What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH

Harold J Burstein, MD, PhD

Professor Giuseppe Curigliano, MD, PhD

Sara A Hurvitz, MD, FACP

Joyce O'Shaughnessy, MD

Moderator

Hope S Rugo, MD

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Dr Bardia — Disclosures
Faculty

Consulting Agreements and Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Merck, Novartis, Pfizer Inc, Radius Health Inc, Sanofi

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Dr Burstein — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Prof Curigliano — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo Inc, Lilly, Menarini Group, Merck, Novartis, Seagen Inc
Contracted Research	Merck
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Dr Hurvitz — Disclosures
Faculty

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Dr O'Shaughnessy — Disclosures
Faculty

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Dr Rugo — Disclosures
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Dr Love — Disclosures

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

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Joyce O'Shaughnessy, MD
Hope S Rugo, MD

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LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

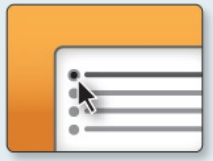
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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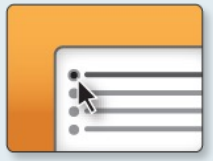
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Moderator

Hope S Rugo, MD

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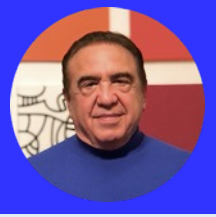
Consulting Oncologists



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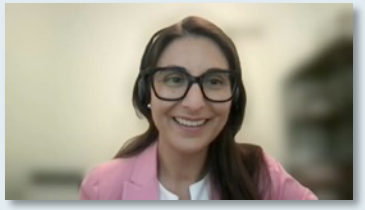

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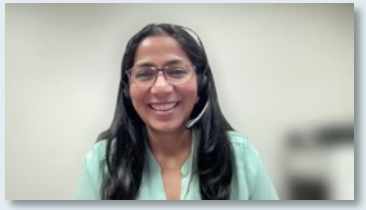

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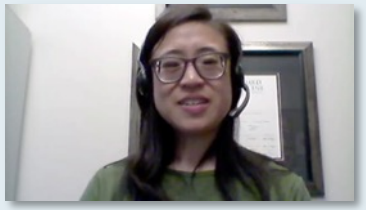

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Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

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Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

Consulting Faculty Comments

Management of brain metastases in HER2-positive breast cancer

Dr Gigi Chen (Pleasant Hill, California)

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QUESTIONS FOR THE FACULTY

For a patient whose disease is controlled systemically on trastuzumab/pertuzumab maintenance who develops an insolated brain metastasis and undergoes resection and stereotactic radiosurgery, how would you approach further systemic therapy?

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QUESTIONS FOR THE FACULTY

In general, what is your preferred second-line therapy for a patient with HER2-positive metastatic breast cancer who receives first-line THP and progresses with multiple systemic and brain metastases after 1 year?

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Consulting Faculty Comments

Strategies to maintain quality of life for patients receiving trastuzumab deruxtecan; identification and management of low-grade interstitial lung disease

Dr Laila Agrawal (Louisville, Kentucky)

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QUESTIONS FOR THE FACULTY

What diagnostic tools do you employ or protocols do you follow to monitor for and detect ILD in patients receiving T-DXd?

How do you approach the management of ILD, particularly when it is Grade 1?

QUESTIONS FOR THE FACULTY

How do you approach the prevention and management of acute “chemotherapy-like” side effects (eg, cytopenias, gastrointestinal toxicity, alopecia) with T-DXd?

Consulting Faculty Comments

Combination therapy with CDK4/6 inhibitors and HER2-targeted therapy for hormone receptor-positive, HER2-positive mBC

Dr Shaachi Gupta (Lake Worth, Florida)

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QUESTIONS FOR THE FACULTY

How do you approach the use of endocrine therapy for patients with HR-positive, HER2-positive mBC?

In what situations, if any, do you use a CDK4/6 inhibitor in combination with HER2-directed therapy for a patient with HR-positive, HER2-positive metastatic disease?

Optimizing the Management of HER2-Positive Metastatic Breast Cancer

Sara A. Hurvitz, MD, FACP

Professor of Medicine
Head, Division of Hematology/Oncology,
University of Washington School of Medicine
Senior Vice President, Clinical Research Division,
Fred Hutchinson Cancer Center

Fred Hutch Cancer Center

UNIVERSITY of WASHINGTON

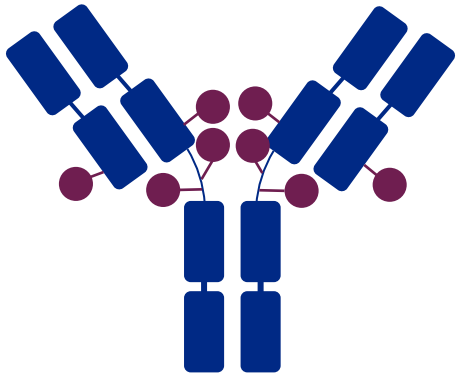
Second Line Therapy
(after trastuzumab/taxane)

Trastuzumab Deruxtecan (T-DXd): a Novel HER2 ADC

Characteristic Differences Between T-DXd and T-DM1

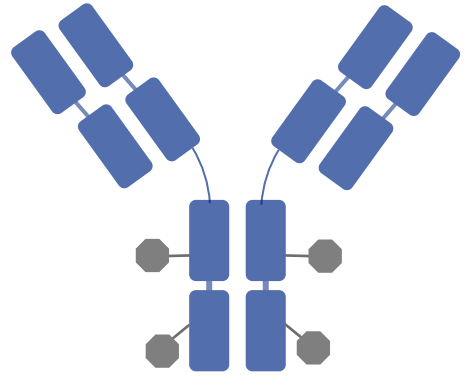
HER2 Targeting ADCs with similar mAb Backbone

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4]	ADC Attributes	T-DM1[4-6]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[1]



Cortés J et al. ESMO 2021;Abstract LBA1.

Abbreviations: ADC, antibody-drug conjugate; MoA, mechanism of action.

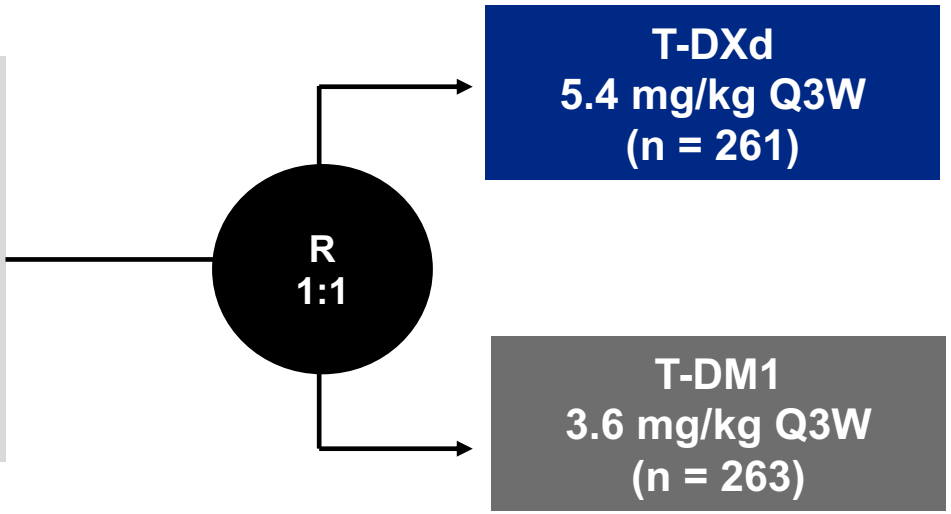
1. Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021. 2. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 3. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 4. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 5. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 6. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

Updated OS Analysis of DESTINY-Breast03

Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

Stratification factors

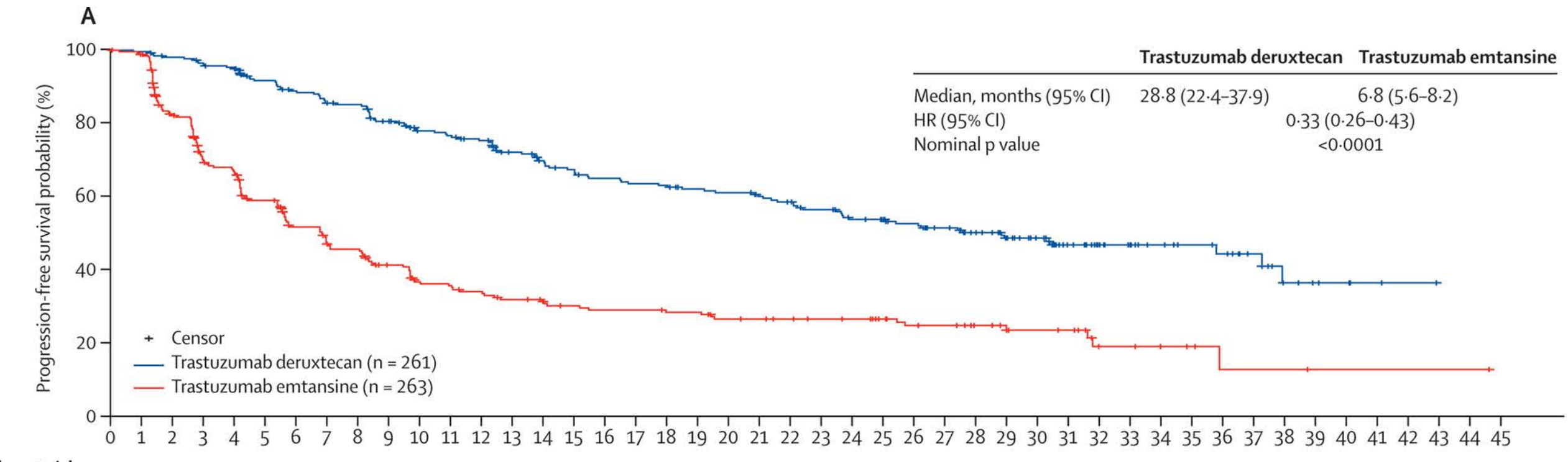
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

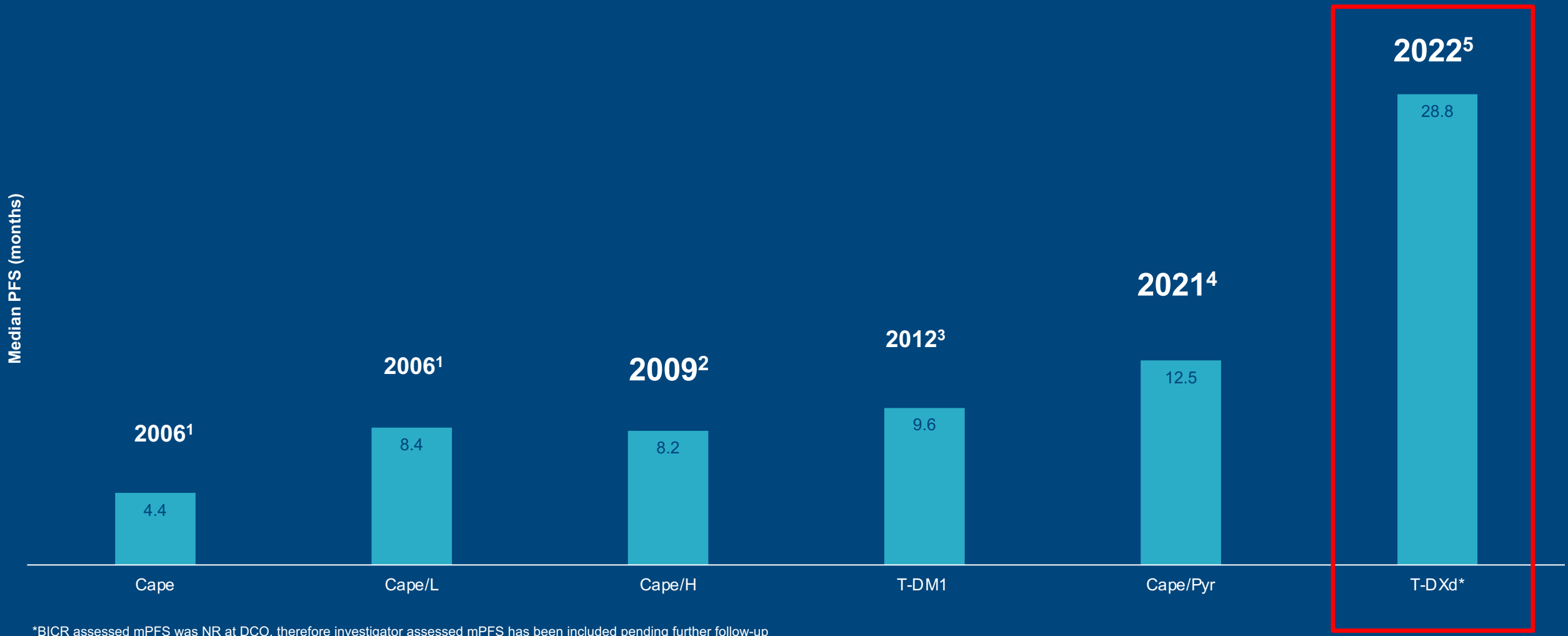
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

Hamilton EP et al. ASCO 2024;Abstract 1025.



Hurvitz SA et al. *Lancet* 2023;401(10371):105-117.

