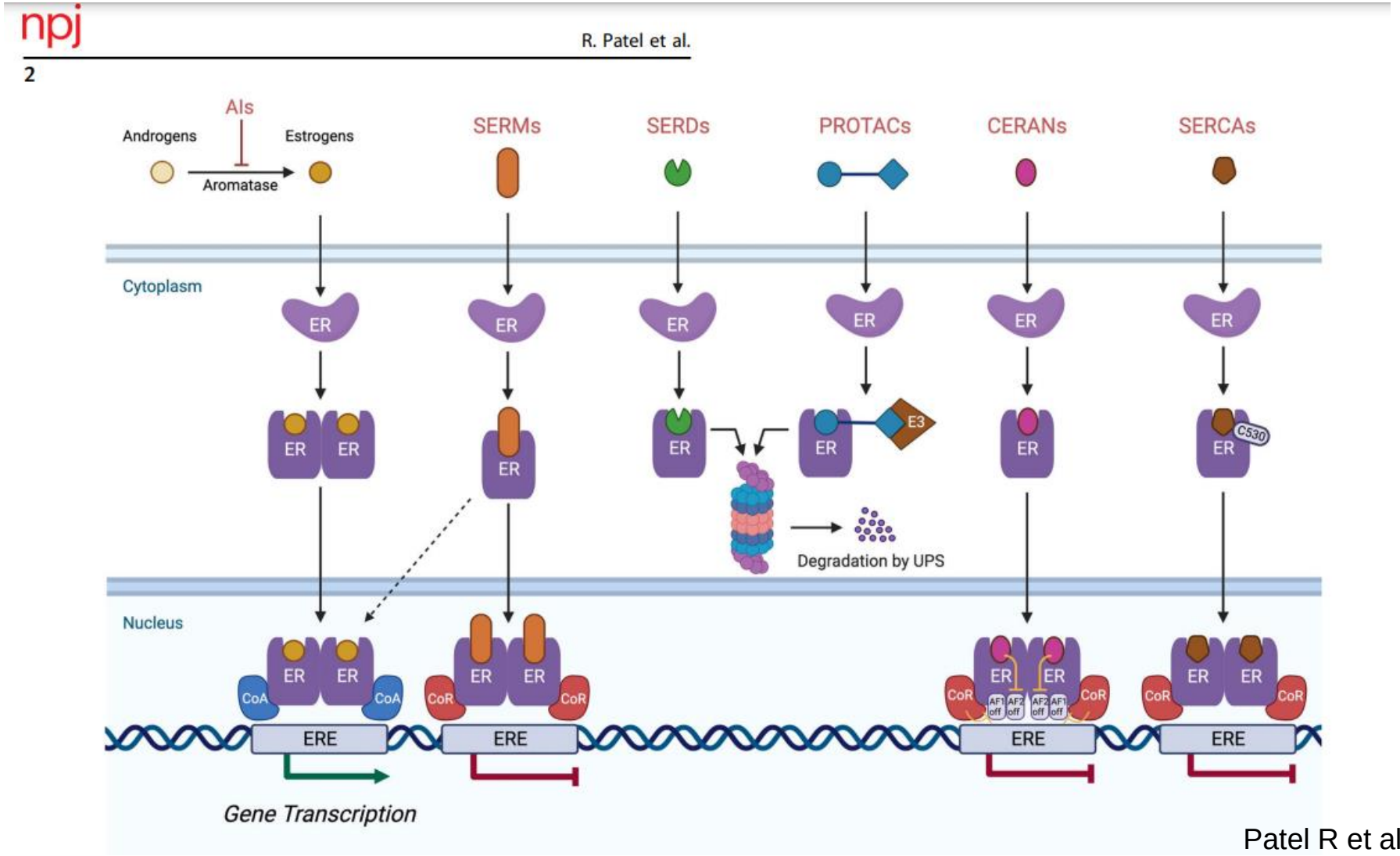
Turner NC et al. *N Engl J* Med 2024; 391:1584-96.;
https://www.roche.com/media/releases/med-cor-2025-01-28

Racial Disparities in Use of PI3K Inhibitors

- Recent study showed that despite equal numbers of PI3K mutations, Black patients were less likely to receive targeted therapy with PI3K inhibitors compared to White patients and were less likely to be enrolled onto a clinical trial
- Significant difference median HbA1c level between Black and White patients with PIK3CA mutations (6.1% vs 5.5%; P = .01).
- PI3K inhibitors cause hyperglycemia and there may be concern for prescribing these medications – education is critical!!

Podany EL et al. JAMA Network Open, 2025.

Novel Endocrine Therapies



- Next generation endocrine therapies are being developed (many in development)
- These are driven by need for agents that overcome mechanisms of resistance to endocrine therapy
- Raises question of how it will impact toxicity from endocrine therapy?

Patel R et al. npj Breast Cancer (2023) 9:20.

More on SERDs

- We know that resistance can develop to tamoxifen and aromatase inhibitors
- SERDs target the estrogen receptor and cause degradation by creating an unstable protein complex and this can overcome resistance
- ESR1 mutations can contribute to acquired resistance by causing constant estrogen receptor activity
- Fulvestrant is a SERD but with modest activity in second line setting and against ESR1 mutations.
- Elacestrant- oral SERD approved for ESR1 mutated MBC
- More in development/awaiting approval

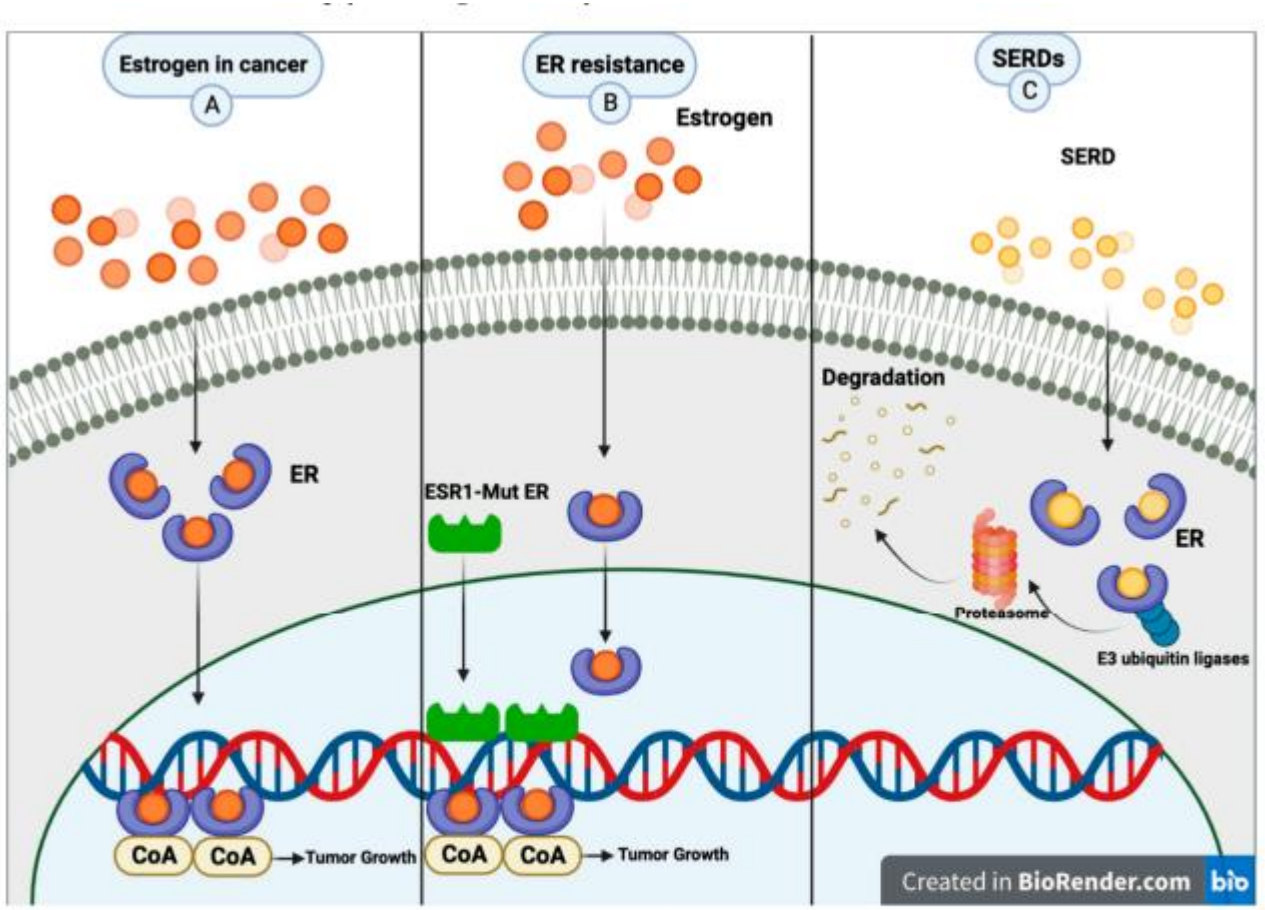


Figure 1. (**A**) Common pathway for estrogen in breast cancer. (**B**) Metastatic breast cancer patients may experience resistance mechanisms to endocrine therapy. A mutation of estrogen receptor 1 (*ESR1*) causes constant ER activity and enhanced transcription of ER-dependent genes without hormones, resulting in resistance to estrogen deprivation and aromatase inhibitor therapy. (**C**) SERDs bind to the estrogen receptor; then, E3 ubiquitin ligases and ubiquitinates the ER, marking it for degradation by the proteasome. The proteasome eventually degrades the ubiquitinated ER. Created with BioRender.com (accessed on 8 June 2023).

Neupane N et al. Cancers, 2024. 16(3):619.

Elacestrant

original reports

Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial

Francois-Clement Bidard, MD[1,2]; Virginia G. Kaklamani, MD[3]; Patrick Neven, MD[4]; Guillermo Streich, MD[5]; Alberto J. Montero, MD[6]; Frédéric Forget, MD[7]; Marie-Ange Mouret-Reynier, MD[8]; Joo Hyuk Sohn, MD[9]; Donatienne Taylor, MD[10]; Kathleen K. Harnden, MD[11]; Hung Khong, MD[12]; Judit Kocsis, MD[13]; Florence Dalenc, MD[14]; Patrick M. Dillon, MD[15]; Sunil Babu, MD[16]; Simon Waters, MD[17]; Ines Deleu, MD[18]; José A. García Sáenz, MD[19]; Emilio Bria, MD[20]; Marina Cazzaniga, MD[21]; Janice Lu, MD[22]; Philippe Aftimos, MD[23]; Javier Cortés, MD[24,25,26,27]; Shubin Liu, MS[28]; Giulia Tonini, PhD[29]; Dirk Laurent, MD[30]; Nassir Habboubi, MD[31]; Maureen G. Conlan, MD[32]; and Aditya Bardia, MD[33]

CONTEXT

Key Objective

What is the efficacy and safety of the novel oral selective estrogen degrader, elacestrant, in women with previously treated, estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer compared with standard-of-care (SOC) endocrine monotherapy?