Evolution of PFS After Trastuzumab/Taxane

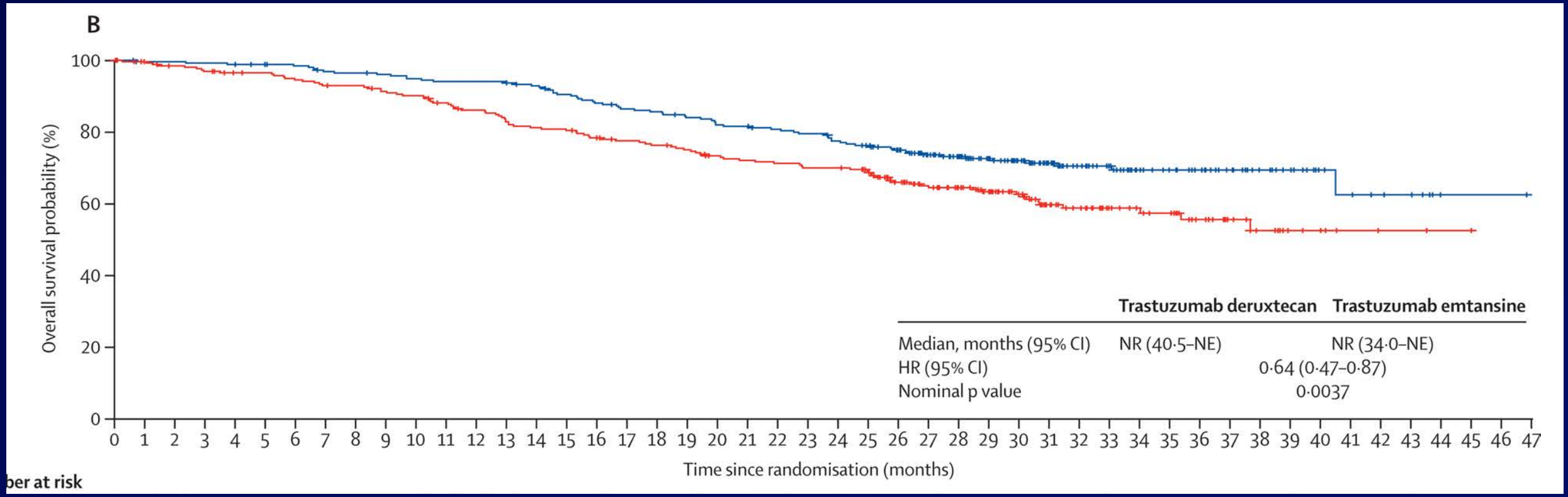


*BICR assessed mPFS was NR at DCO, therefore investigator assessed mPFS has been included pending further follow-up

Cape=capecitabine; DCO=data cut-off; H=trastuzumab; L=lapatinib; (m)PFS=(median) progression-free survival; Pyr=pyrotinib; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

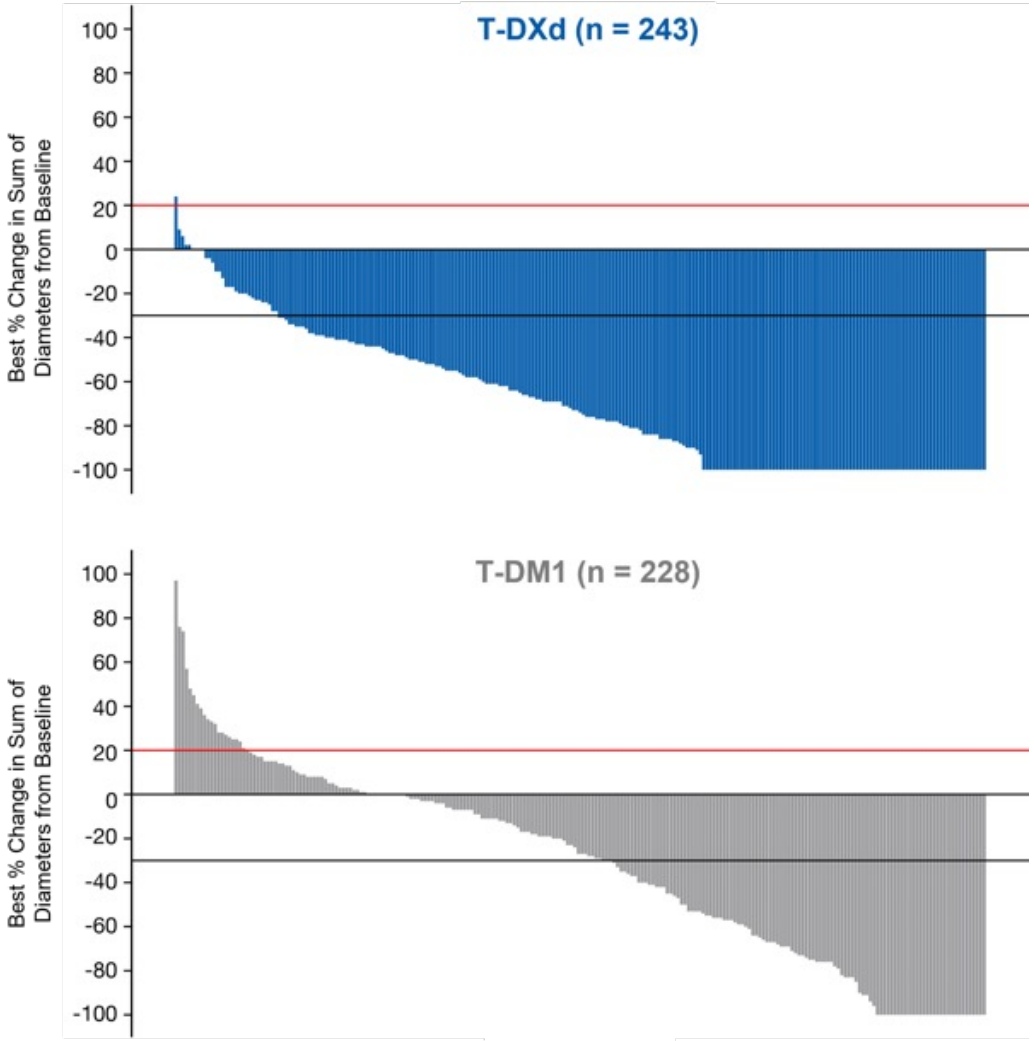
1. Geyer C, et al. *N Engl J Med*. 2006;355:2733-2743. 2. Von Minckwitz G, et al. *J Clin Oncol*. 2009;27:1999-2006. 3. Verma S, et al. *N Engl J Med*. 2012;367:1783-1791. 4. Xu B, et al. *Lancet Oncol*. 2021;22:351-360.
5. Hurvitz S et al. The Lancet 2022

DESTINY-Breast03: Overall Survival



Hurvitz SA et al. Lancet 2023;401(10371):105-117.

Confirmed ORR and Other Efficacy Endpoints



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

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

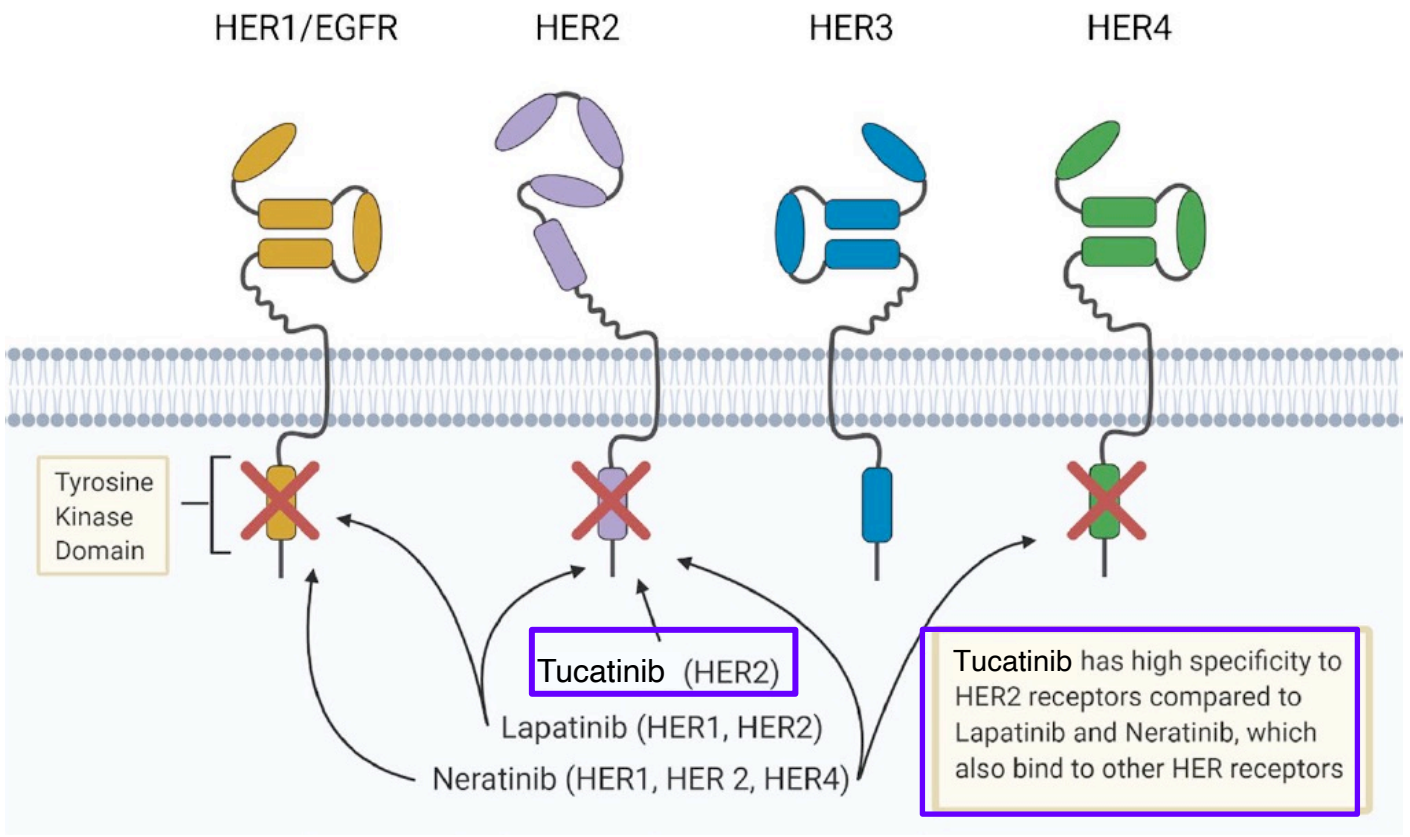
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.

[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

Hurvitz S, et al SABCS 2022

Tucatinib Is a HER2-Selective TKI

Mechanism of Action of Tucatinib[1]



1. Dent SF, et al. Curr Oncol Rep. 2021;23:128. 2. Murthy R, et al. Lancet Oncol. 2018;19:880-888.

HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy were allowed on study

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

T-DM1 + Tucatinib

T-DM1 3.6 mg/kg IV and Tucatinib 300 mg PO BID

T-DM1 + Placebo

T-DM1 3.6 mg/kg IV and Placebo PO BID

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

-44% of patients had CNS metastases (~half were active)

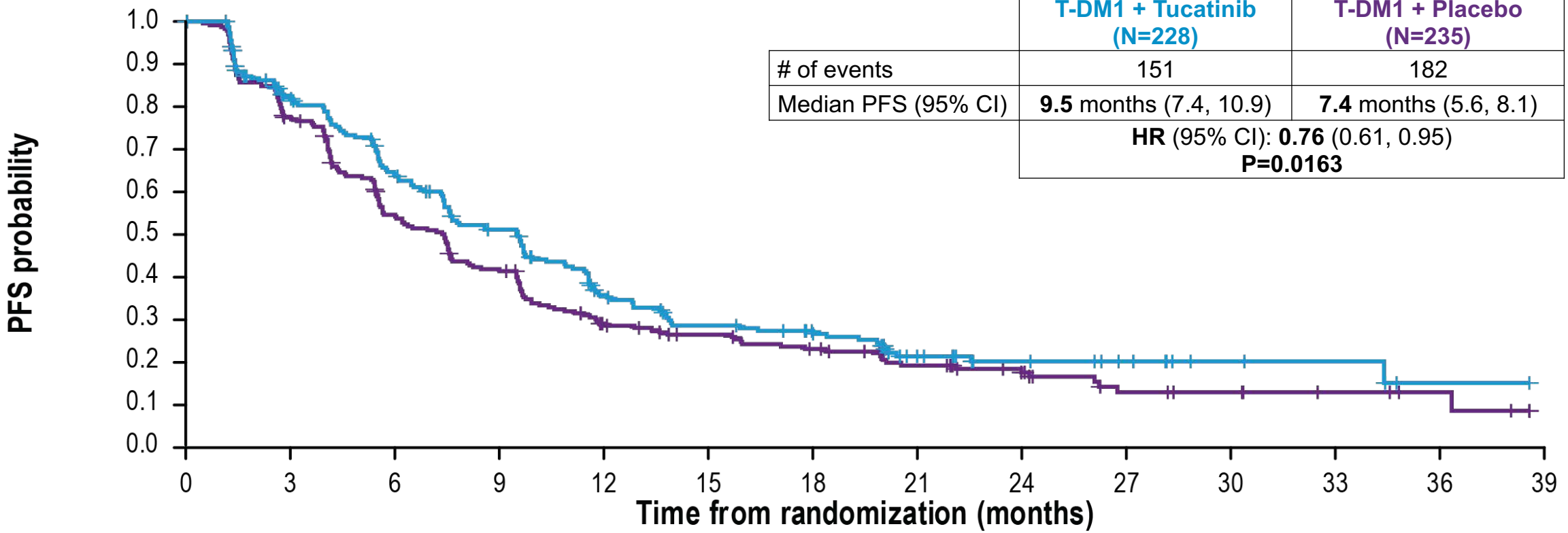
~90% had previously received pertuzumab

Median 1 prior line of therapy in metastatic setting (range 0-8)

No prior T-DXd or tucatinib

Progression-Free Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	



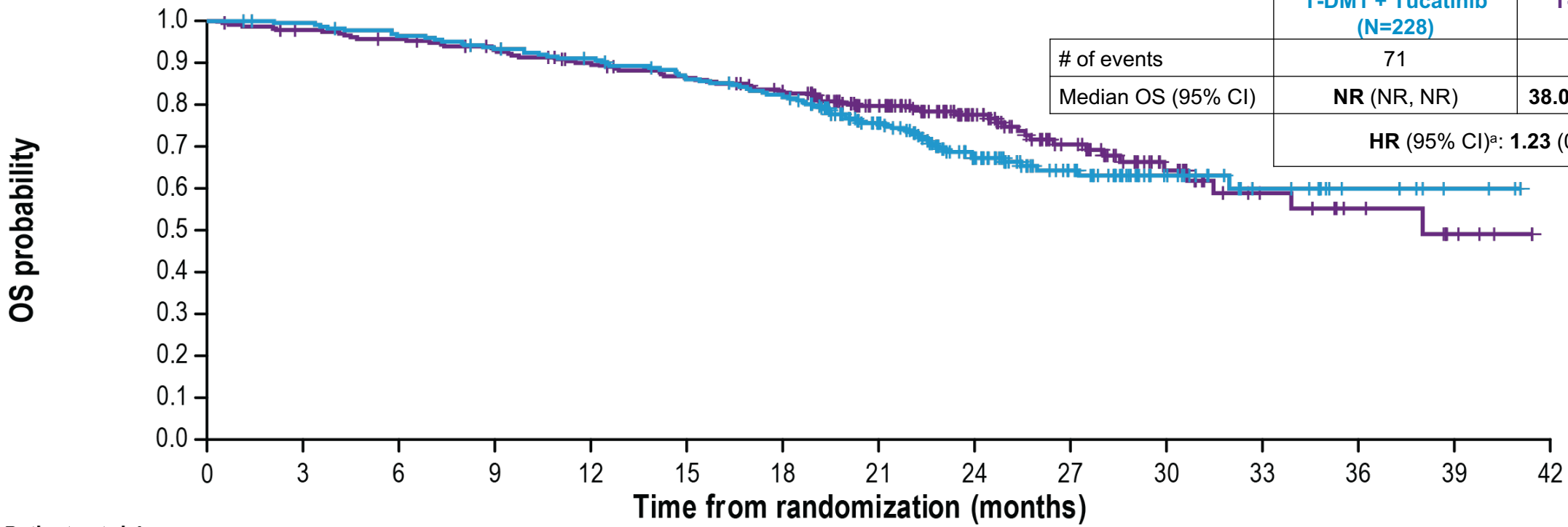
Patients at risk

T-DM1 + Tucatinib	228	165	126	96	62	47	40	22	14	10	5	4	1	0
T-DM1 + Placebo	235	177	120	91	58	48	40	29	19	10	8	5	3	0

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Overall Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
HR (95% CI)[a]: **1.23** (0.87, 1.74)		



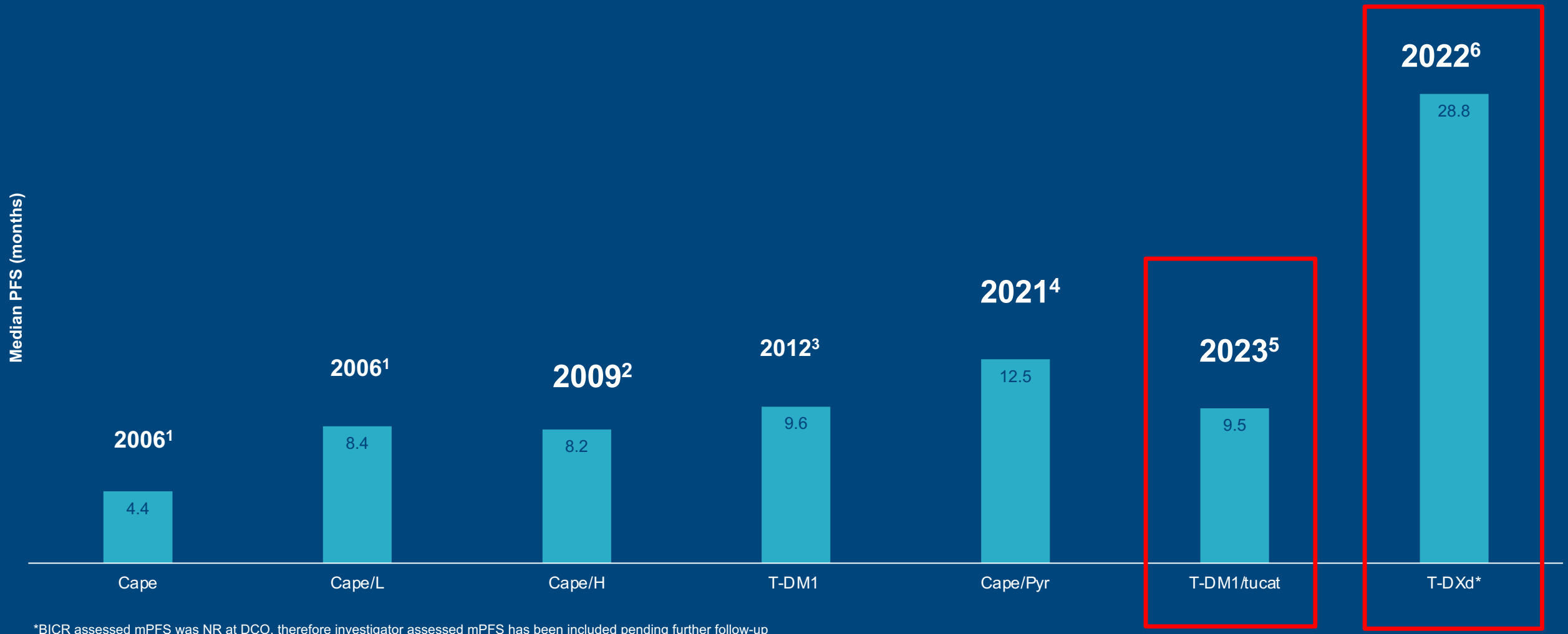
Patients at risk

T-DM1 + Tucatinib	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
T-DM1 + Placebo	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of P≤0.0041.

a The proportional hazard assumption was not maintained post-18 months, with extensive censoring on both arms.
HR, hazard ratio; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Evolution of PFS After Trastuzumab/Taxane



*BICR assessed mPFS was NR at DCO, therefore investigator assessed mPFS has been included pending further follow-up

Cape=capecitabine; DCO=data cut-off; H=trastuzumab; L=lapatinib; (m)PFS=(median) progression-free survival; Pyr=pyrotinib; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

1. Geyer C, et al. *N Engl J Med*. 2006;355:2733-2743. 2. Von Minckwitz G, et al. *J Clin Oncol*. 2009;27:1999-2006. 3. Verma S, et al. *N Engl J Med*. 2012;367:1783-1791. 4. Xu B, et al. *Lancet Oncol*. 2021;22:351-360.
5. Hurvitz S et al. SABCS 2023; 6. Hurvitz S et al. The Lancet 2022

Third Line Therapy
(after T-DM1)

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

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

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

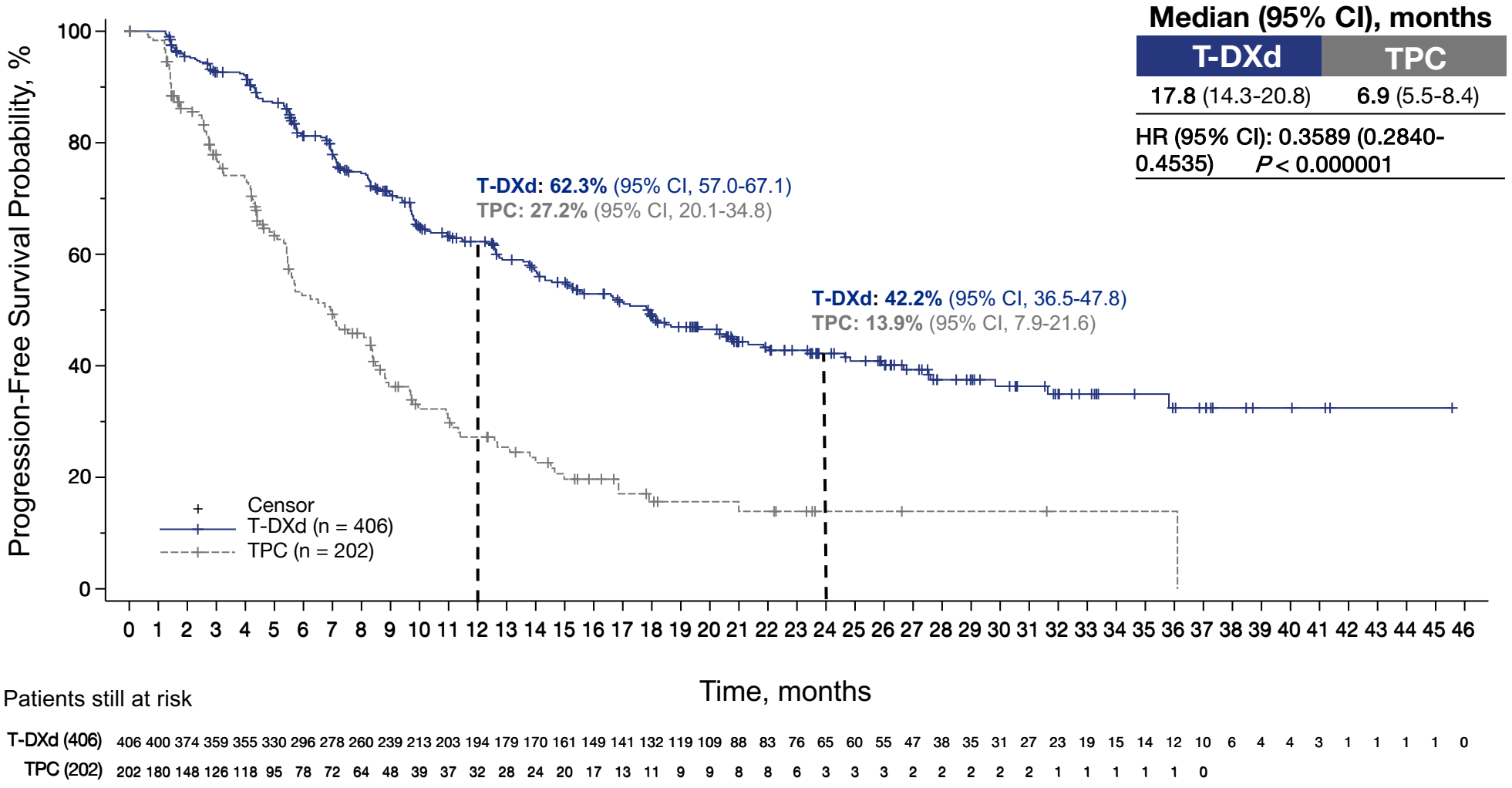
Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Krop I et al. SABCS 2022;Abstract GS2-01.

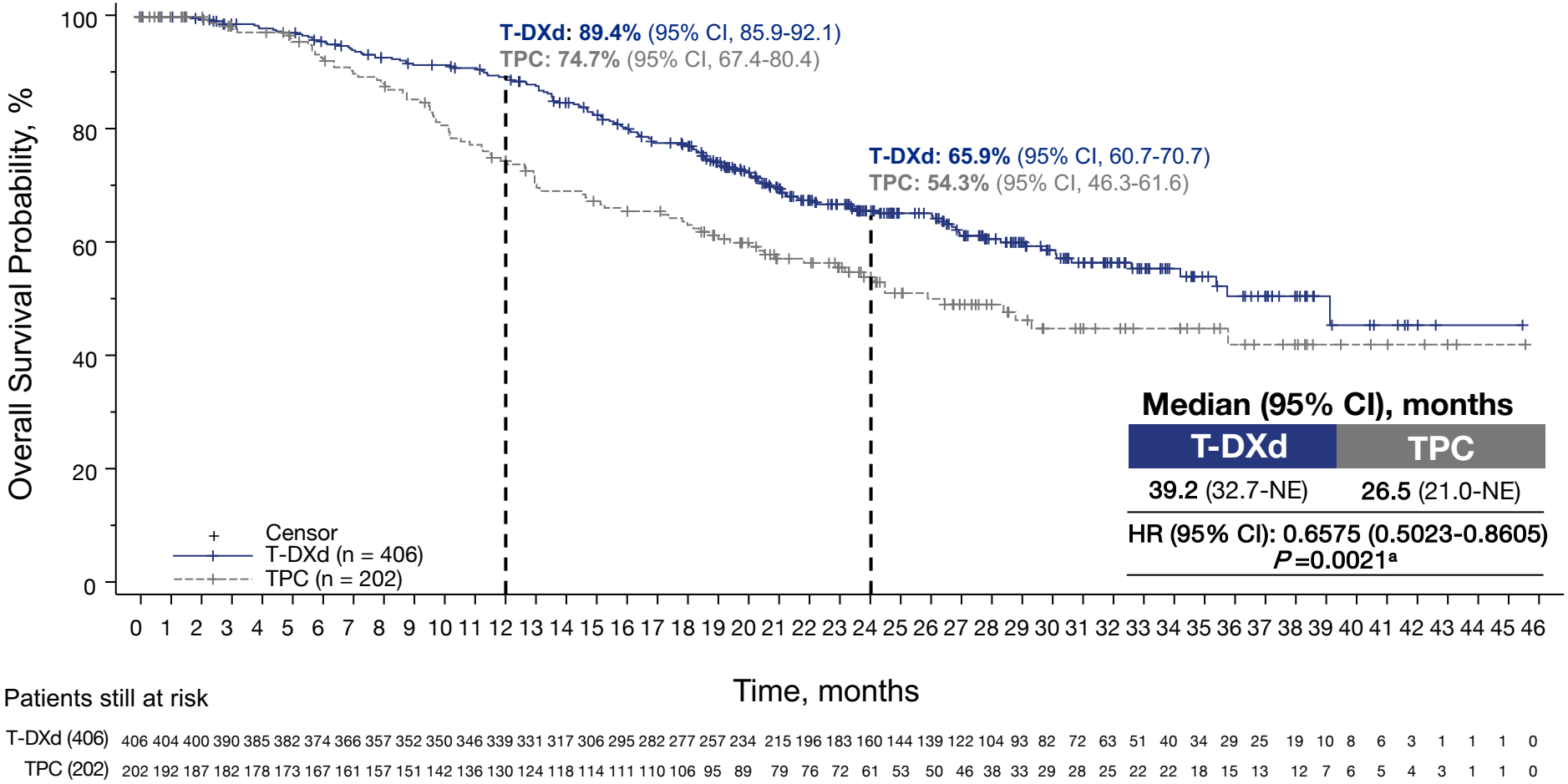
Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Krop I et al. SABCS 2022;Abstract GS2-01. André F et al. *Lancet* 2023;401(10390):1773-1785.

Key Secondary Endpoint: OS



In the TPC arm

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

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

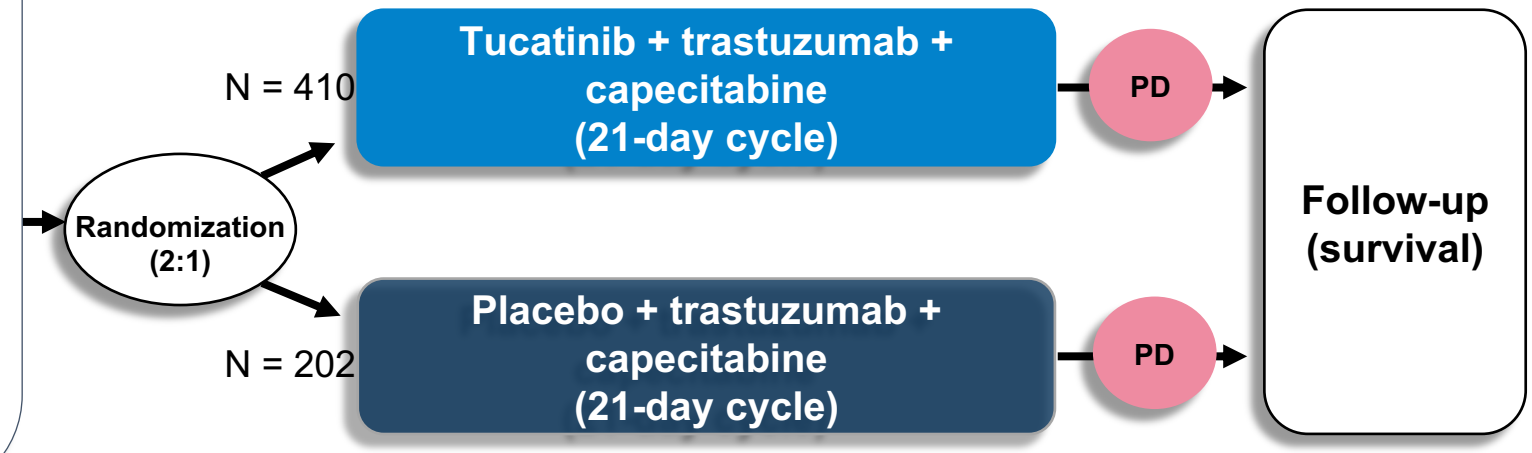
Krop I et al. SABCS 2022;Abstract GS2-01. André F et al. *Lancet* 2023;401(10390):1773-1785.