Knowledge Generated

Among these patients, 43% of whom had two prior lines of endocrine therapy, elacestrant significantly reduced the risk of progression or death compared with SOC by 30% in the overall cohort ($P = .002$) and by 45% in patients with *ESR1* mutation ($P = .0005$). The most common adverse event was nausea, which occurred in 35% of patients receiving elacestrant and 19% of patients receiving SOC. Elacestrant was discontinued for an adverse event in 6% of patients, and SOC was discontinued in 4% of patients.

Relevance

These data represent an opportunity to potentially offer a new oral endocrine therapy option to patients with previously treated metastatic hormone receptor–positive breast cancer, including *ESR1*-mutant breast cancer.

- Approved by the FDA in January 2023 for postmenopausal women or adult men with ER-positive, HER2-negative, **ESR1-mutated** advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

- Most common side effects: nausea, fatigue, vomiting, decreased appetite, joint pain, diarrhea, back pain, increased liver enzymes, headache, constipation, hot flashes, dyspepsia
- Need to monitor lipid profile before starting and during treatment

Clement Bidard F et al. JCO 2022.

EMBER-3 Study Design

Imlunestrant is a next generation, brain-penetrant oral SERD and pure ER antagonist that delivers continuous ER inhibition.

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research

ER+, HER2- ABC

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

Prior therapy:

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

Stratification Factors:

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

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

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

Primary Endpoints

Investigator-assessed PFS for[f]:

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

Key Secondary Endpoints

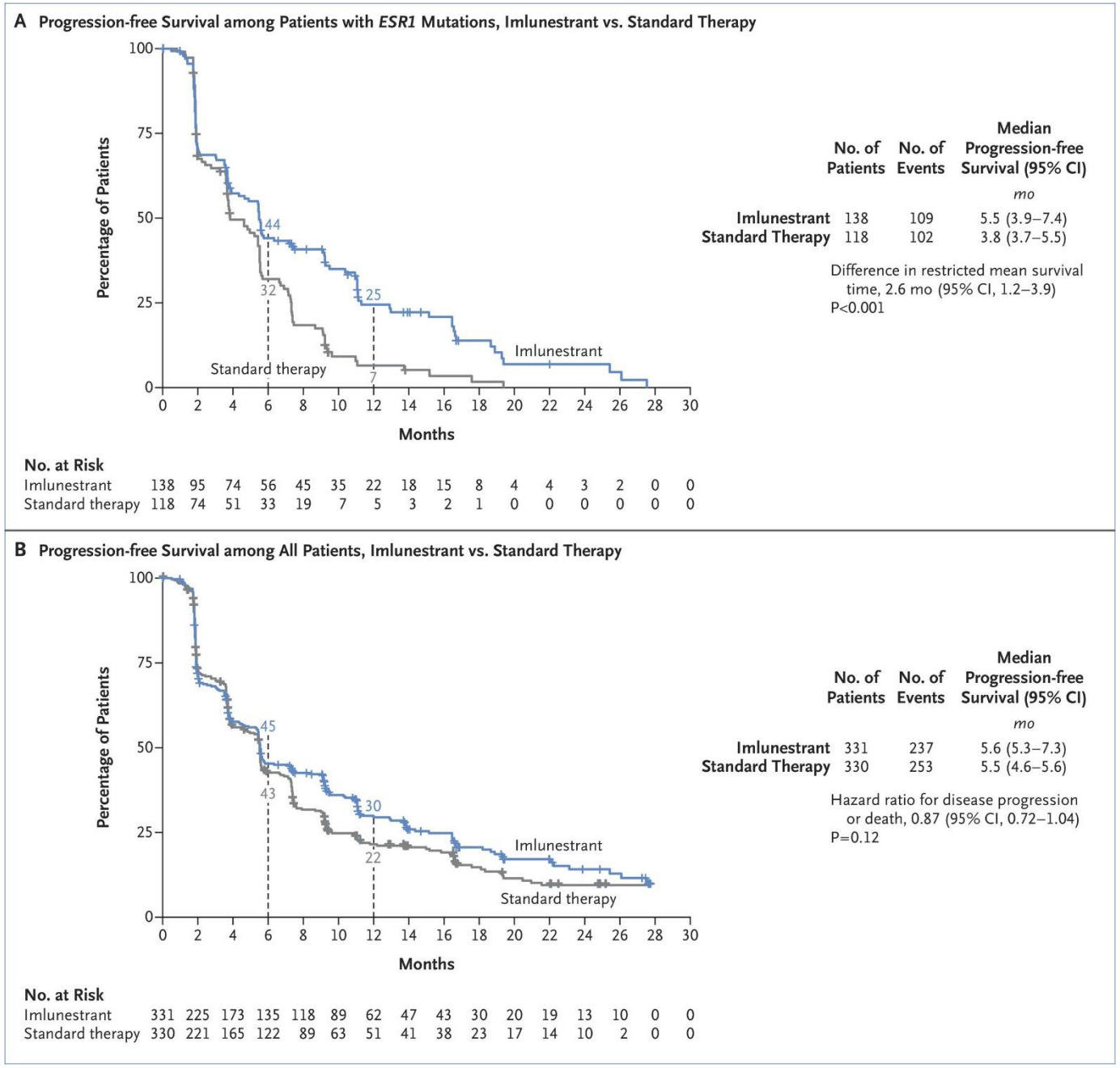
- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

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

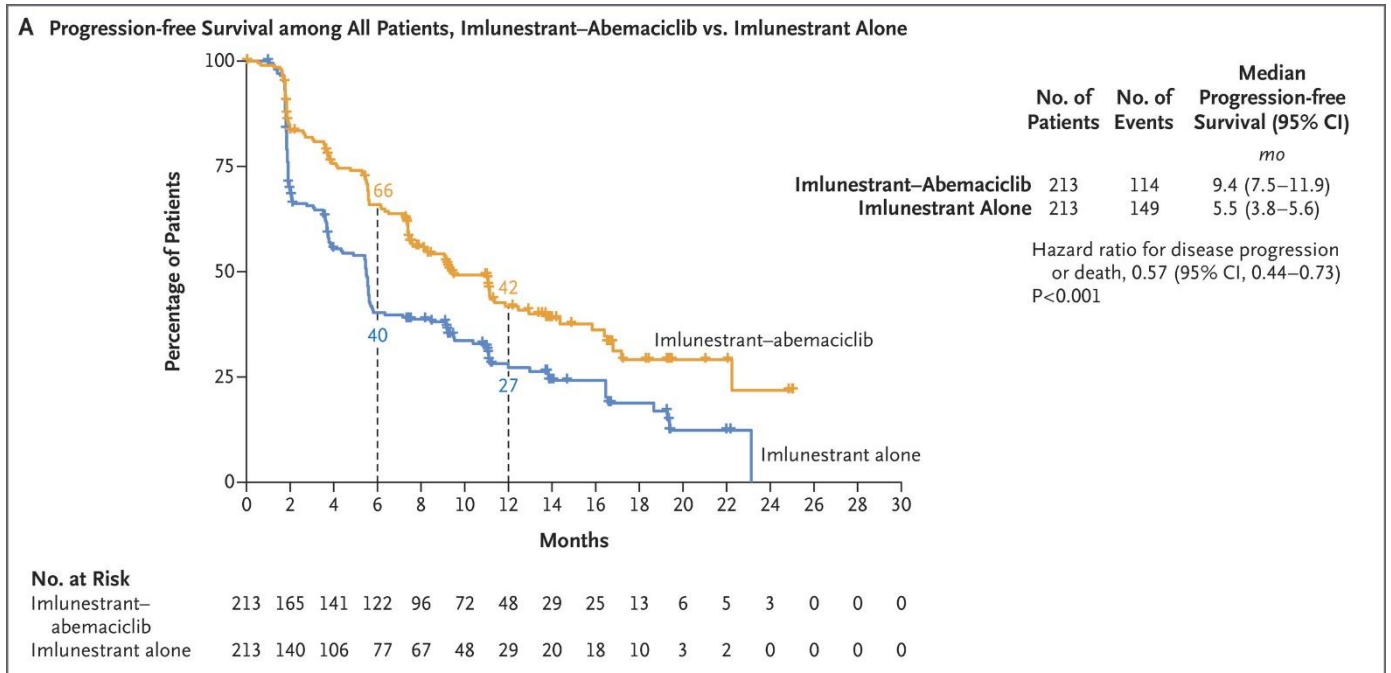
ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

Jhaveri K. SABCS 2024, General Session 1.



- Imlunestrant vs standard of care ET led to a 38% reduction in risk of progression or death in patients with ESR1 mutations (HR 0.62).
- PFS difference not statistically significant of imlunestrant vs standard of care ET in all patients.

Jhaveri K et al. NEJM, 2024.



- Imlunestrant + abemaciclib led to a 43% reduction in risk of progression or death compared to imlunestrant alone in all patients
- For patients who had previously received CDK 4/6 inhibitor treatment, most had received palbociclib or ribociclib
- Consistent benefit of imlunestrant+ abemaciclib regardless of ESR1 mutation status and across all key clinical subgroups (including PI3K pathway mutation and prior CDK 4/6 inhibitor treatment)
- Trend toward lower rates of CNS progression with imlunestrant vs SOC ET (*low event rate)
- Most common AEs with imlunestrant: fatigue, diarrhea, nausea, arthralgia, AST/ALT increased, back pain, anemia and constipation
- **Not yet FDA approved (as of 3/2025)**

Jhaveri K et al. NEJM, 2024.

Camizestrant demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival in 1st-line advanced HR-positive breast cancer with an emergent ESR1 tumour mutation in SERENA-6 Phase III trial

First and only next-generation oral SERD and complete ER antagonist to demonstrate 1st-line benefit in combination with widely approved CDK4/6 inhibitors

PUBLISHED
26 February 2025

Awaiting more info at upcoming meeting. Will it be practice changing?

Positive high-level results from a planned interim analysis of the SERENA-6 Phase III trial showed that AstraZeneca's camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) demonstrated a highly statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS). The trial evaluated switching to the camizestrant combination versus continuing standard-of-care treatment with an aromatase inhibitor (AI) (anastrozole or letrozole) in combination with a CDK4/6 inhibitor in the 1st-line treatment of patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer whose tumours have an emergent *ESR1* mutation.

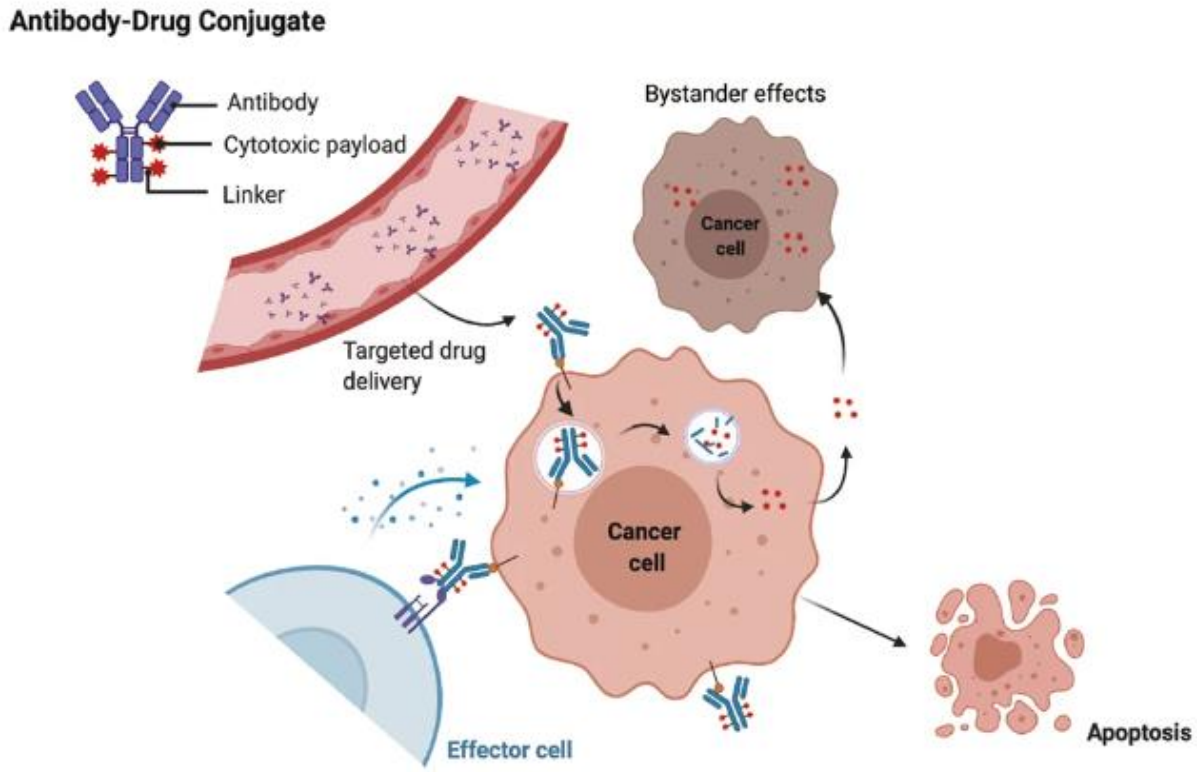
The key secondary endpoints of time to second disease progression (PFS2) and overall survival (OS) were immature at the time of this interim analysis. However, the camizestrant combination demonstrated a trend toward improvement in PFS2. The trial will continue as planned to further assess key secondary endpoints.

SERENA-6 is the first global, double-blind, registrational Phase III trial to use a circulating tumour DNA (ctDNA)-guided approach to detect the emergence of endocrine resistance and inform a switch in therapy before disease progression. The novel trial design used ctDNA monitoring at the time of routine tumour scan visits to identify patients for early signs of endocrine resistance and the emergence of *ESR1* mutations. Following detection of an *ESR1* mutation without disease progression, the endocrine therapy of patients was switched to camizestrant from ongoing treatment with an AI, while continuing combination with the same CDK4/6 inhibitor.

https://www.astrazeneca.com/media-centre/press-releases/2025/camizestrant-improved-pfs-in-1l-hr-breast-cancer.html

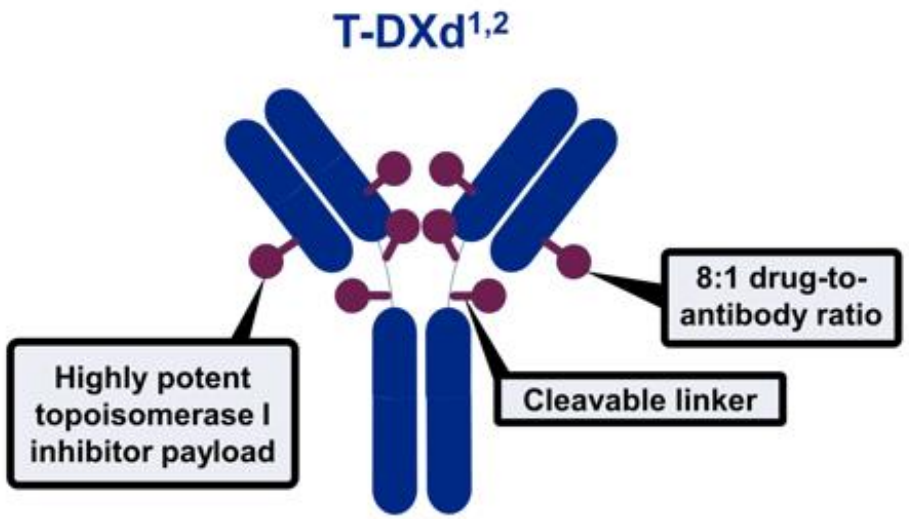
Antibody-Drug Conjugates (ADCs)

- Class of drugs that contain a monoclonal antibody chemically linked to a cytotoxic drug
- Monoclonal antibody binds to specific proteins or receptors found on certain types of cells, including cancer cells
- Linked drug then enters the cells and can cause cell death
- “The biological missile” for targeted cancer therapy
- Have a bystander effect (toxin diffuses in tissues outside of the targeted region)- can be effective but can cause toxicity

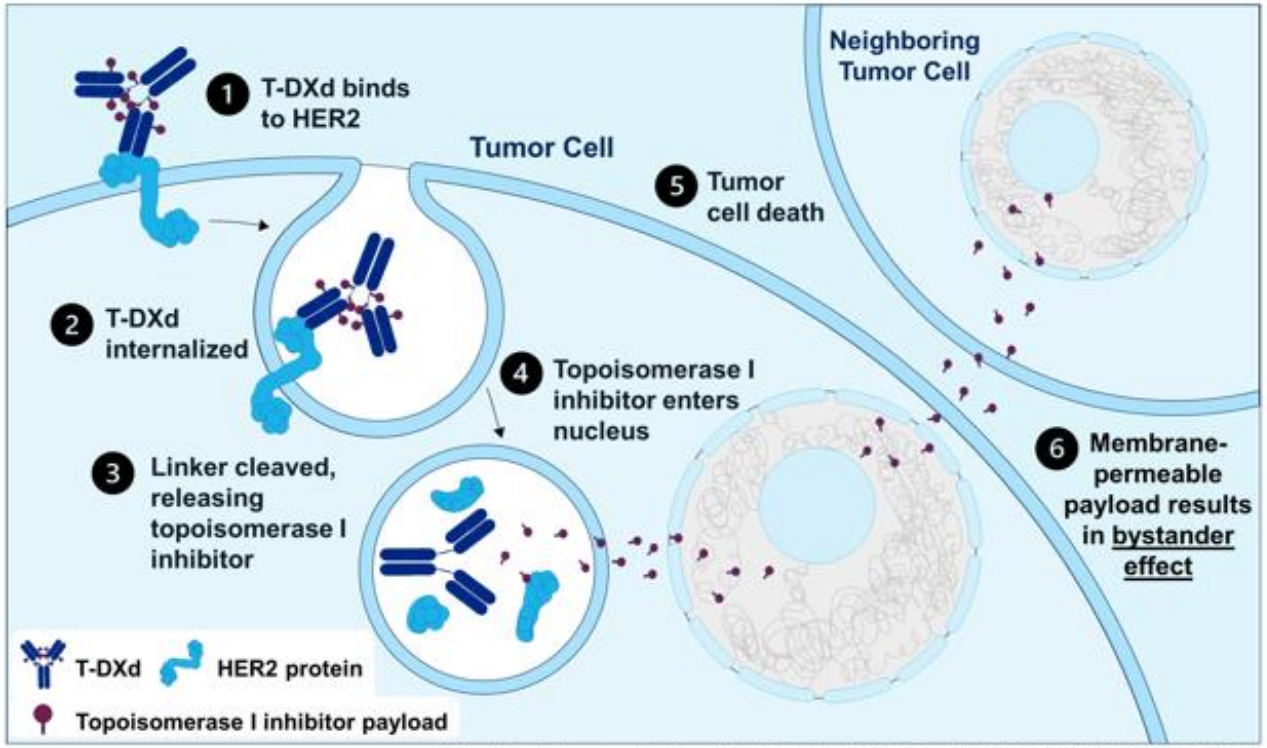


Fu et al. Nature Signal Transduction and Targeted Therapy, 2022.

Trastuzumab Deruxtecan (Enhertu)



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- Approved for HER2+ positive and HER2-low and ultra low metastatic breast cancer

HER2 Low Breast Cancer & DESTINY-Breast 04 Trial

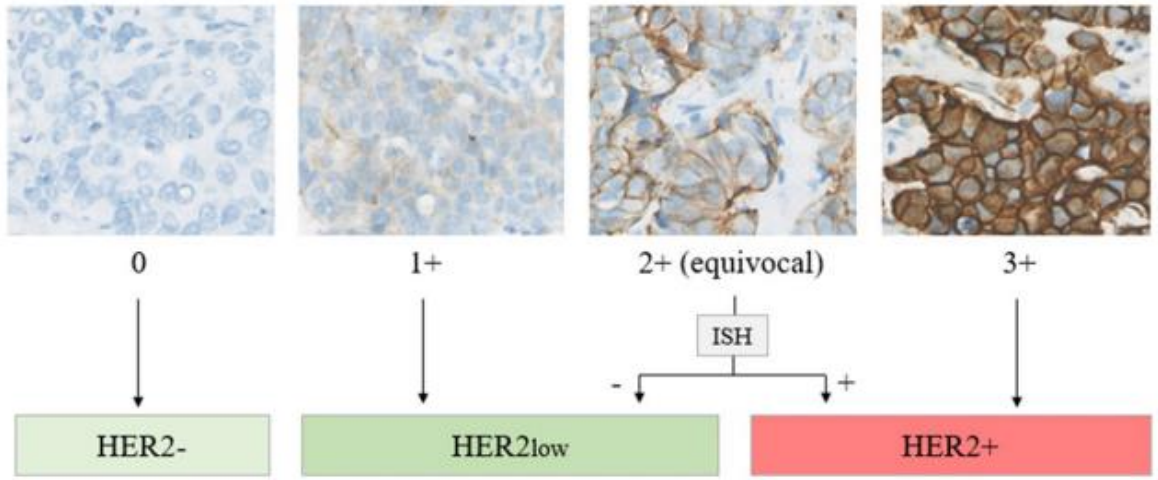
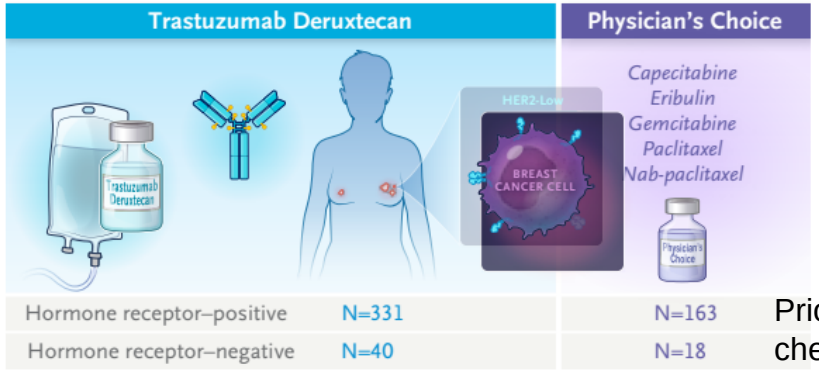


Figure 5. A schematic overview of HER2 scoring in breast cancer, as used in this study. Breast carcinomas are considered HER2- if the IHC score is 0. An IHC score 1+ or 2+ without HER2 amplification (after ISH) is categorized as HER2low. Breast cancers with an IHC score of 2+ with amplification (after ISH) or 3+ are HER2+ (80× magnification). ISH = in situ hybridization.