HER2CLIMB

Tucatinib + Trastuzumab + Capecitabine vs Placebo + Trastuzumab + Capecitabine

Inclusion criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- *Brain MRI at baseline*
  - *No evidence of brain metastases, or*
  - *Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy*



Stratification variables

- Presence of brain metastases (yes/no)
- ECOG status (0 or 1)
- Region of the world (US or Canada or rest of world)

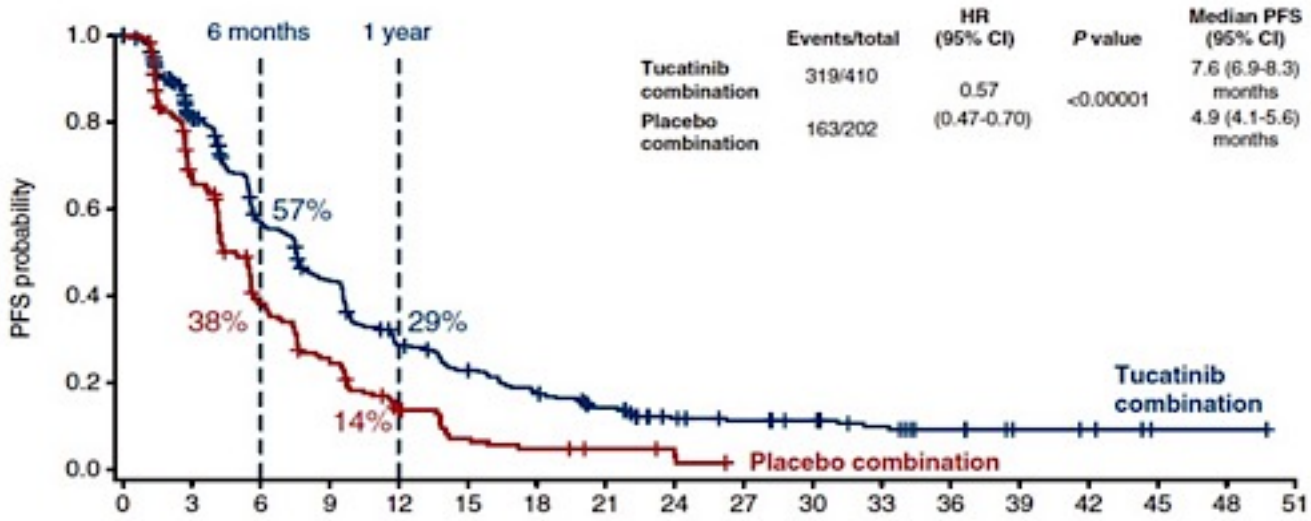
Endpoints

- Primary: PFS (first 480 patients randomized)
- Secondary: OS (total population), PFS among patients with brain metastases, ORR

Notable baseline characteristic: *48% of patients had CNS metastases*

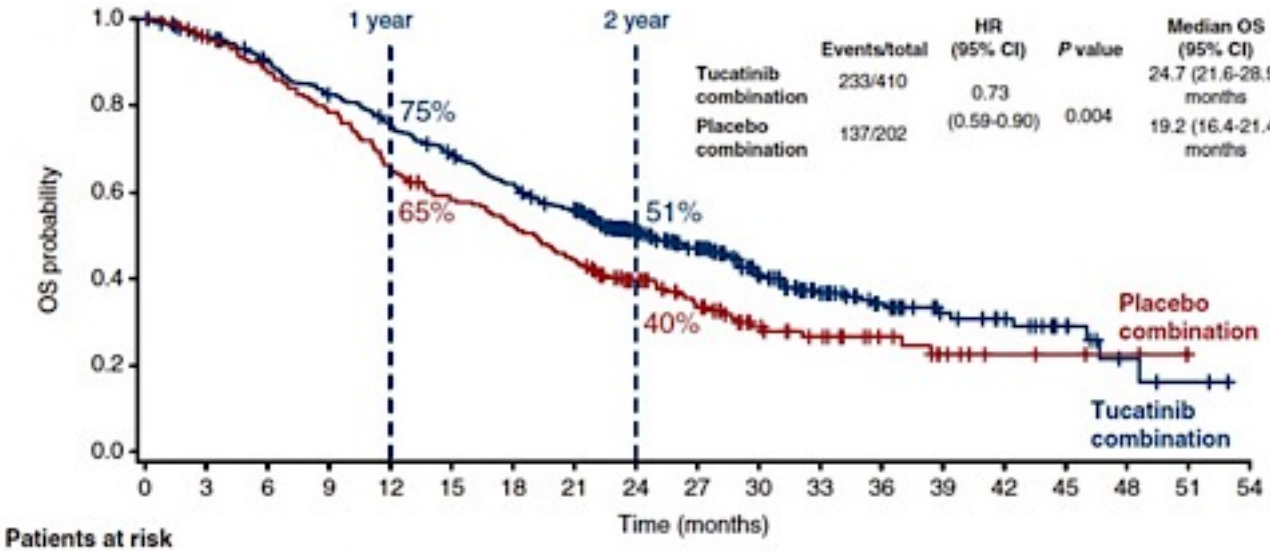
Murthy R, et al. *N Engl J Med.* 2020;382:597-609.

HER2CLIMB: Progression-Free Survival (PFS)



	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

Final Overall Survival Analysis



	Events/total	HR (95% CI)	*P* value	Median OS (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	0.004	24.7 (21.6-28.9) months
Placebo combination	137/202			19.2 (16.4-21.4) months

Patients at risk

Tucatinib combination	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo combination	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

Considerations for patients with CNS metastases

HER2+ brain metastases increase by line of therapy

Using longitudinal US Flatiron Health de-identified database, EMR >2.6 million pts with cancer in ~800 unique sites of care.

A cumulative incidence function was used to estimate the risk of BM in this pt cohort.

Index date: date of first antineoplastic therapy in the metastatic setting

Prevalence of BM per line of therapy,%	HR+, HER2+ (1L N=3062)	HR-, HER2+ (1L N=902)
1	6.3	11.2
2	17.6	31.2
3	21.5	36.3
4	26.1	37.1
5+	26.5	36.9

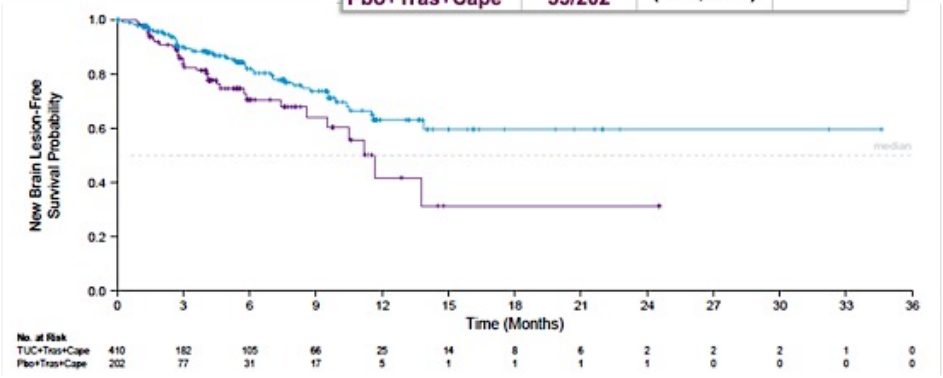
N=16063 included pts, 1955 patients with incident BM were recorded during the follow-up

Excluding patients with brain metastases at diagnosis (6.1%), cumulative incidence of BM at 60 months was

- 23% in HR+/HER2+
- 34% in HR-/HER2+: Early Event

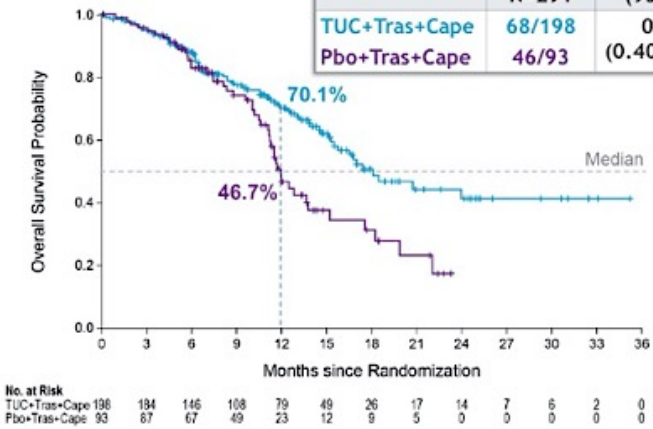
HER2CLIMB: New Brain Lesion-Free Survival

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005
Pbo+Tras+Cape	33/202		



OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



Risk of death was reduced by 42% in patients with brain metastases

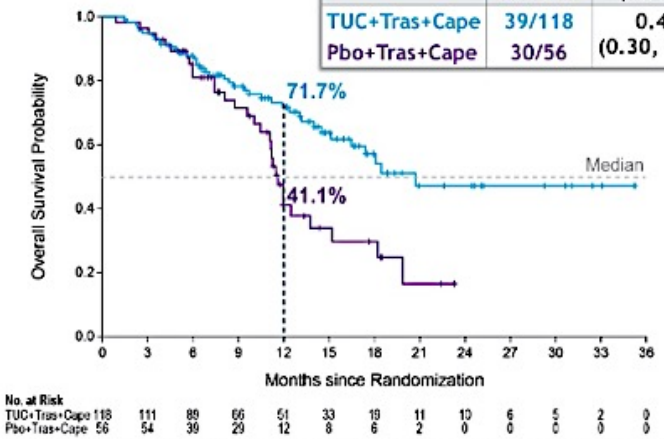
One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 71.7% (61.4, 79.7)	Pbo+Tras+Cape 41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

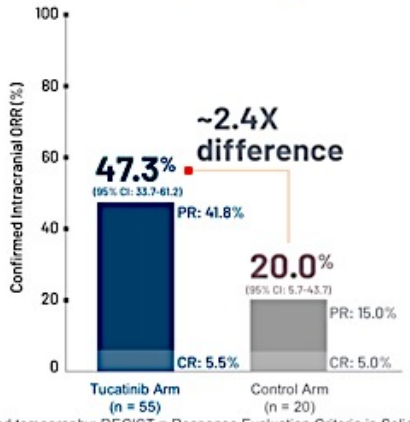
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

CNS SUBGROUP ANALYSIS

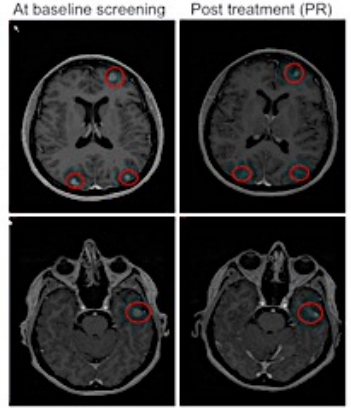
ASCO 2020 UPDATE: POST HOC EXPLORATORY ANALYSES

CONFIRMED INTRACRANIAL OBJECTIVE RESPONSE RATE[1*]

Confirmed intracranial ORR by RECIST 1.1 (n = 75) in patients with active brain metastases and measurable intracranial lesions at baseline per investigator assessment[1]



Brain CT scans of a patient in the tucatinib arm[†]



CT = computed tomography; RECIST = Response Evaluation Criteria in Solid Tumors.

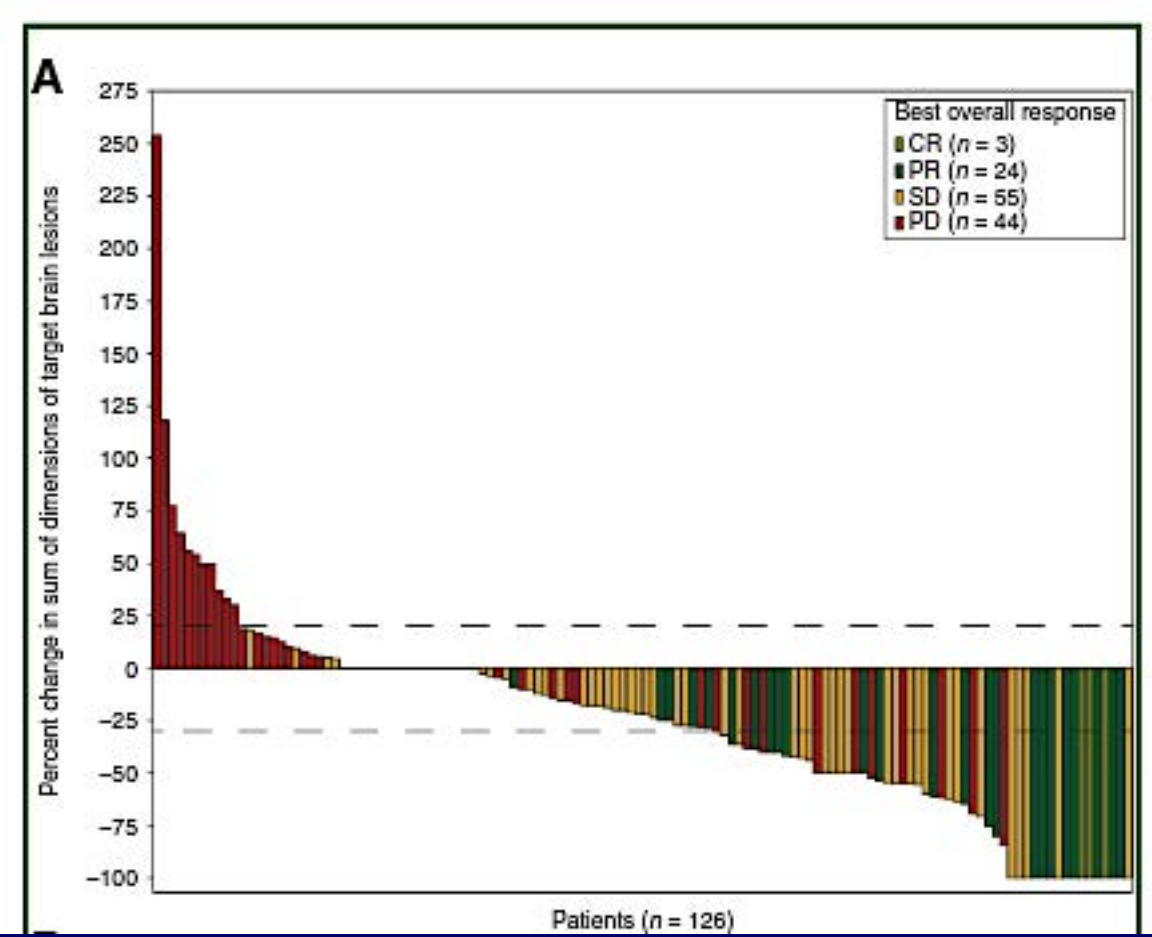
* Results of this exploratory analysis are descriptive, not in the approved labeling, and not controlled for type 1 error, as HER2CLIMB was not powered to test this analysis. results are estimates (not exact numbers). Due to a high rate of censoring of patients owing to extra-CNS progression (new or enlarging extracranial lesions) or death, resu should be interpreted with caution. †Individual results may vary.

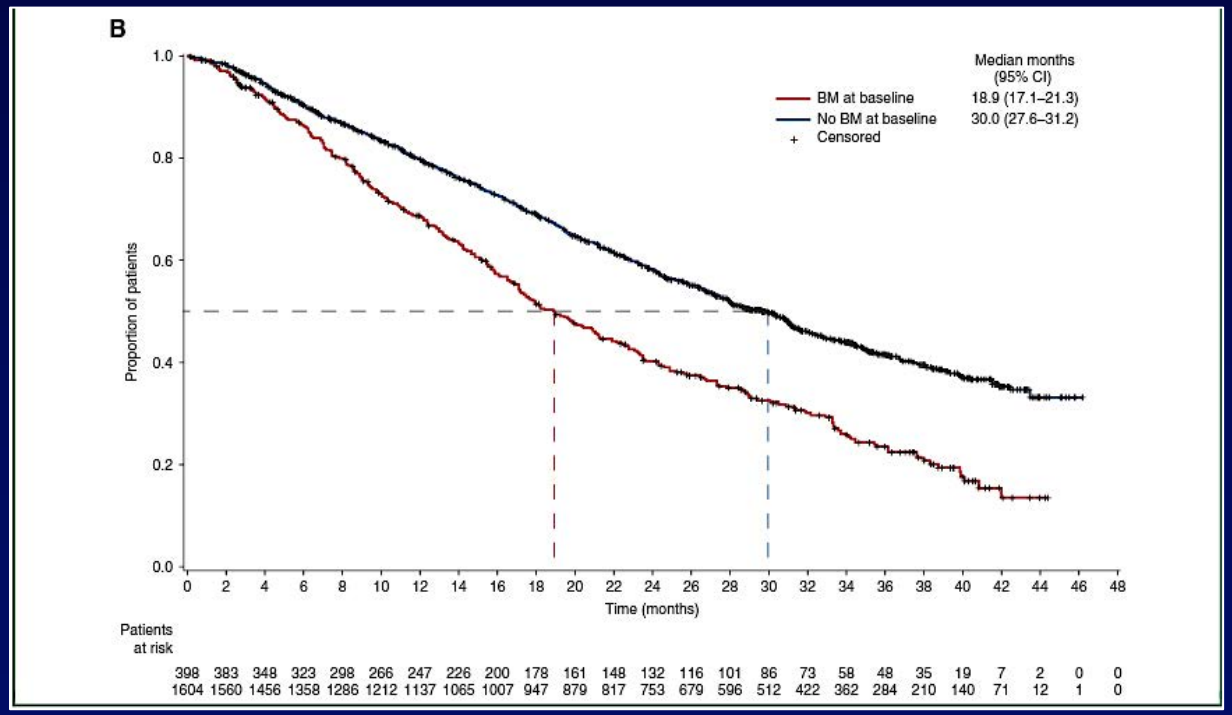
1. Lin NU et al. *J Clin Oncol*. 2020;38:2610-2619.

Please see Important Safety Information on slides 32-35 and refer to the full Prescribing Information available at this event.

T-DM1 Clinical Activity in CNS Mets

KAMILLA, Phase IIIB, 2002 pts treated T-DM1, 398 had baseline BM. 126 patients with measurable BM.



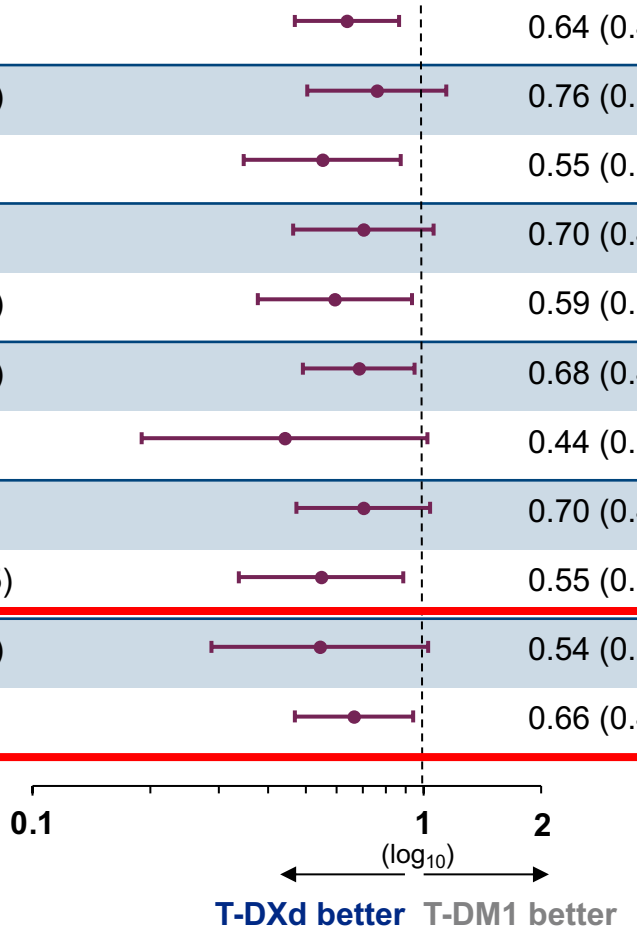


Intracranial ORR: 21%, CBR 43%
mPFS 5.5m
mOS 19m

Montemurro F et al. *Ann Oncol* 2020;31(10):1350-1358.

T-DXd DESTINY-Breast03: Overall Survival by Subgroups

		Number of Events		Median OS time (months, 95% CI)		Hazard Ratio for Death (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		72/261	97/263	NR (40.5-NE)	NR (34.0-NE)	0.64 (0.47-0.87)
Hormone receptor status	Positive (n = 272)	42/133	51/139	NR (40.5-NE)	37.7 (34.0-NE)	0.76 (0.50-1.14)
	Negative (n = 248)	30/126	45/122	NR (NE-NE)	NR (28.5-NE)	0.55 (0.35-0.87)
Prior pertuzumab	Yes (n = 320)	41/162	50/158	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.46-1.06)
	No (n = 204)	31/99	47/105	NR (NE-NE)	31.5 (22.7-NE)	0.59 (0.38-0.93)
Baseline visceral disease	Yes (n = 384)	64/195	80/189	NR (40.5-NE)	35.4 (29.9-NE)	0.68 (0.49-0.95)
	No (n = 140)	8/66	17/74	NR (NE-NE)	NR (NE-NE)	0.44 (0.19-1.02)
Prior lines of systemic therapy[a]	<3 (n = 379)	44/188	57/191	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.47-1.04)
	≥3 (n = 145)	28/73	40/72	NR (27.4-NE)	22.8 (16.1-31.5)	0.55 (0.34-0.89)
Baseline BM	Yes (n = 82)	17/43	22/39	NR (23.8-NE)	25.1 (12.6-NE)	0.54 (0.29-1.03)
	No (n = 442)	55/218	75/224	NR (40.5-NE)	NR (37.7-NE)	0.66 (0.47-0.94)

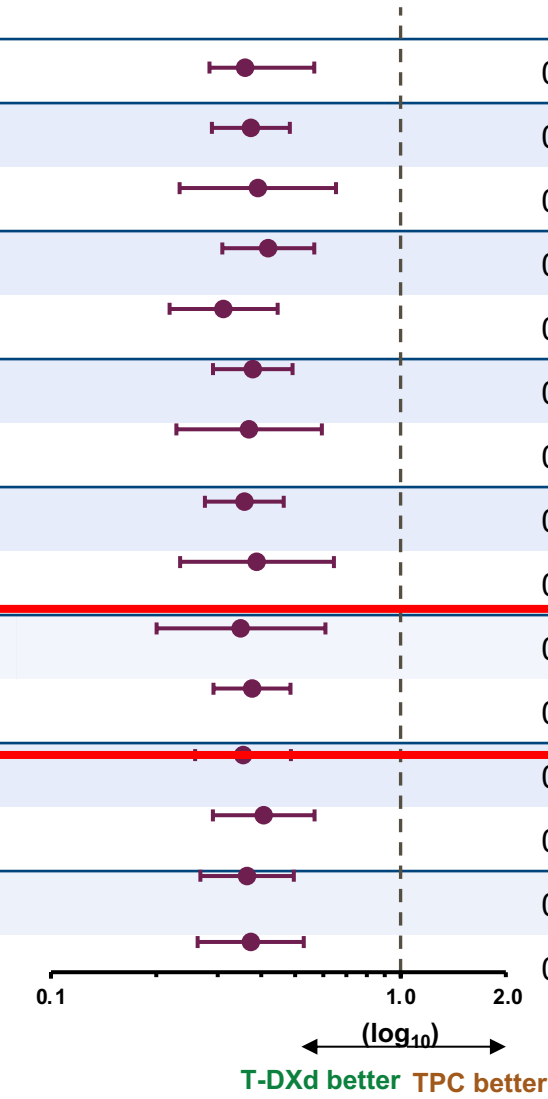


BM, brain metastases; NE, not estimable; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Prior lines of systemic therapy not including hormone therapy.

Hurvitz S, et al SABCS 2022

T-DXd DESTINY-Breast02: PFS in Key Subgroups

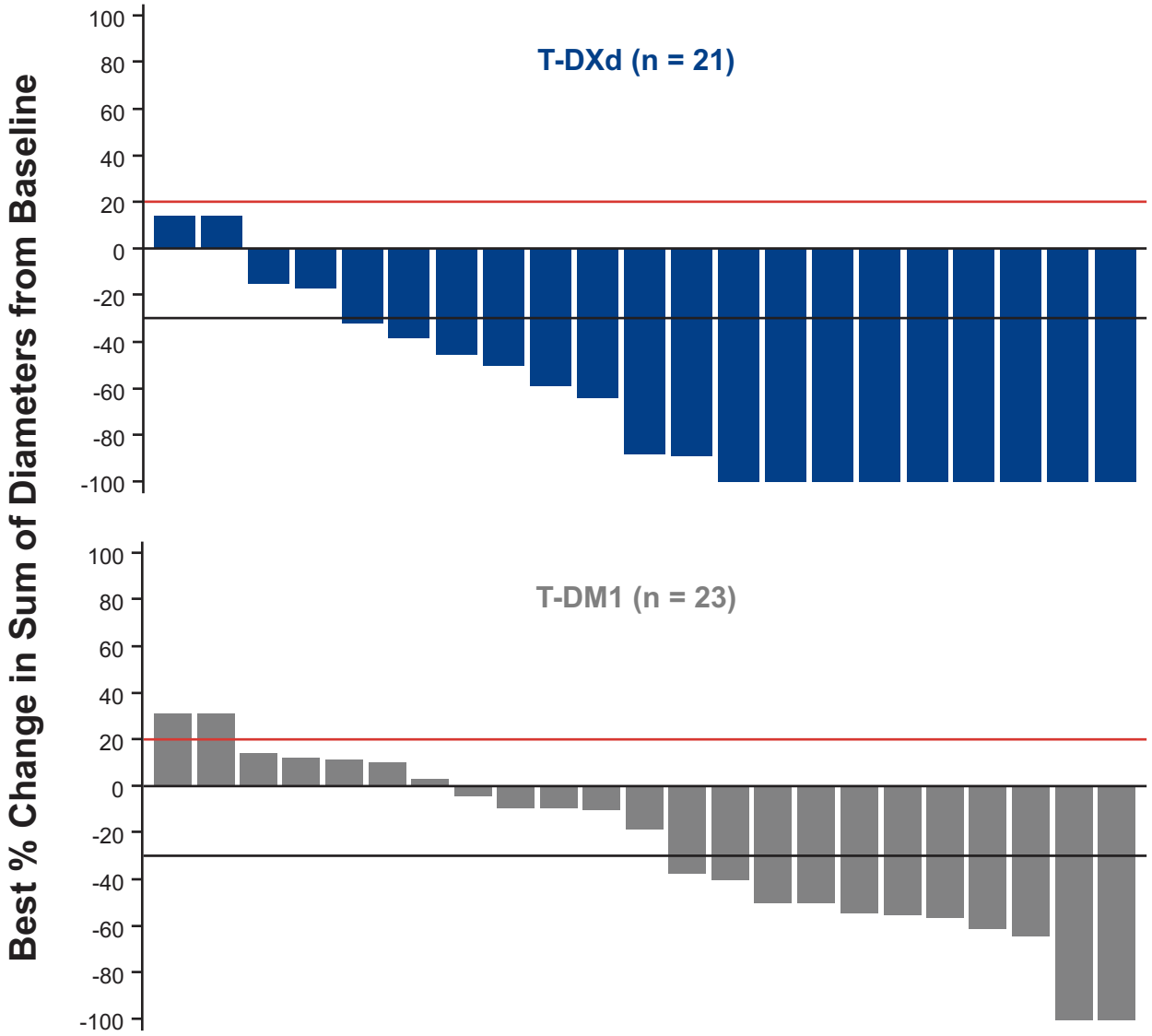
		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	TPC	T-DXd	TPC	
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45)
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor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



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Subgroup values are derived from baseline. [b]Lines of prior systemic therapy not including hormone therapy.

Krop I et al. SABCS 2022;Abstract GS2-01.