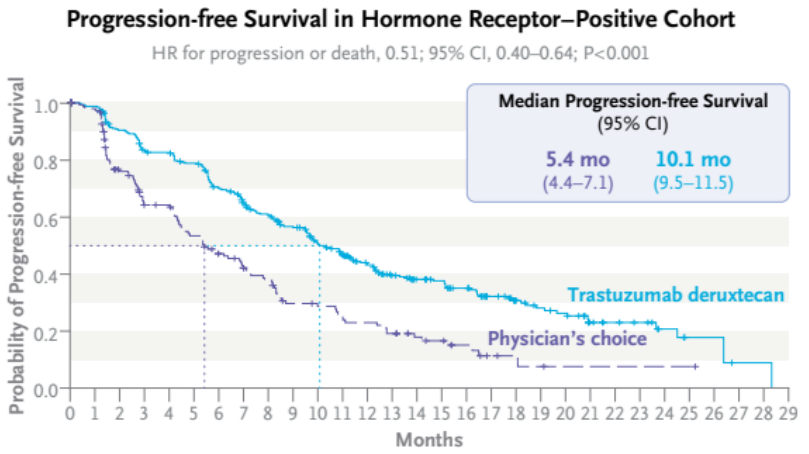
CONCLUSIONS

Trastuzumab deruxtecan significantly prolonged progression-free and overall survival among previously treated patients with HER2-low metastatic breast cancer, regardless of hormone-receptor status.

Ultralow: between 0 and 1+ with faint membrane staining.



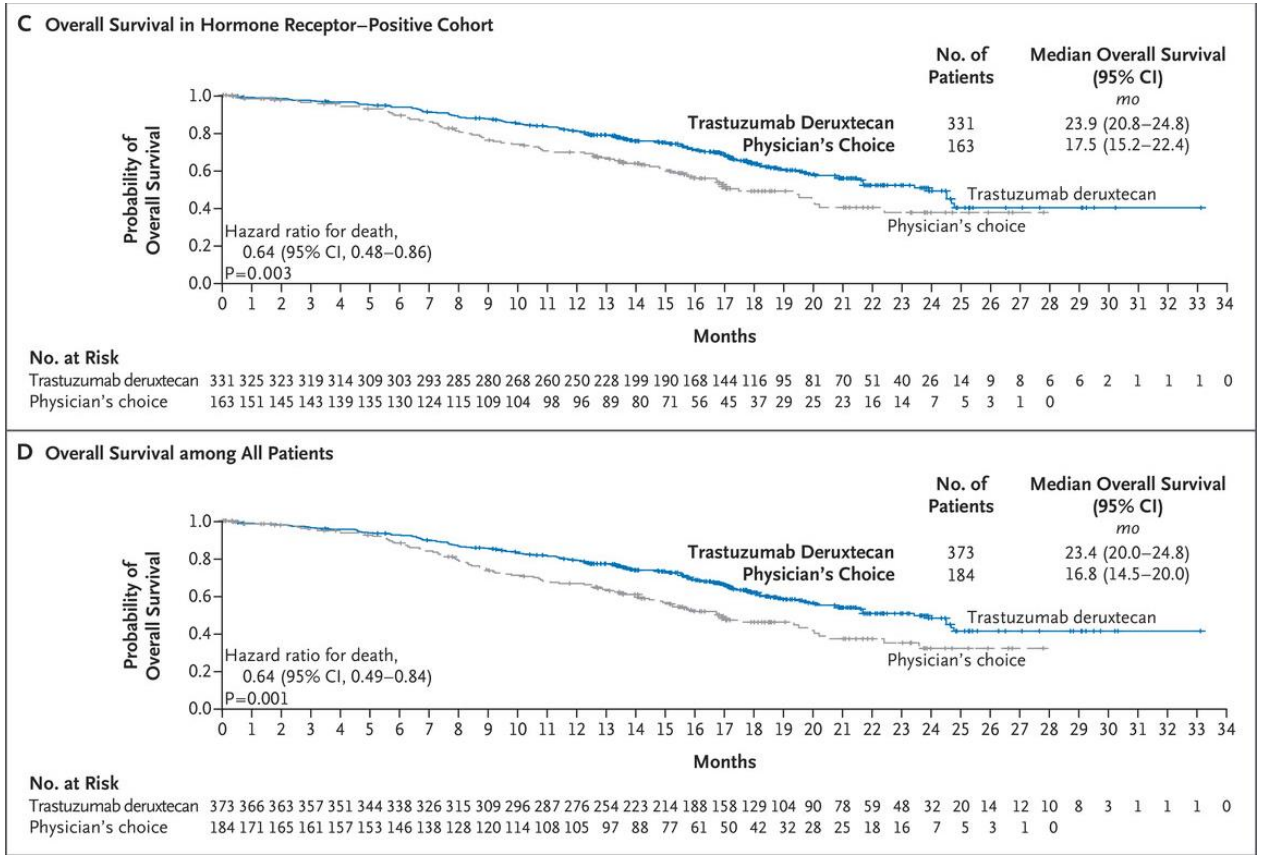
Prior 1-2 lines of chemotherapy



PFS in HR- cohort: 8.5 months for T-DXd vs 2.9 mo in physician's choice); PFS in overall population 9.9 mo vs 5.1 months, HR 0.50 (95% CI, 0.4-0.63).

Van den Ende NS et al. Nature Scientific Reports 2022; Modi S et al. NEJM, 2022.

More on DESTINY-Breast 04 Trial



- Median overall survival in HR-negative cohort was 18.2 months in T-DXd vs 8.3 months in physician's choice group (HR 0.48, 95% CI, 0.24 to 0.95)

Most common toxicities in T-DXd Arm:

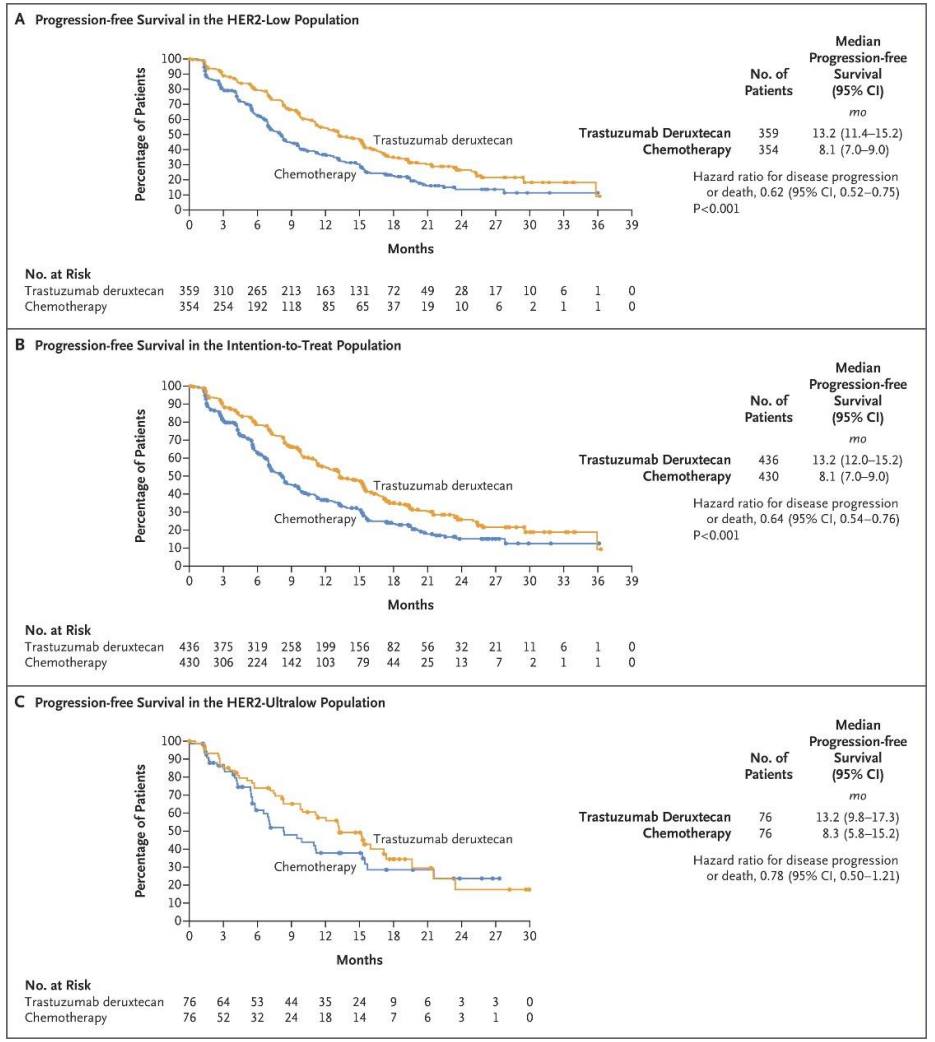
- Neutropenia (33.2%)
- Anemia (33.2%)
- Thrombocytopenia (23.7%)
- Leukopenia (23.2%)
- Nausea (73%)
- Vomiting (34%)
- Diarrhea (22.4%)
- Constipation (21.3%)
- Increased AST (liver) levels (23.5%)
- Fatigue (47.7%)
- Decreased appetite (28.6%)
- Alopecia (37.7%)

Grade ≥3: Neutropenia (13.7%), anemia (8.1%), thrombocytopenia (5.1%), leukopenia (6.5%), nausea (4.6%), vomiting (1.3%), diarrhea (1.1%), increased AST (3.2%), fatigue (7.5%), decreased appetite (2.4%)

Modi S et al. NEJM, 2022.

Destiny-Breast 06: T-DXd in HER2 Ultra Low MBC

- Phase 3, multi-center trial with hormone receptor positive MBC with low HER2 expression or ultralow HER2 expression who had received one or more lines of endocrine-based therapy and no previous chemotherapy for MBC
- Patients randomized 1:1 to T-DXd or physician's choice of chemotherapy



Bardia A et al. NEJM 2024; 391: 2110-2122.

FDA approves fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer

On January 27, 2025, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.

FDA also approved the Ventana's PATHWAY anti-HER-2 (4B5) Rabbit Monoclonal Primary Antibody assay as a companion diagnostic device to identify patients with HER2-ultralow (IHC 0 with membrane staining) breast cancer for treatment with Enhertu. This assay was previously approved to identify patients with HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer for treatment with Enhertu.