Intracranial Response per BICR using RECIST 1.1



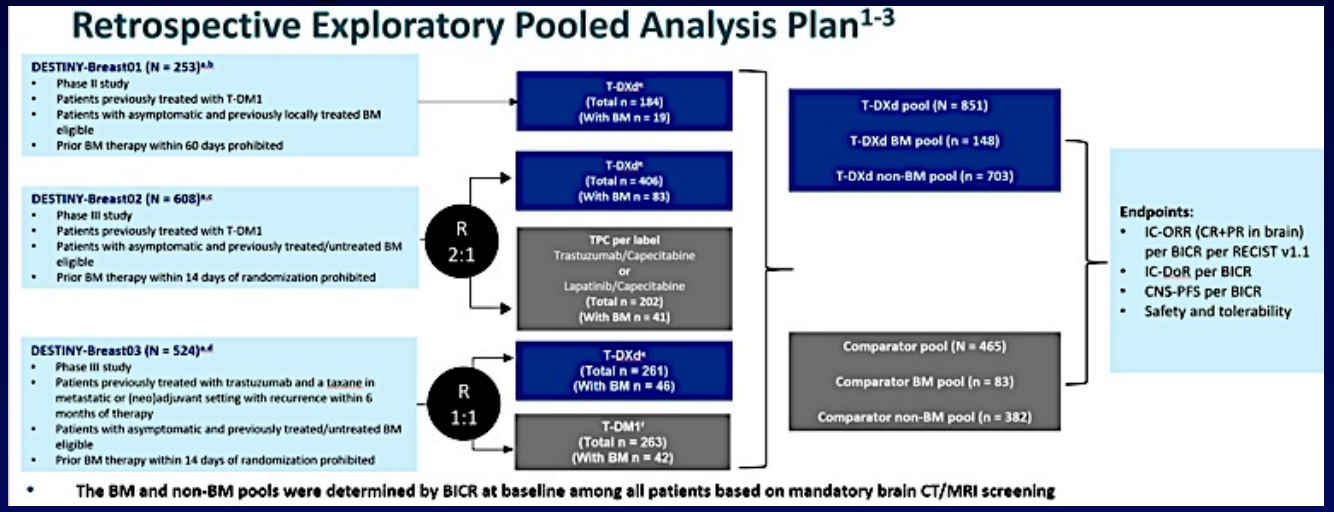
	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Hurvitz SA et al. Presented at: SABCS 2021 Annual Meeting

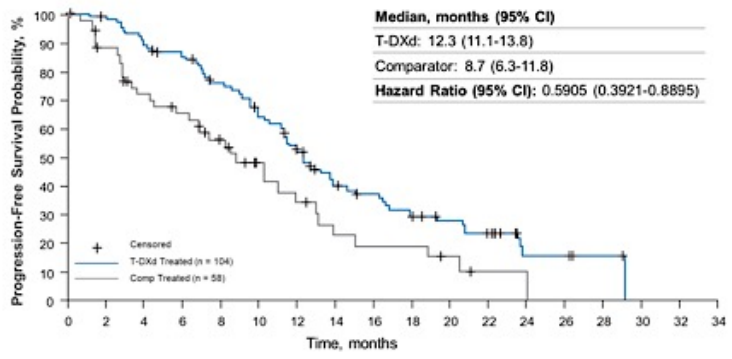
Pooled Analysis of T-DXd in CNS Mets

Retrospective Exploratory Pooled Analysis Plan[1-3]



- The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening

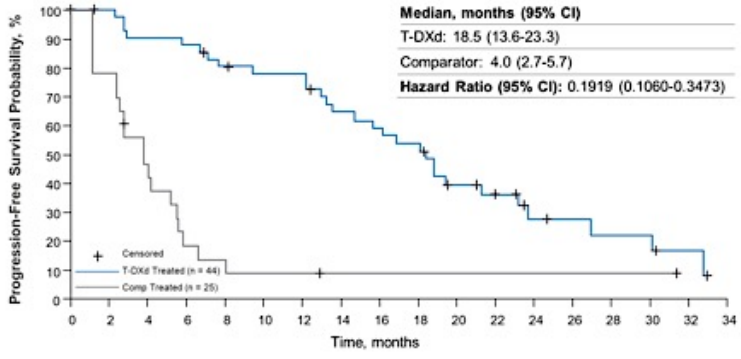
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

Untreated/Active BMs



Patients still at risk

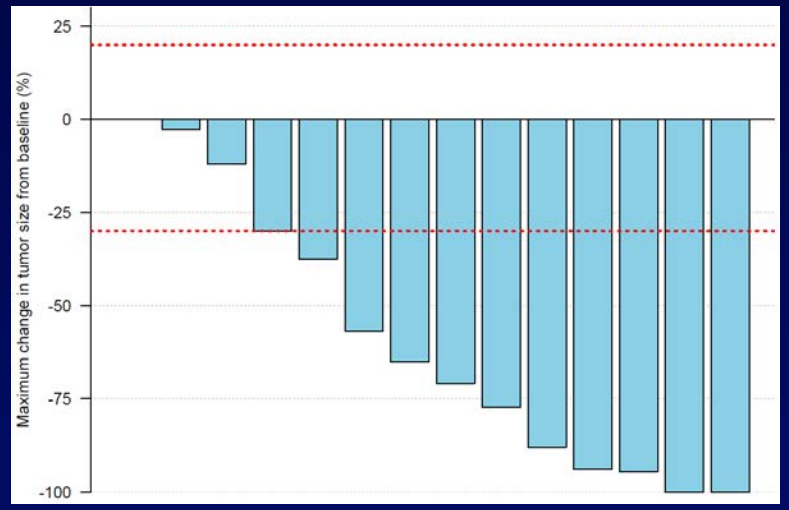
T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

- **T-DXd demonstrated a trend towards prolonged CNS-PFS over comparator, with a noticeably greater advantage for patients with untreated/active BMs**

BICR, blinded independent central review; BM, brain metastasis; CNS, central nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
CNS-PFS was defined by BICR as only radiological progression.

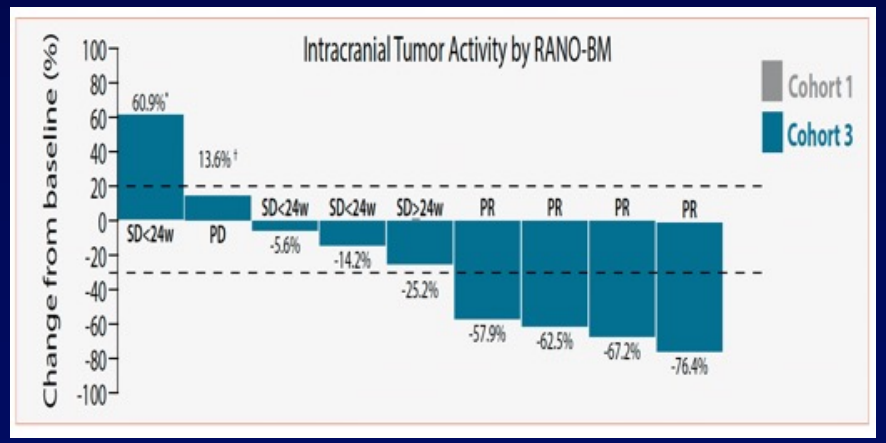
Hurvitz, ESMO 2023

Activity T-DXd in Active CNS Metastases



TUXEDO-1 trial
Bartsch et al, Nat Med 2022

ORR-IC = **73%** in pts with active BM



DEBBRAH trial
Vaz Batista et al, Neuro Oncol 2023

ORR-IC =**44%** in pts with Active BM

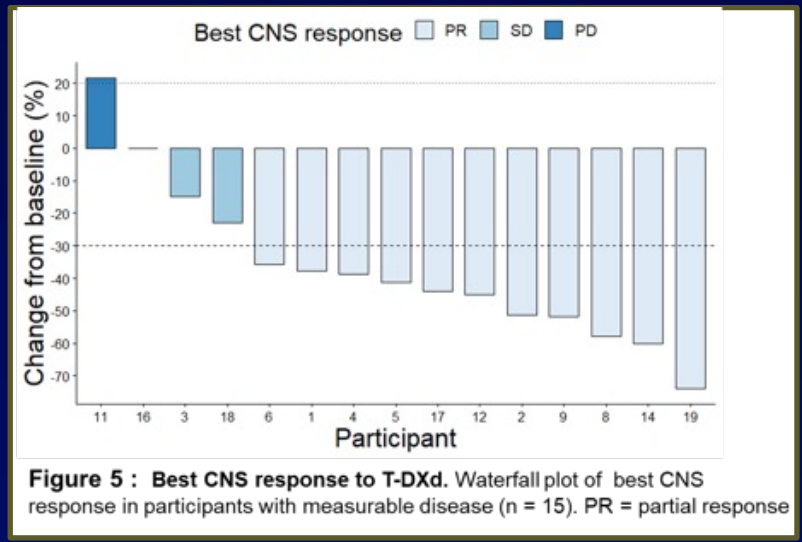


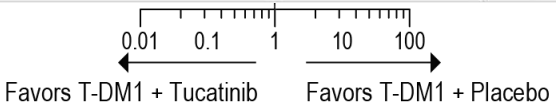
Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

DFCI/Duke/MDACCC series
Kabraji et al, Clin Ca Res 2022

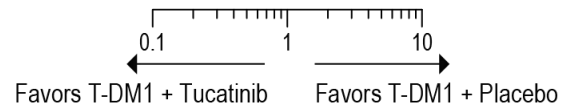
ORR-IC =**73%**
(70% in pts with active BM)

HER2CLIMB-02: Tucatinib + T-DM1 PFS in Prespecified Subgroups

	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N	Hazard Ratio with 95% CI
ITT Analysis	151/228	182/235	0.76 (0.61, 0.95)
Baseline brain metastasis			
Yes	70/99	85/105	0.64 (0.46, 0.89)
No	80/127	97/130	0.88 (0.65, 1.19)
Line of treatment for metastatic disease			
First	16/26	21/28	0.51 (0.23, 1.12)
Other	135/202	161/207	0.79 (0.63, 1.00)
ECOG performance status			
0	86/137	109/141	0.66 (0.49, 0.89)
1	65/91	73/94	0.91 (0.65, 1.28)
Hormone receptor status			
Positive	85/137	107/140	0.75 (0.56, 1.01)
Negative	66/91	75/95	0.82 (0.58, 1.15)
Region			
North America	68/105	69/93	0.88 (0.62, 1.26)
Europe/Israel	36/53	57/77	0.75 (0.46, 1.20)
Asia-Pacific	47/70	56/65	0.74 (0.49, 1.12)



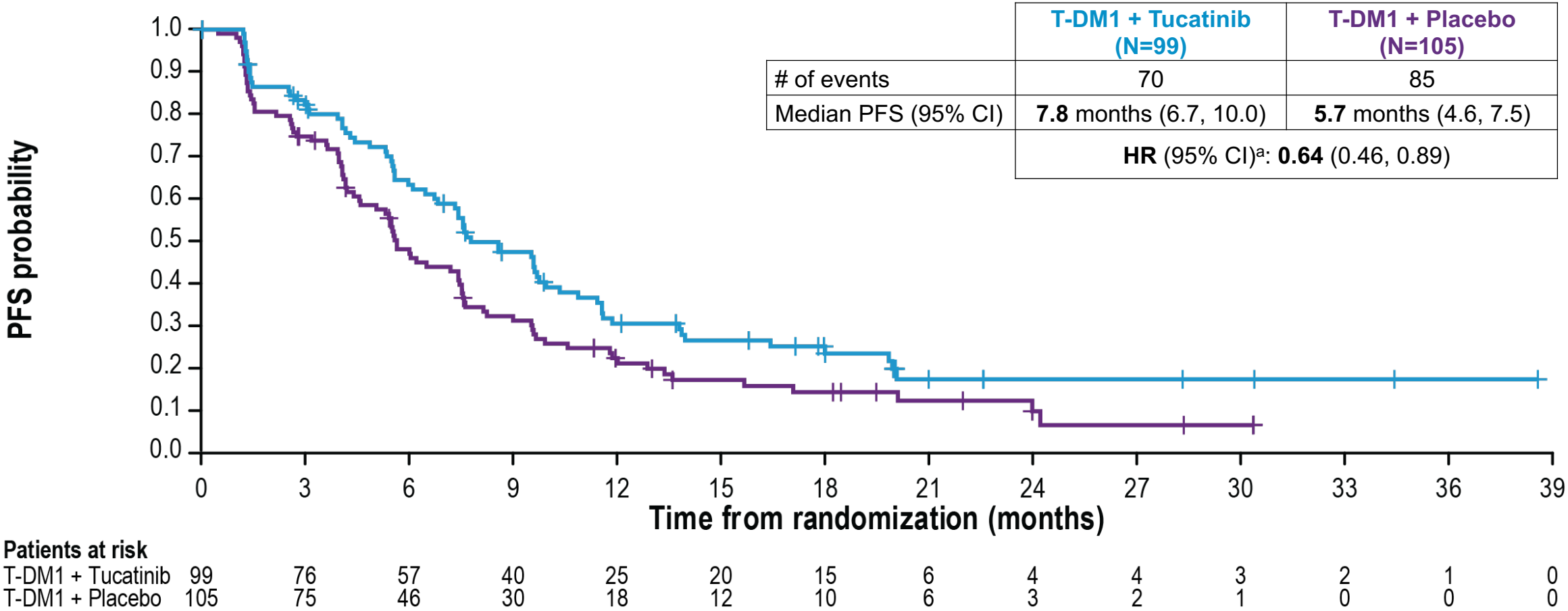
	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N	Hazard Ratio with 95% CI
Age			
<65 years	126/186	155/201	0.80 (0.62, 1.02)
≥65 years	25/42	27/34	0.61 (0.33, 1.11)
Race			
White	68/101	76/102	0.79 (0.55, 1.13)
Asian	45/66	58/65	0.73 (0.49, 1.11)
Others	38/61	48/68	0.79 (0.48, 1.28)
Initial diagnosis			
0-III	81/120	100/130	0.72 (0.53, 0.99)
IV	67/103	79/98	0.77 (0.55, 1.08)
Prior pertuzumab			
Yes	137/203	166/214	0.78 (0.62, 0.99)
No	14/25	16/21	0.74 (0.29, 1.87)



ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

HER2CLIMB-02: Tucatinib + T-DM1
PFS in Patients with Brain Metastases

	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	



a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Hurvitz et al. San Antonio Breast Cancer Symposium®, December 5-9, 2023

Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Reducing the dose of ribociclib due to toxicity versus switching to another CDK4/6 inhibitor; choice of CDK4/6 inhibitor for older patients

Dr Laila Agrawal
(Louisville, Kentucky)

Dr Sunil Gandhi
(Lecanto, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For individuals having significant difficulty tolerating a CDK4/6 inhibitor in the metastatic setting, do you generally attempt aggressive dose holds/reductions to keep the patient on that therapy, or are you more inclined to switch to a different agent in the class?

QUESTIONS FOR THE FACULTY

How do you generally approach the choice of CDK4/6 inhibitor for elderly patients with metastatic disease?

What specific comorbidities will compel you to select one CDK4/6 inhibitor versus the others?

QUESTIONS FOR THE FACULTY

Does the presence of liver or visceral metastases, negative PR status or high tumor grade influence your choice of CDK4/6 inhibitor in the metastatic setting?

Consulting Faculty Comments

Treatment options for patients with PIK3CA-mutated, ER-positive, HER2-negative mBC

Dr Shaachi Gupta (Lake Worth, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you think it is essential that community-based clinicians assess PIK3CA mutation status for all patients with newly diagnosed HR-positive metastatic disease?

Regulatory and reimbursement issues aside, for which patients will you be considering the use of the triplet regimen of inavolisib/palbociclib/fulvestrant if/when it becomes available?

RTP
RESEARCH
TO PRACTICE

1st Line Therapy for ER+ Advanced Breast Cancer

Harold J. Burstein, MD, PhD

Harvard Medical School

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

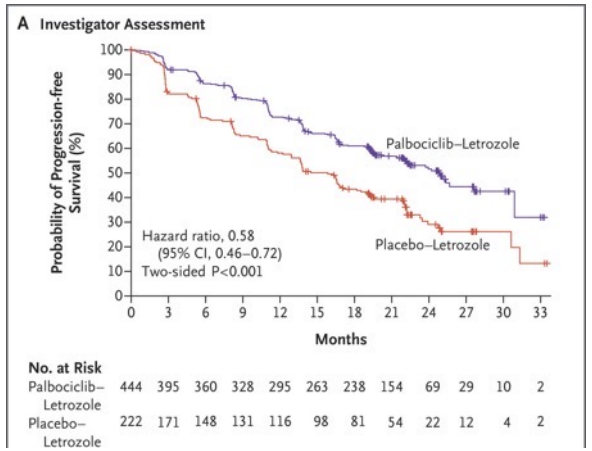
PALOMA-2

MONALEESA-2

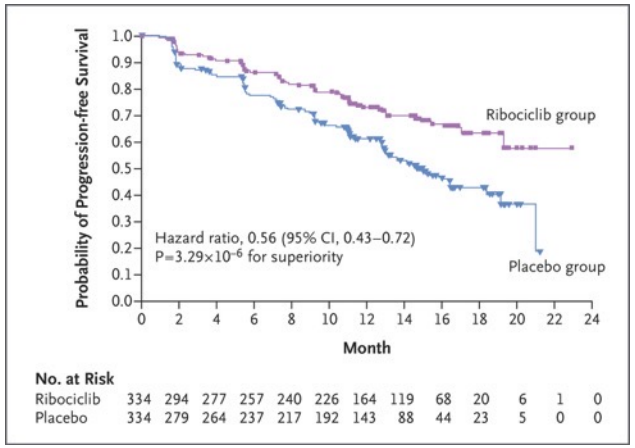
MONALEESA-7

MONARCH 3

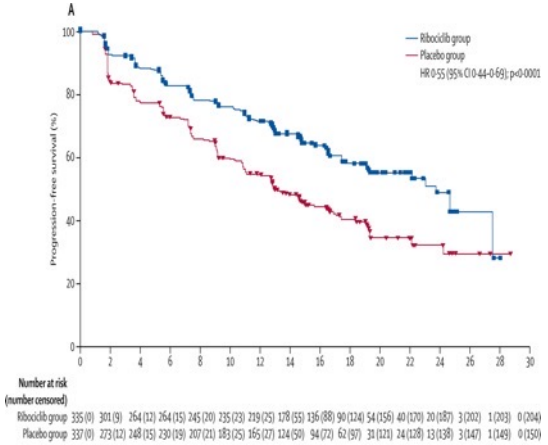
PFS



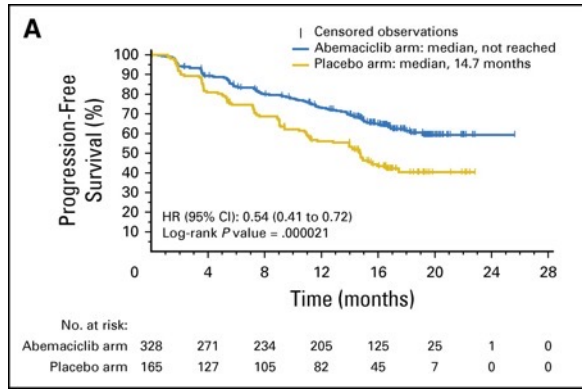
NEJM 2016;375:1925



NEJM 2016;375:1738

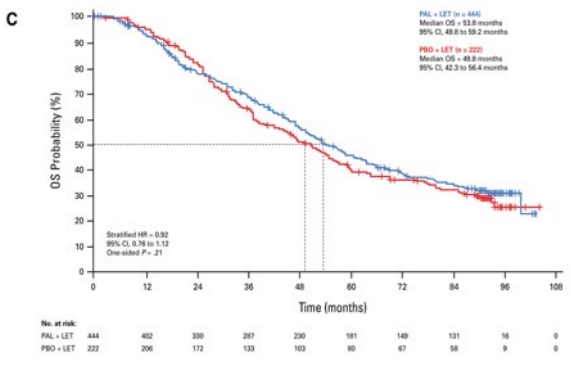


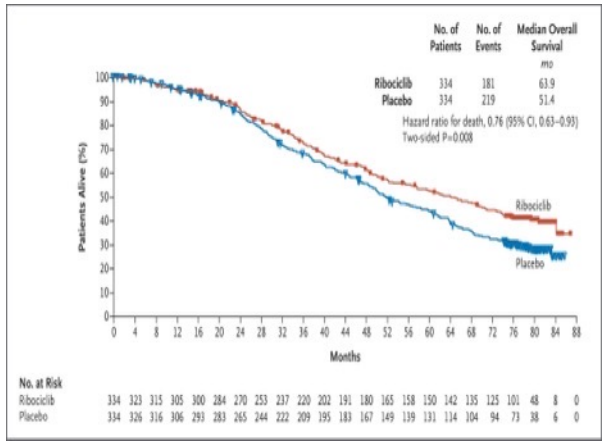
Lancet Oncol 2018;19:904

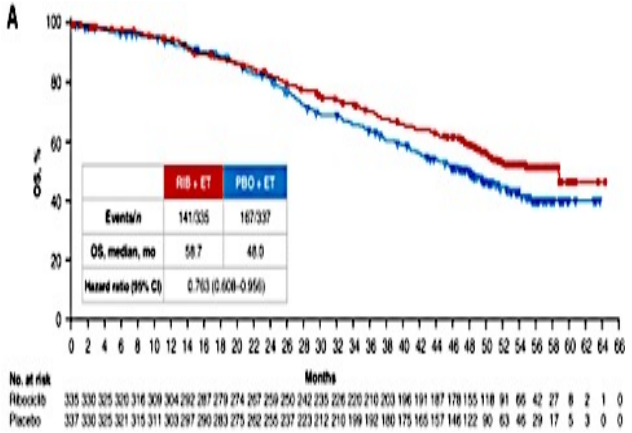


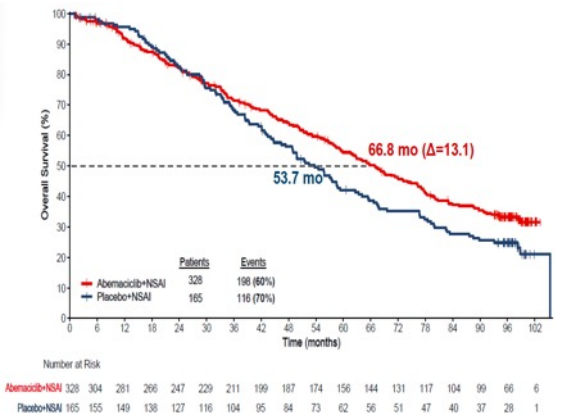
JCO 2017;35

OS









Journal of Clinical Oncology 2024 42;994-1000

NEJM 2022;386:942-950

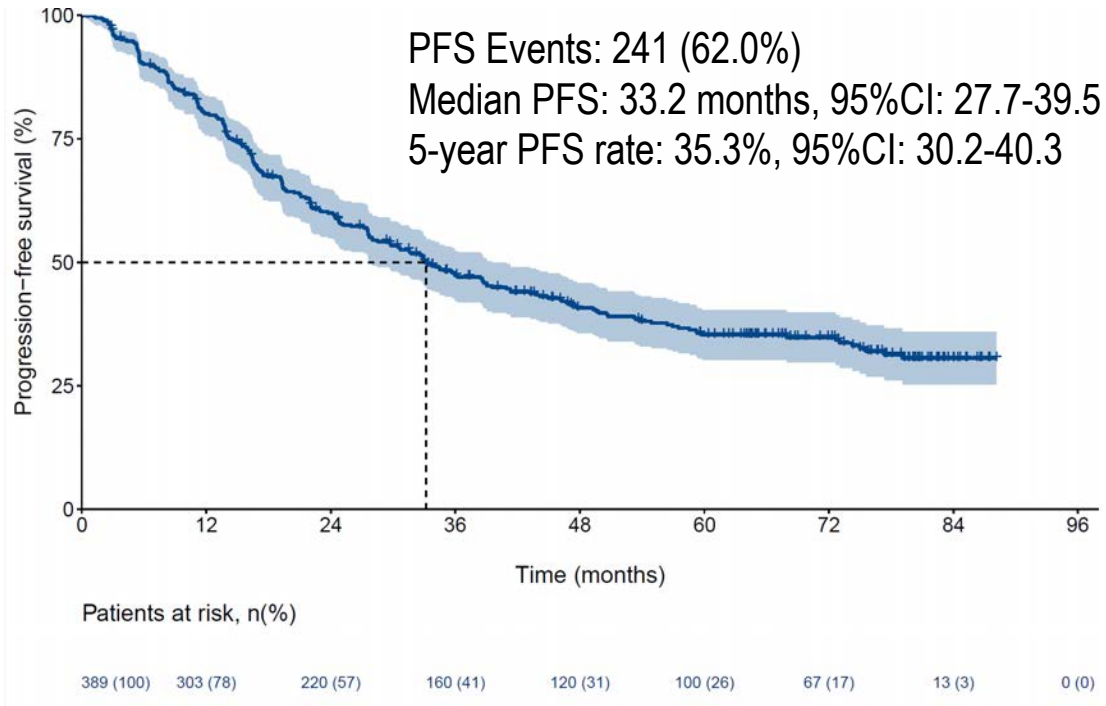
CCR 2022;28:851

Goetz SABCS 2023

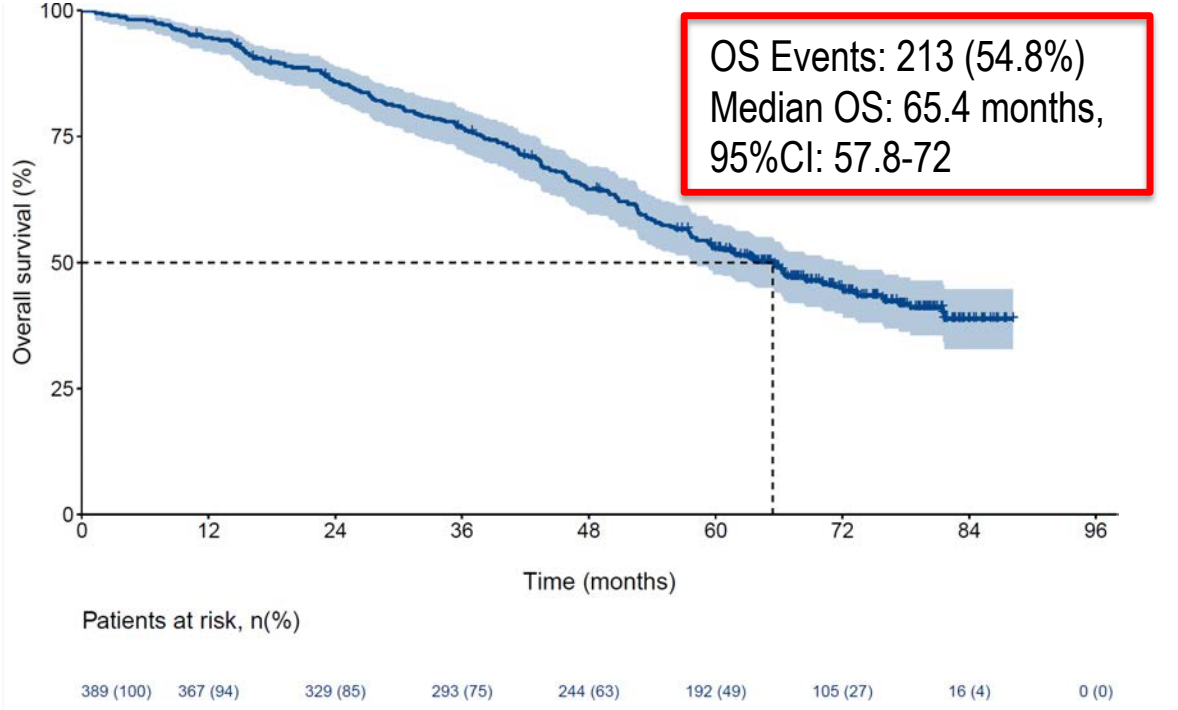
PARSIFAL-LONG:
Results: PFS and OS of both cohorts combined (n=389)

Median follow-up: 59.7 months

Progression-Free Survival



Overall Survival

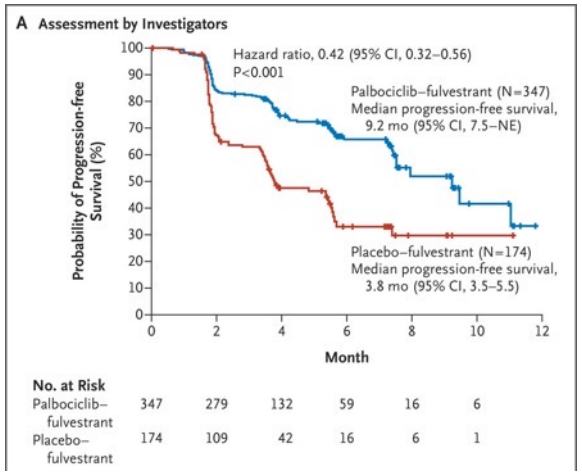


n (%), number of patients (percentage based on N); N: number of patients; OS: overall survival; PFS: progression-free survival