Full prescribing information for Enhertu will be posted on Drugs@FDA.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-hr-positive-her2-low-or-her2

Interstitial Lung Disease with T-DXd

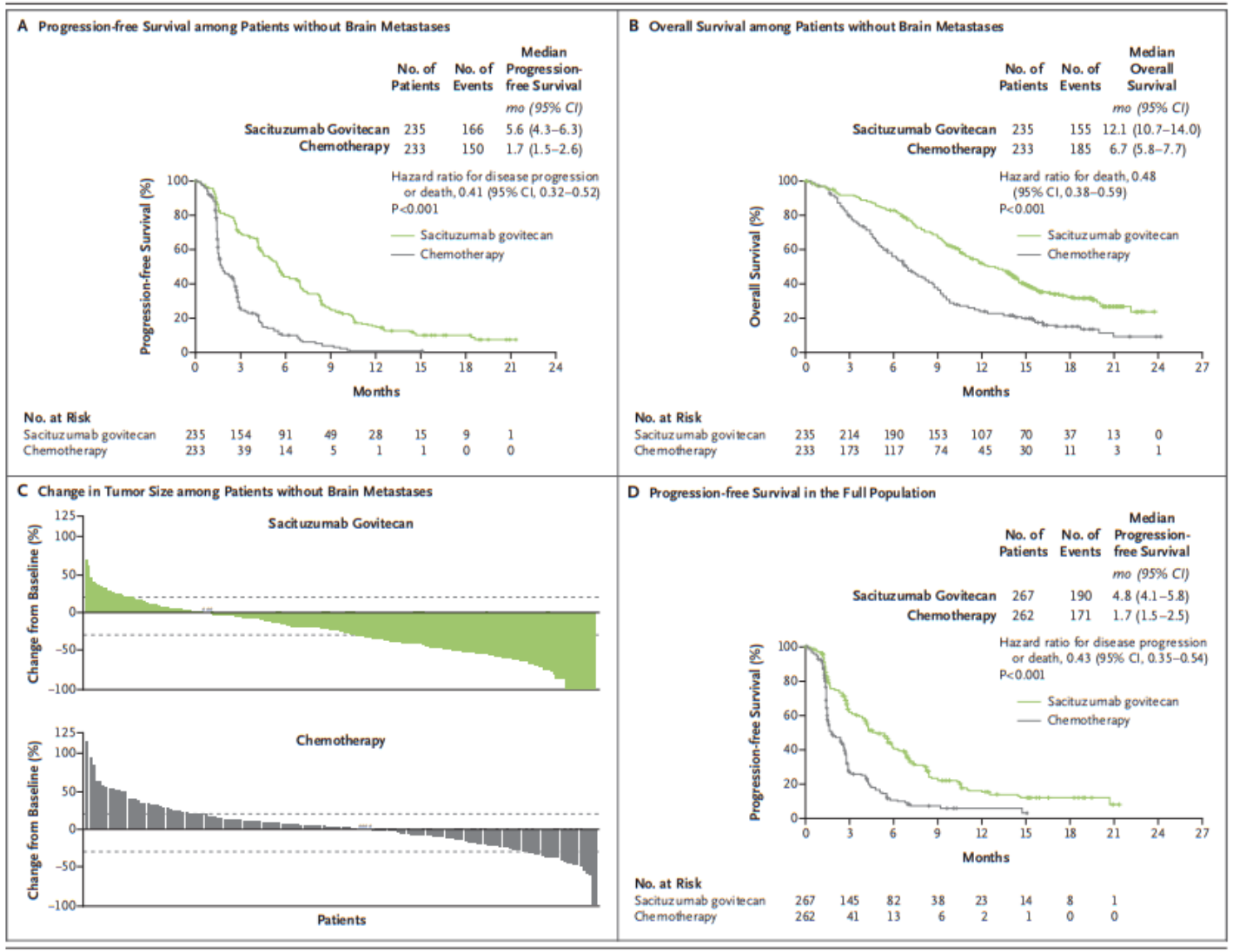
- Group of pulmonary diseases occurring secondary to inflammation and scarring of the pulmonary interstitial tissue
- Symptoms can be non-specific and can include cough, chest pain, shortness of breath, chest tightness, dyspnea on exertion, fever
- Incidence is approximately 12% (majority are Grade 1 or 2)
  - Median time to onset 5.5 months (range 0.9 to 31.5 months)
  - Fatal outcomes due to ILD/pneumonitis occurred in 0.9% of patients treated
- Education about symptoms and prompt diagnostic work-up and subsequent intervention is critical
- Suspicion of symptoms → HOLD T-DXd, imaging, initiate steroids

Sacituzumab Govitecan (Trodelvy) for TNBC and HR+/HER2- MBC

- ADC composed of Trop-2 antibody coupled to SN-38 (active metabolite of irinotecan and a topoisomerase I inhibitor) through a hydrolyzable linker
  - Allows for targeted delivery of SN-38 to tumor cells and also has a bystander effect because it is membrane permable
- Phase 3 ASCENT Trial: Sacituzumab govitecan versus chemotherapy of physician's choice (eribulin, vinorelbine, capecitabine or gemcitabine) in patients with relapsed or refractory metastatic TNBC
  - After two or more prior standard chemotherapy regimens (at least 1 for metastatic disease)
- Starting dose is 10 mg/kg on IV on days 1 and 8 of each 21 day cycle

Bardia A et al. N Engl J Med 2021;384:1529-1541.

ASCENT Results



Updated 2024 Results:

Overall survival: 11.8 months SG vs 6.9 months TPC (HR 0.514)

Progression-free survival:
4.8 months SG vs 1.7 months TPC (HR 0.413)

Trop-2 testing is not required for SG Treatment

Bardia A et al. N Engl J Med 2021;384:1529-1541.

Sacituzumab Govitecan Side Effects from ASCENT

Table 3. Summary of Treatment-Related Adverse Events in the Safety Population.*

Adverse Event	Sacituzumab Govitecan (N=258)			Chemotherapy (N=224)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	252 (98)	117 (45)	48 (19)	192 (86)	71 (32)	33 (15)
Hematologic event						
Neutropenia†	163 (63)	88 (34)	44 (17)	96 (43)	45 (20)	29 (13)
Anemia‡	89 (34)	20 (8)	0	54 (24)	11 (5)	0
Leukopenia§	41 (16)	23 (9)	3 (1)	25 (11)	10 (4)	2 (1)
Thrombocytopenia¶	14 (5)	2 (1)	2 (1)	25 (11)	3 (1)	0
Febrile neutropenia	15 (6)	12 (5)	3 (1)	5 (2)	4 (2)	1 (<1)
Gastrointestinal event						
Diarrhea	153 (59)	27 (10)	0	27 (12)	1 (<1)	0
Nausea	147 (57)	6 (2)	1 (<1)	59 (26)	1 (<1)	0
Vomiting	75 (29)	2 (1)	1 (<1)	23 (10)	1 (<1)	0
Constipation	44 (17)	0	0	32 (14)	0	0
Abdominal pain	29 (11)	3 (1)	0	9 (4)	1 (<1)	0
General disorders and administration-site conditions						
Fatigue	115 (45)	8 (3)	0	68 (30)	12 (5)	0
Asthenia	31 (12)	2 (1)	0	23 (10)	3 (1)	0
Skin and subcutaneous disorders: alopecia‖	119 (46)	0	0	35 (16)	0	0
Metabolism and nutrition disorders: decreased appetite	51 (20)	4 (2)	0	32 (14)	1 (<1)	0
Nervous system disorders**††	64 (25)	1 (<1)	0	53 (24)	5 (2)	0
Respiratory, thoracic, and mediastinal disorders††	41 (16)	5 (2)‡‡	0	17 (8)	1 (<1)	0
Musculoskeletal and connective-tissue disorders††	32 (12)	0	0	28 (12)	3 (1)	0
Infections and infestations††	30 (12)	6 (2)	1 (<1)	22 (10)	4 (2)	3 (1)

Bardia A et al. N Engl J Med 2021;384:1529-1541.

TROPICS-02: SG in HR+/HER2- MBC

- Sacituzumab govitecan in patients with endocrine resistant HR+/HER2- MBC vs single agent chemotherapy (eribulin, capecitabine, gemcitabine or vinorelbine)
- Must have had prior CDK 4/6 inhibitor, prior taxane, 2-4 prior chemotherapy regimens for metastatic disease
- FDA approved February 2023

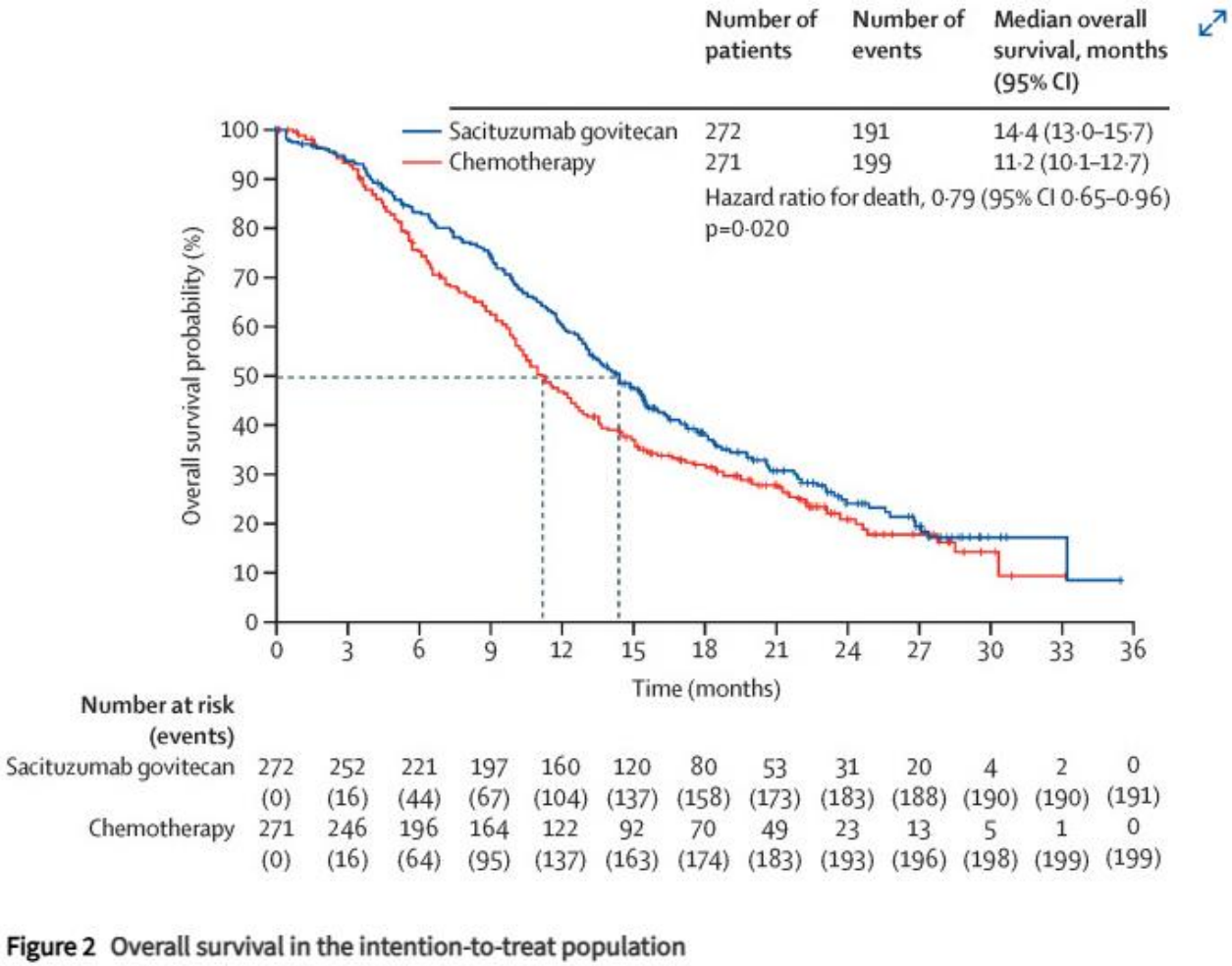


Figure 2 Overall survival in the intention-to-treat population

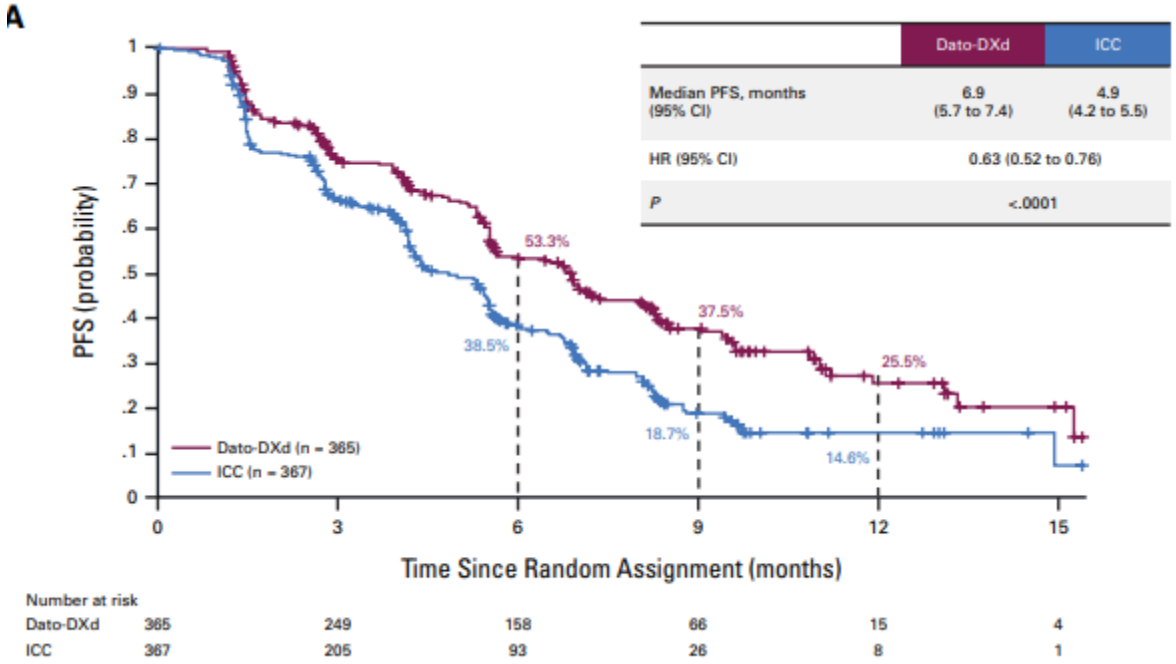
Rugo H et al. J Clin Oncol, 2022.

Datopotamab Deruxtecan (Dato-DXd)

- Newly approved by the FDA (January 2025) for patients wit hormone receptor positive/HER2 negative MBC who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease
- TROP2-directed antibody attached to deruxtecan (same antibody as sacituzumab govitecan and same payload as T-DXd)
- Tropion-Breast 01 Trial: Dato-DXd versus investigator’s choice of chemotherapy (capecitabine, vinorelbine or gemcitabine). Prior ADCs were not permitted.

Bardia A et al. J Clin Oncol, 2024.

Tropion-Breast 01 Results



- Improvement in PFS but no improvement seen in Tropion-Breast 01 in overall survival
- A lot of ongoing discussion about sequencing and choice of ADCs (Dato-DXd, T-DXd or SG) – based on side effects, efficacy.
- Most common side effects include nausea, stomatitis, alopecia, fatigue, dry eyes, vomiting, constipation, keratitis, decreased appetite, asthenia, anemia, low blood counts, diarrhea, elevated liver enzymes
- 3.3% incidence of ILD (lower than T-DXd)
- Ocular toxicities: patients need to use lubricating eye drops and avoid using contact lenses

Bardia A et al. J Clin Oncol, 2024.

Current Treatment Landscape for HER2+ MBC

Cell Reports Medicine
Review

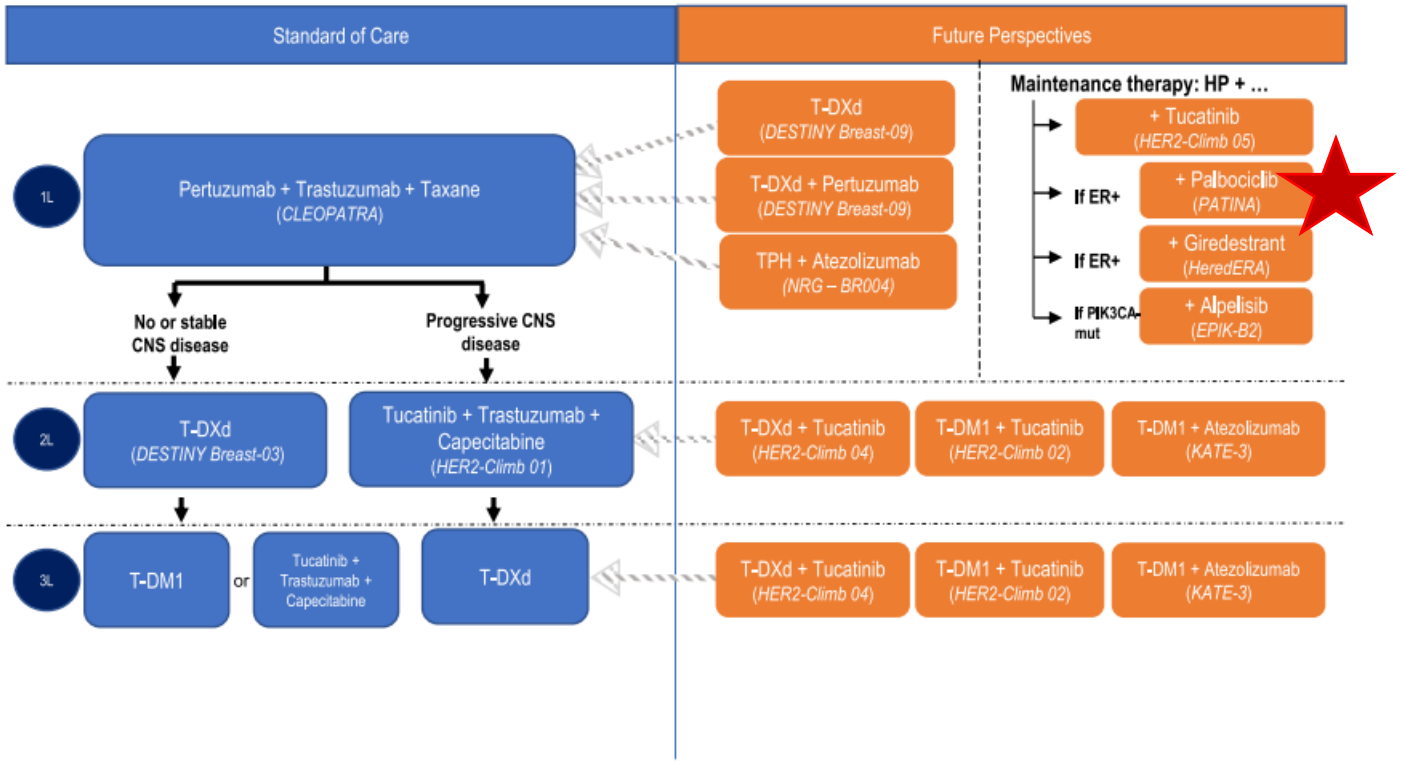


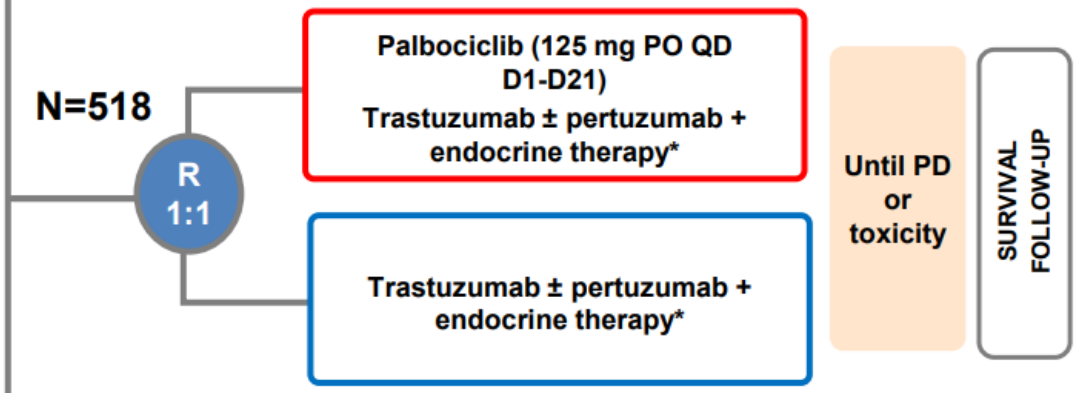
Figure 2. Standard of care and future perspective in the treatment landscape of HER2-positive advanced breast cancer

Agostinetto E et al. Cell Rep Med. 2024; 5(6): 101575.

AFT-38 PATINA Study Design

Registration
- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria
- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)



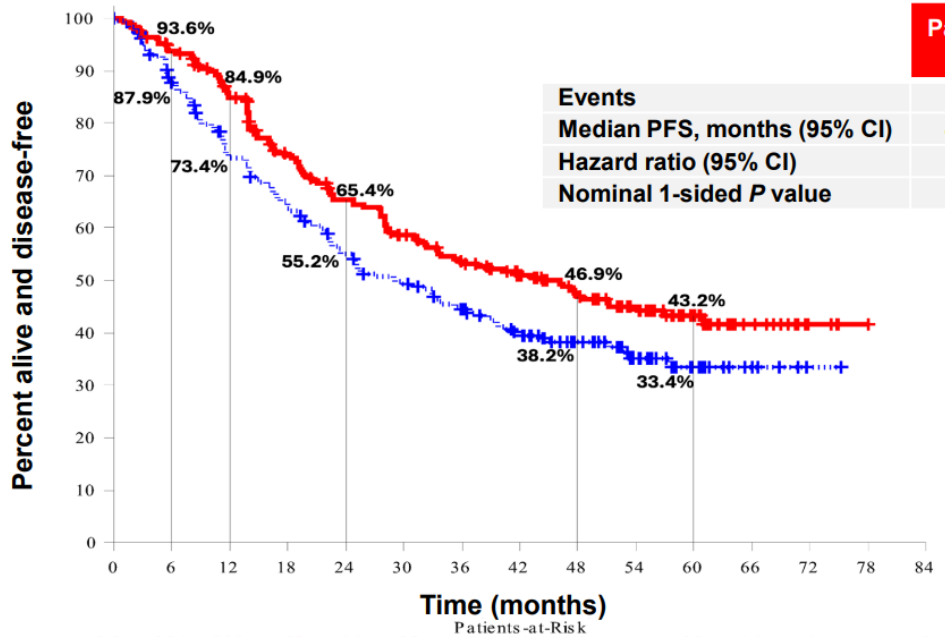
Stratification factors
- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

- CDK 4/6 inhibitors currently in HR+/HER2- breast cancer
- Current standard of care for 1L therapy for HR+/HER2+ metastatic breast cancer: taxane + anti HER2 therapy → HER2 therapy maintenance with addition of endocrine therapy (assuming stable/improved disease)

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Metzger O. SABCS 2024 General Session 2.

Primary Endpoint: PFS (Investigator-Assessed)



	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

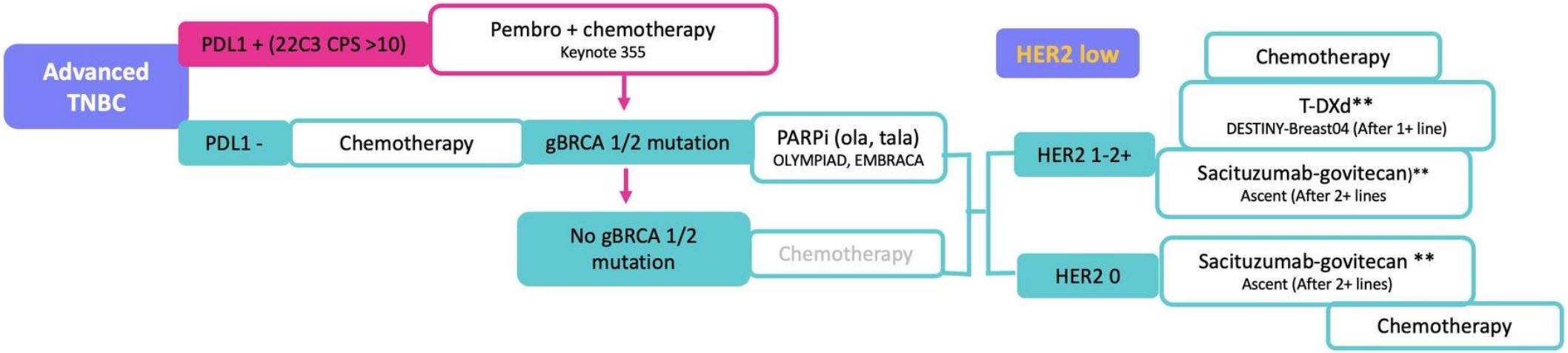
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

- Palbociclib added to anti HER2 and endocrine therapy improved progression free survival by 15.2 months (HR 0.74) and ***may represent a new standard of care for this patient population.***
- 5-year overall survival (interim analysis): 74.3 months vs 69.8 months (HR 0.86, 0.6-1.24)
- No new safety signals

Metzger O. SABCS 2024 General Session 2.

Current Treatment Landscape for Triple Negative MBC

- First line treatment is chemotherapy in PD-L1 negative disease and chemotherapy + immunotherapy in PD-L1+ disease



** No data about ADC sequencing , ~60 of patients in DESTINY-breast04 had HER2 low, HR- disease

@ilanaSchlam

Dr. Ilana Schlam @ilanaschlam, December 13, 2024, X.

Immunotherapy (Immune checkpoint inhibitors)

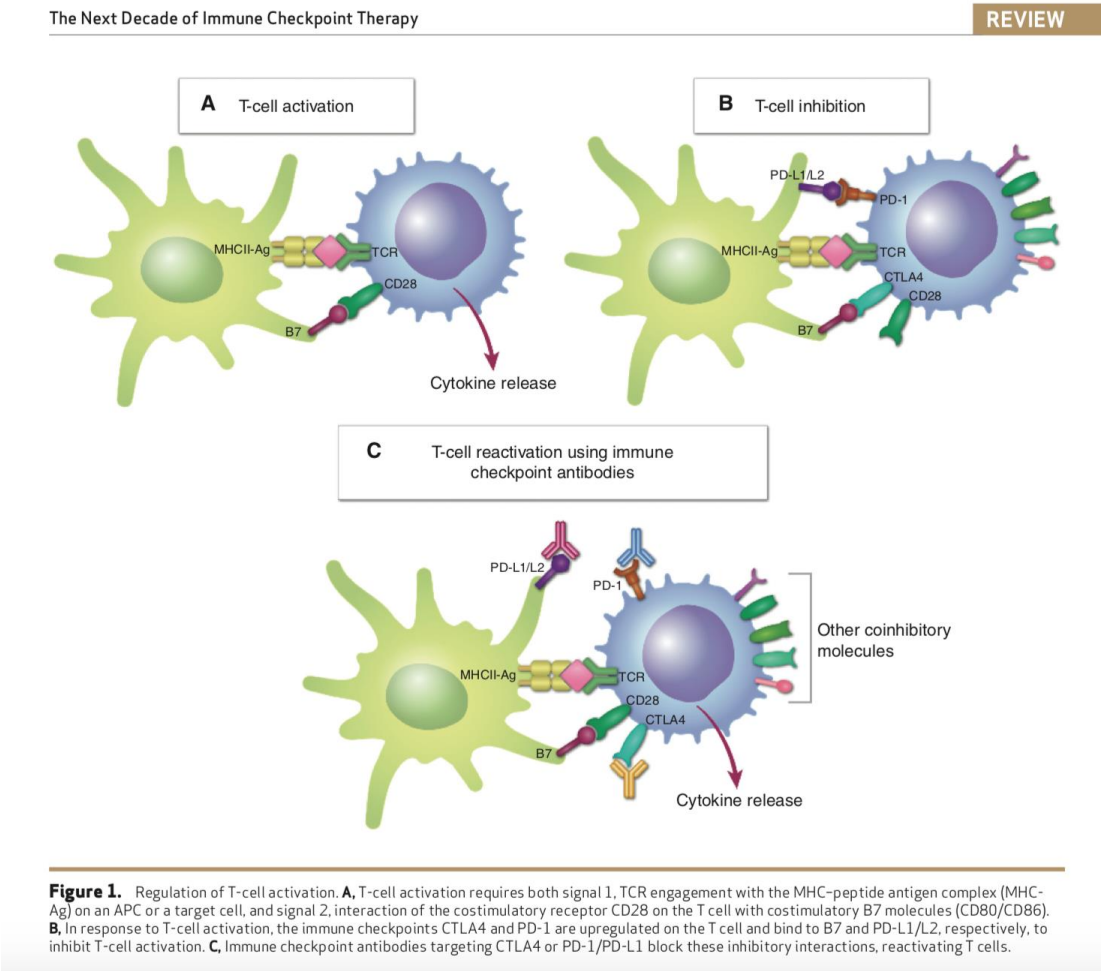
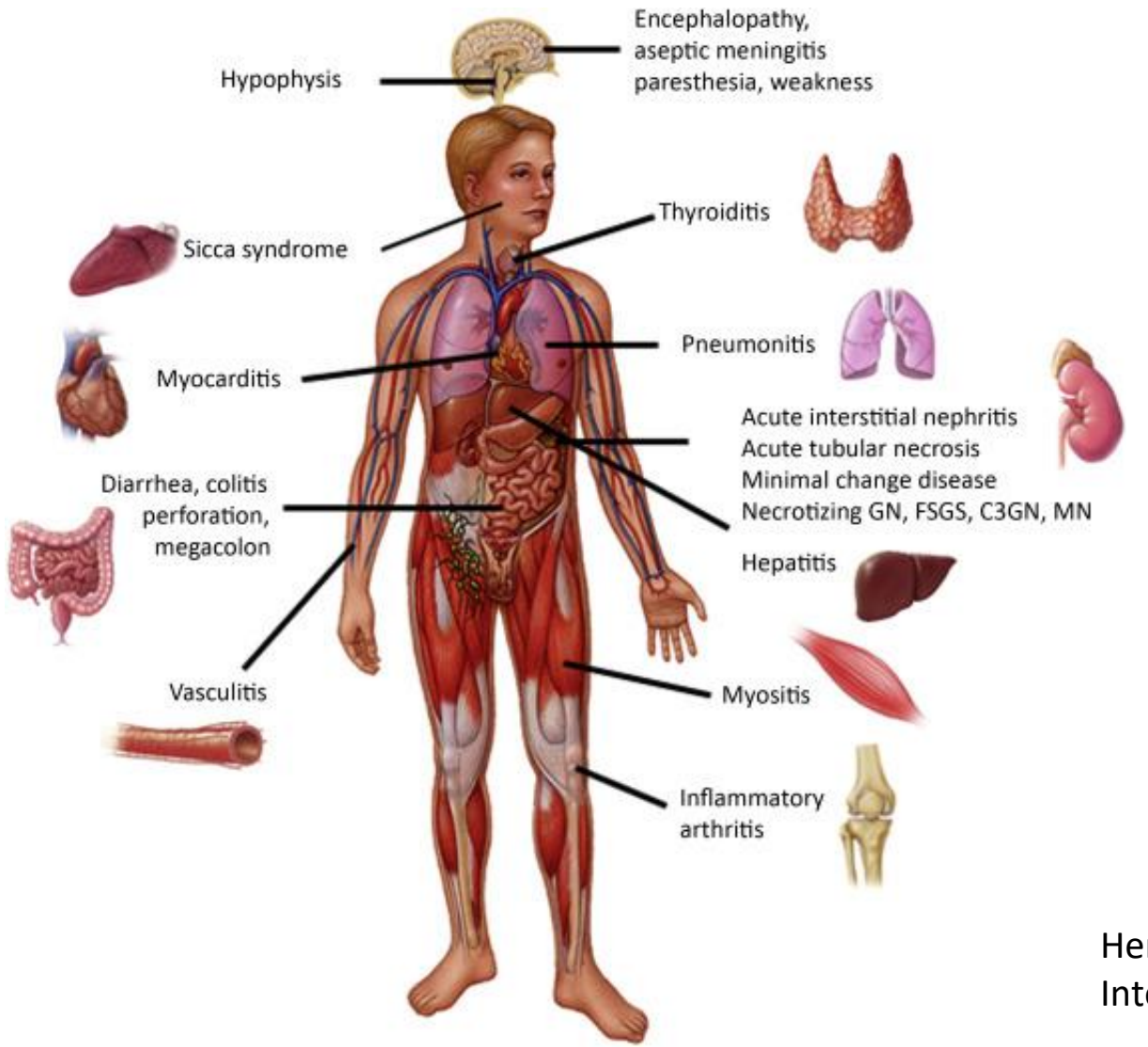


Figure 1. Regulation of T-cell activation. **A,** T-cell activation requires both signal 1, TCR engagement with the MHC-peptide antigen complex (MHC-Ag) on an APC or a target cell, and signal 2, interaction of the costimulatory receptor CD28 on the T cell with costimulatory B7 molecules (CD80/CD86). **B,** In response to T-cell activation, the immune checkpoints CTLA4 and PD-1 are upregulated on the T cell and bind to B7 and PD-L1/L2, respectively, to inhibit T-cell activation. **C,** Immune checkpoint antibodies targeting CTLA4 or PD-1/PD-L1 block these inhibitory interactions, reactivating T cells.

- Cancer cells are able to evade the immune system through different mechanisms, including increasing expression of ligands that can bind inhibitory T cell receptors
- ICIs are monoclonal antibodies that **stimulate the anti-tumor immune response** by interrupting co-inhibitory signaling pathways and promoting the immune-mediated elimination of tumor cells
- This can affect activate autoreactive T cells, resulting in various immunotherapy-related adverse events (irAEs) similar to autoimmune diseases
- ICIs are broadly used in multiple tumor types and have revolutionized cancer outcomes- Pembrolizumab is approved in many cancer types and in breast cancer, is approved for PD-L1 positive triple negative metastatic breast cancer in combination with chemotherapy (KEYNOTE 355) and in stage 2-3 triple negative breast cancer in addition to standard chemotherapy (KEYNOTE 522)

Sharma P et al. *Cancer Discovery*, 2021; Johnson DB et al. *Nat Rev Clin Oncol*, 2022; Choi J and Lee SY. *Immune Netw,* 2020.

Immunotherapy Adverse Events



Hermann SM and Perazella MA. Kidney International Reports, 2020.

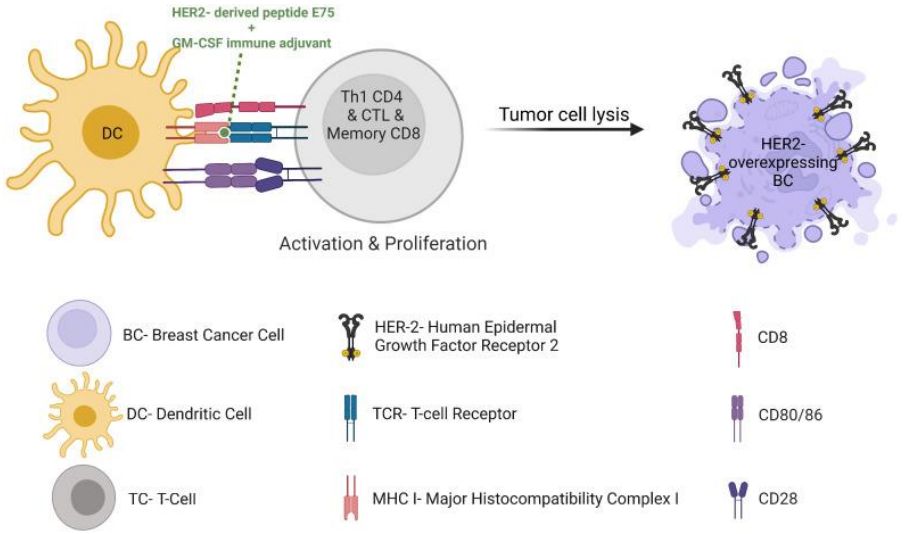
Many trials ongoing for metastatic TNBC

- Tropion-Breast02: Datapotamab deruxtecan versus chemotherapy in patients previously untreated with locally recurrent unresectable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy
- Tropion-Breast 05: Dato-DXd with or without durvalumab versus chemotherapy + pembrolizumab in patients with PD-L1+ metastatic TNBC
- Saci-IO TNBC: Sacituzumab govitecan with or without pembrolizumab in PD-L1 negative metastatic TNBC

…and many more!

Vaccine Trials in Breast Cancer

- No vaccine has been approved for clinical use in breast cancer to date but there are several ongoing clinical trials
- Types of vaccines: therapeutic peptide and protein-based, autologous tumor cells, B-cell based, dendritic cell-based and TLR agonists, DNA/mRNA based

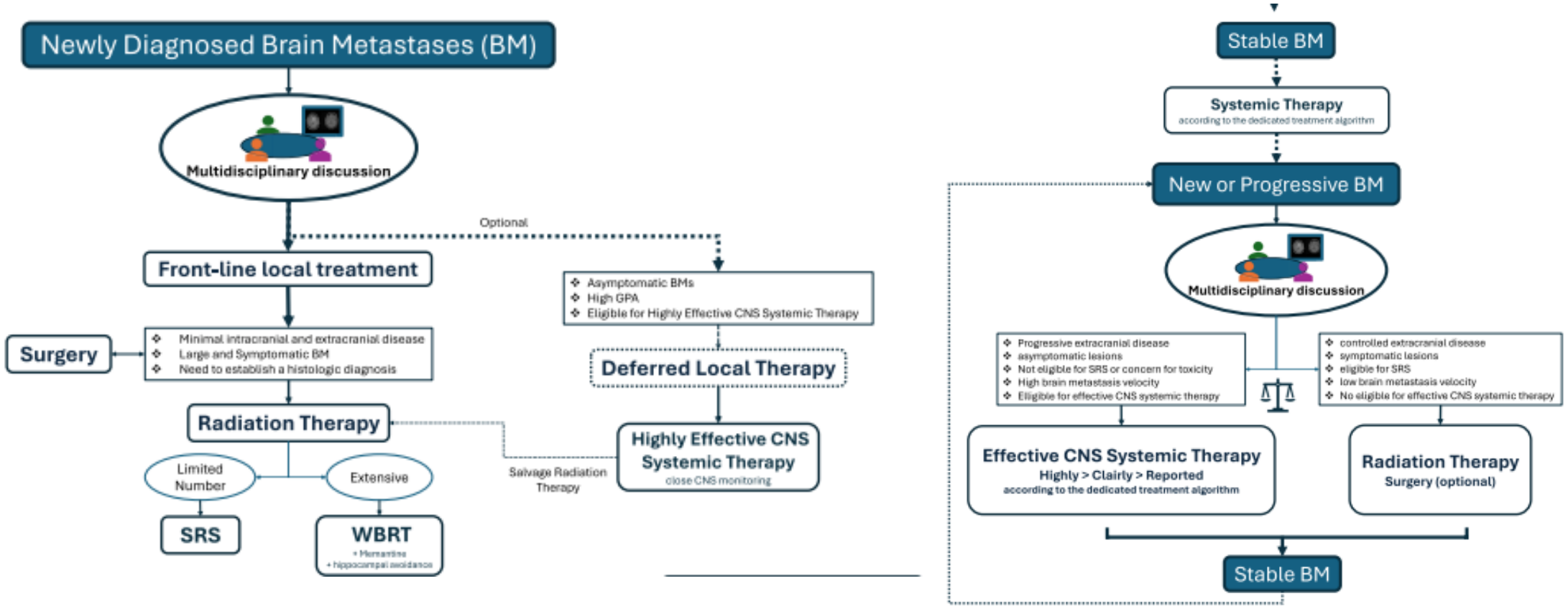


For example: the HER2 peptide vaccine is derived from the HER2 protein and can stimulate the immune system and trigger an immune response → helps the immune system create its own defense against HER2 positive cancer

Much more research is needed in this space – need to see efficacy

Alaluf E et al. Front Immunol 2024.

Updates in Brain Metastases (BM)



Grinda T et al. Curr Treat Options in Oncol 2025. 26:14-35.

Updates in Brain Metastases

Effective CNS Systemic Therapy

Highly
- Tucatinib regimen
- T-Dxd for HER2-positive

Clearly
- TDM1
- TDM1 + Tucatinib
- Pertuzumab + high dose trastuzumab
- Laptatinib/Neratinib + Capecitabine

Reported

Endocrine therapy
- Tamoxifen
- Aromatase inhibitors

Targeted Therapy
- Abemaciclib
- Alpelisib
- Bevacizumab
- Olaparib
- Pembrolizumab

Chemotherapy
- Capecitabine
- Platinums
- Anthracyclines
- Irinotecan
- Eribulin

ADC
- T-Dxd (HER2-low)
- Sacituzumab Govitecan
- Datopotamab-Deruxtecan

Table 2 Recruiting or Not Yet recruiting clinical trials on systemic treatment in Breast Cancer Patients with CNS M

NCT Number ACRONYM	Trial Name	Interventions
MBC patients with Brain Metastases		
HER2-POSITIVE		
NCT04334330	Palbociclib, Trastuzumab, Pyrotinib and Fulvestrant Treatment in Patients with BM From ER/PR Positive, HER-2 Positive BC: A Multi-center, Prospective Study in China	Palbociclib, Trastuzumab, Pyrotinib and Fulvestrant
NCT06152822	Pyrotinib Combined with Capecitabine and Bevacizumab for Patients with HER2 Positive BC and BM	Pyrotinib Combined with Capecitabine and Bevacizumab
NCT05553522	Tucatinib, Trastuzumab, and Capecitabine with SRS for BM From HER-2 Positive BC	Combined use of SRS with Tucatinib, Trastuzumab, and Capecitabine
NCT04582968	Pyrotinib Combined with Brain Radiotherapy in BC Patients With BM	Pyrotinib Plus Capecitabine combined with brain radiotherapy
NCT03417544	Atezolizumab + Pertuzumab + Trastuzumab in CNS Mets In BC	Atezolizumab + Pertuzumab + Trastuzuma
NCT04760431 HER2BRAI	TKIs vs. Pertuzumab in HER2 + BC Patients with Active BM (HER2BRAIN)	Anti-HER2 TKI versus Pertuzumab in Combination with Dose-dense Trastuzumab and Taxane
NCT05042791	A Study of Pyrotinib Plus Capecitabine Combined with SRT in HER2 + MBC With BM	Pyrotinib Plus Capecitabine Combined With SRT
NCT05018702	ARX788 in HER2-positive BC Patients With BM	ARX788 ((HER2-targeting ADC)
NCT06361979	SHR-A1811 Combined with Bevacizumab in HER2-positive BC With BM	SHR-A1811 (HER2-targeting ADC) Combined with Bevacizumab
NCT05769010	Study of SHR-A1811 in HER2-expression MBC er with BM	SHR-A1811 (HER2-targeting ADC) plus Pyrotinib and Bevacizumab
NCT05323955 BRIDGET	Secondary BM Prevention After Isolated Intracranial Progression on Trastuzumab/Pertuzumab or T-DM1 in Patients With aDvanced Human Epidermal Growth Factor Receptor 2 + BC With the Addition of Tucatinib	Tucatinib plus Trastuzumab/Pertuzumab or T-DM1
NCT06015113	Efficacy and Safety of Disitamab Vedotin Plus Pyrotinib or Naratinib in HER2-positive BC Patients With BM	Disitamab Vedotin Plus Pyrotinib or Naratinib
NCT05041842 InTTercePT	Treatment With Tucatinib in Patients with an Isolated Brain Progression of a MBC	Tucatinib with Pertuzumab/Trastuzumab (and endocrine therpy)
NCT03765983	GDC-0084 in Combination with Trastuzumab for Patients with HER2-Positive BC BM	GDC-0084 (inhibitor of PI3K and mTOR) in Combination with Trastuzumab
NCT06088056	A Phase II Study of T-DXd Plus SRT in HER2-positive BC BM	T-DXd Plus stereotactic radiotherapy

CNS metastases are an unmet need associated with poor prognosis. Outcomes have improved with advances in treatments but more work is needed.

Just some of the ongoing trials in brain metastasis!

Many are focused on novel ADCs, CAR-T therapy, genomic guided treatment choices and novel drug combinations

Grinda T et al. Curr Treat Options in Oncol 2025. 26:14-35.

Conclusion

- Metastatic breast cancer treatment continues to evolve with innovative therapies that are improving patient outcomes
- New drug approvals and emerging research are shaping the future of MBC treatment and management
- Balancing efficacy with tolerability and quality of life remains the key to optimizing treatment strategies
- Ongoing clinical trials will further expand treatment options and refine personalized approaches for people living with MBC
- Efforts to improve accrual and diversify clinical trials are critical