PFS

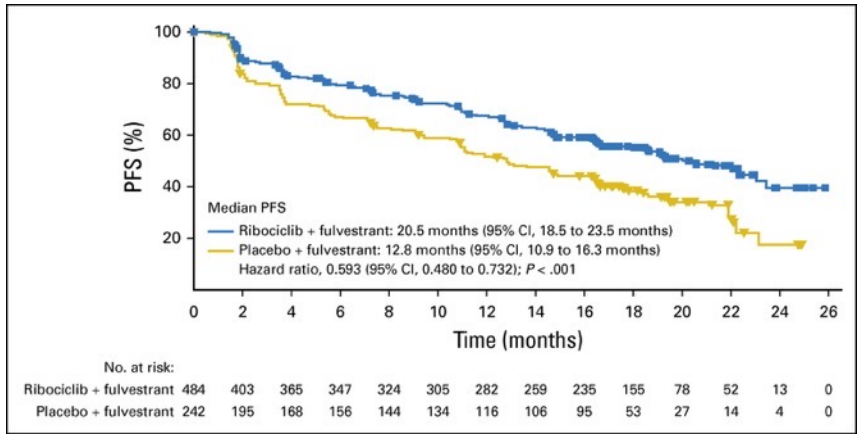
OS

PALOMA-3



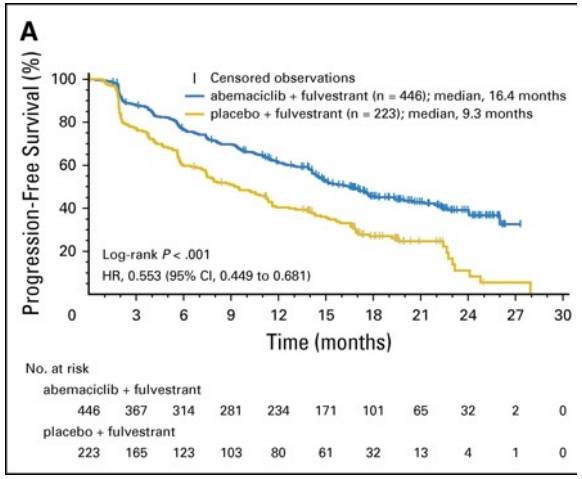
NEJM 2015;373:209-219

MONALEESA-3

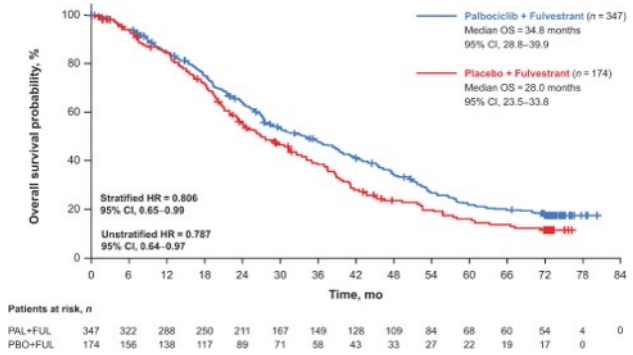


JCO 2018;36:2465

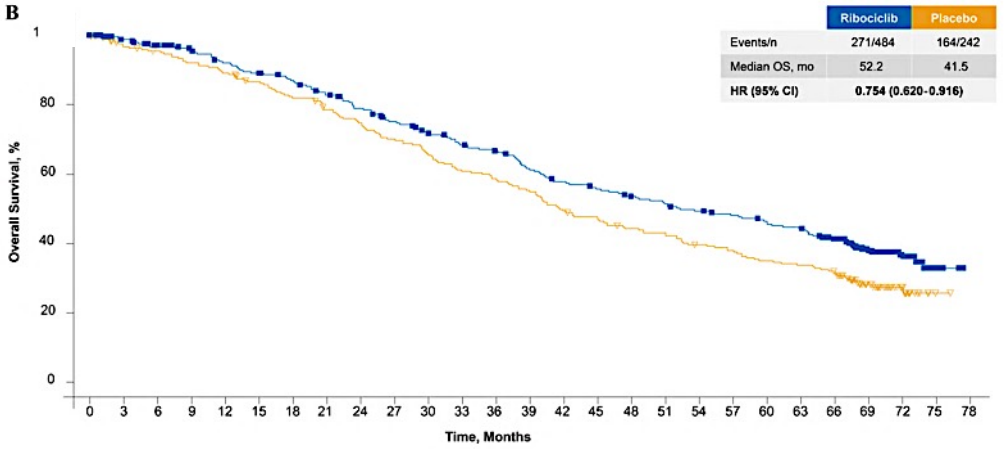
MONARCH 2



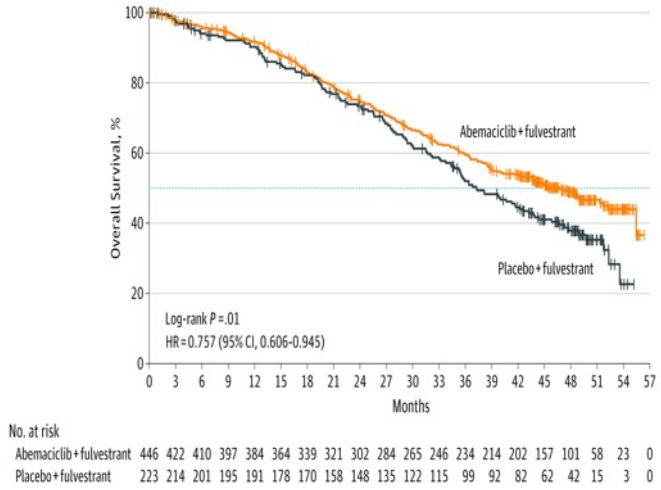
JCO 2017;35:2875



Clin Cancer Res 2022;28:3433-3442



Breast Cancer Res 2023;25:103



JAMA Oncol 2020;6:116

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

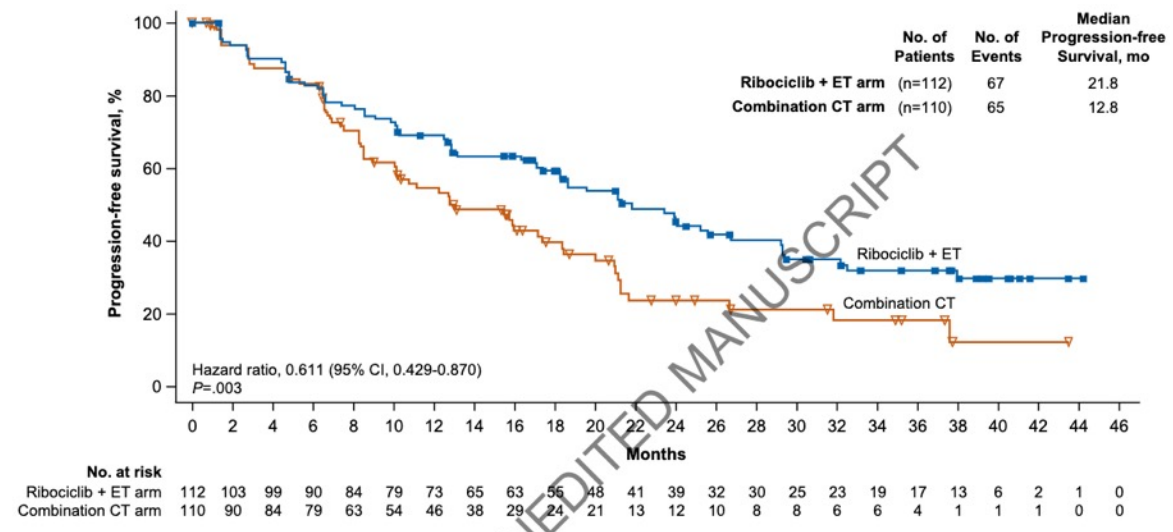
Primary endpoint
- PFS (locally assessed per RECIST 1.1)

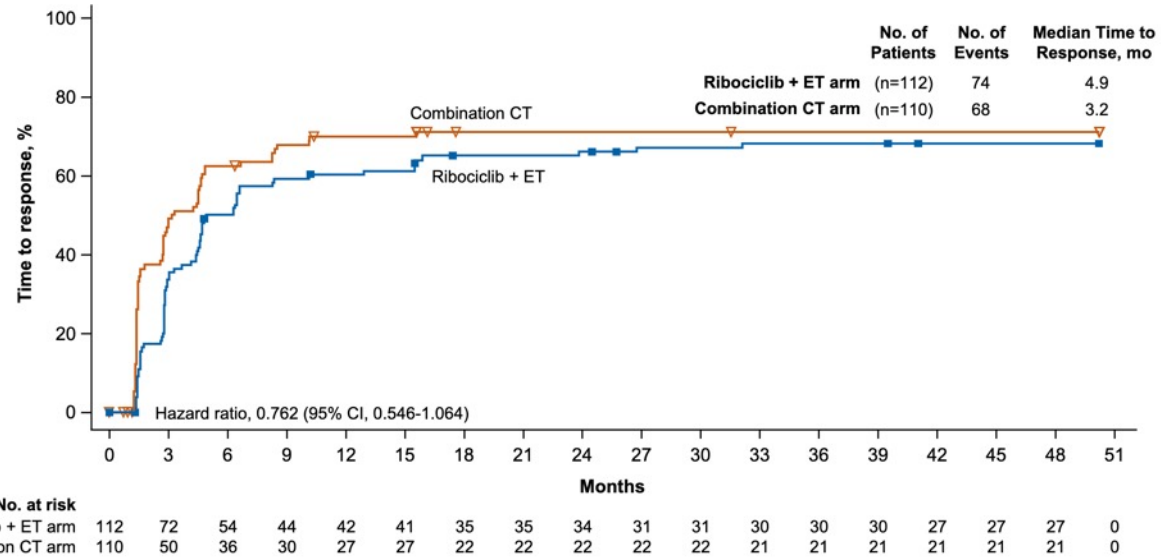
Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

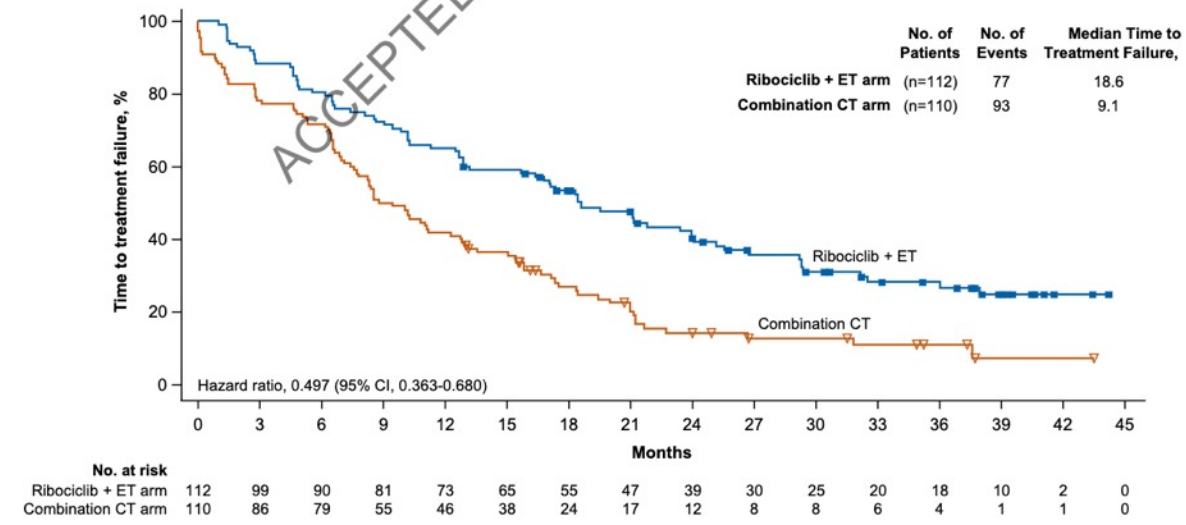
ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

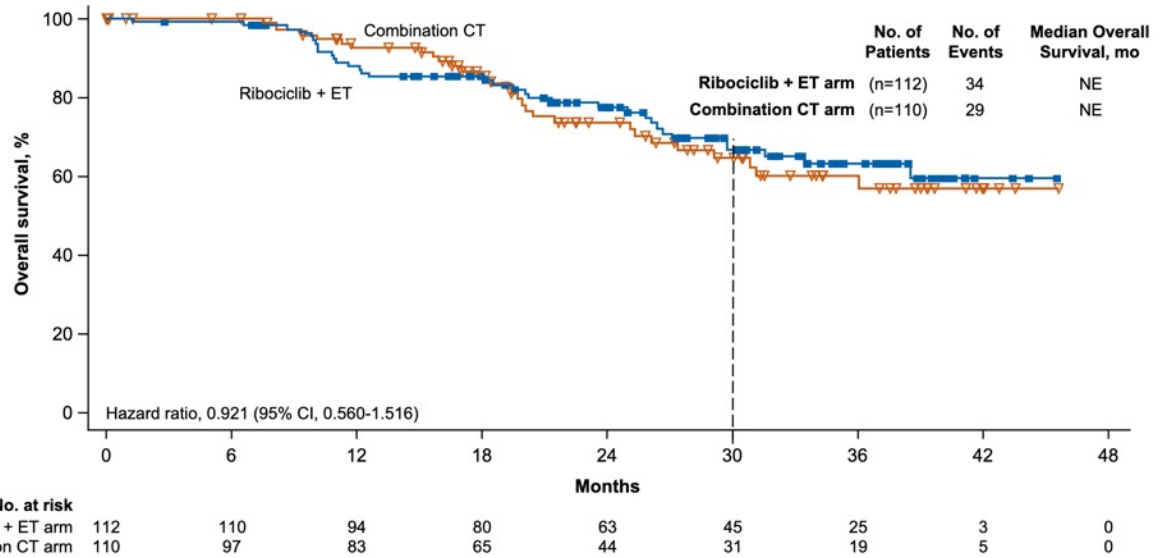
RIGHT Choice





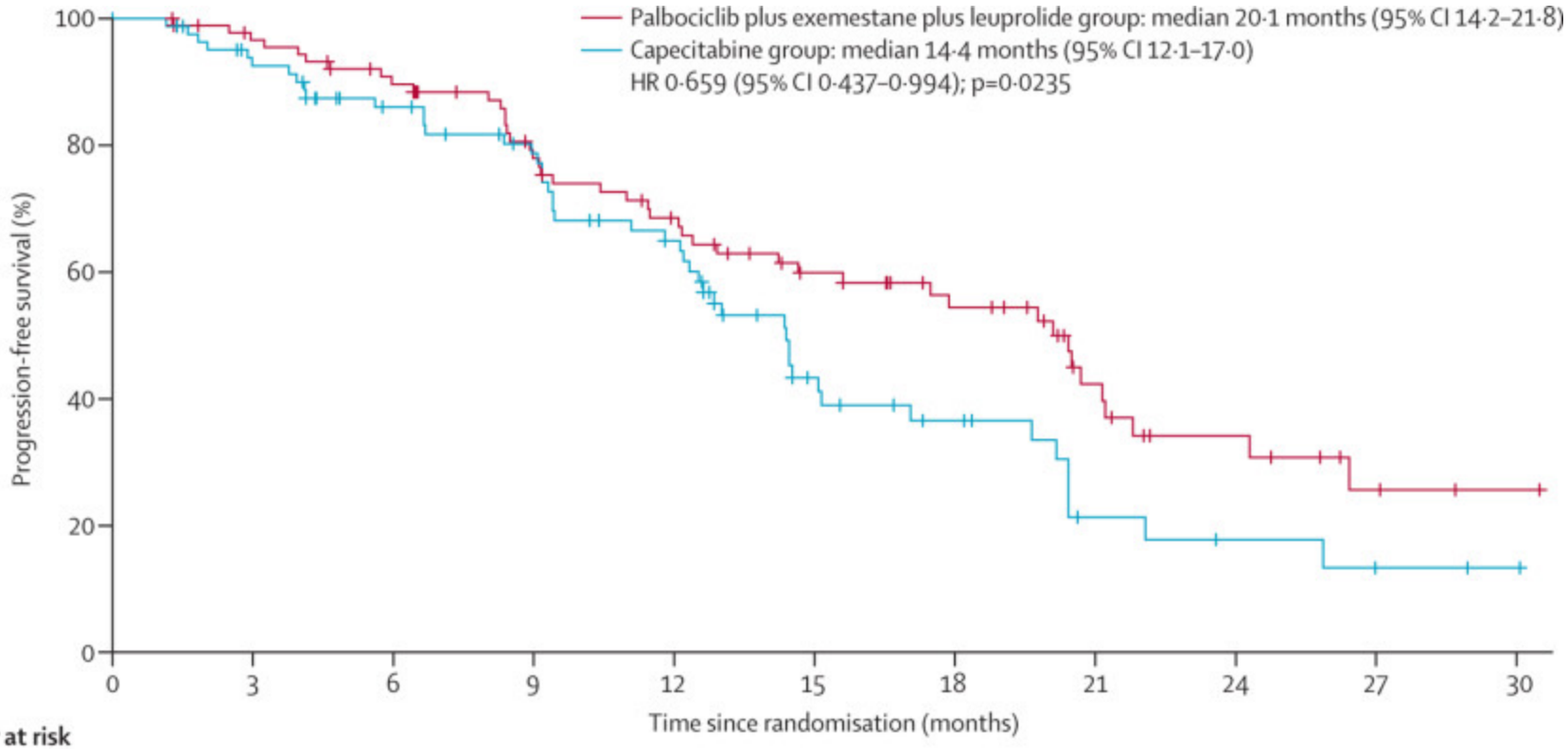
B.





Lu, et al. JCO 2024 (e-published May 2024)

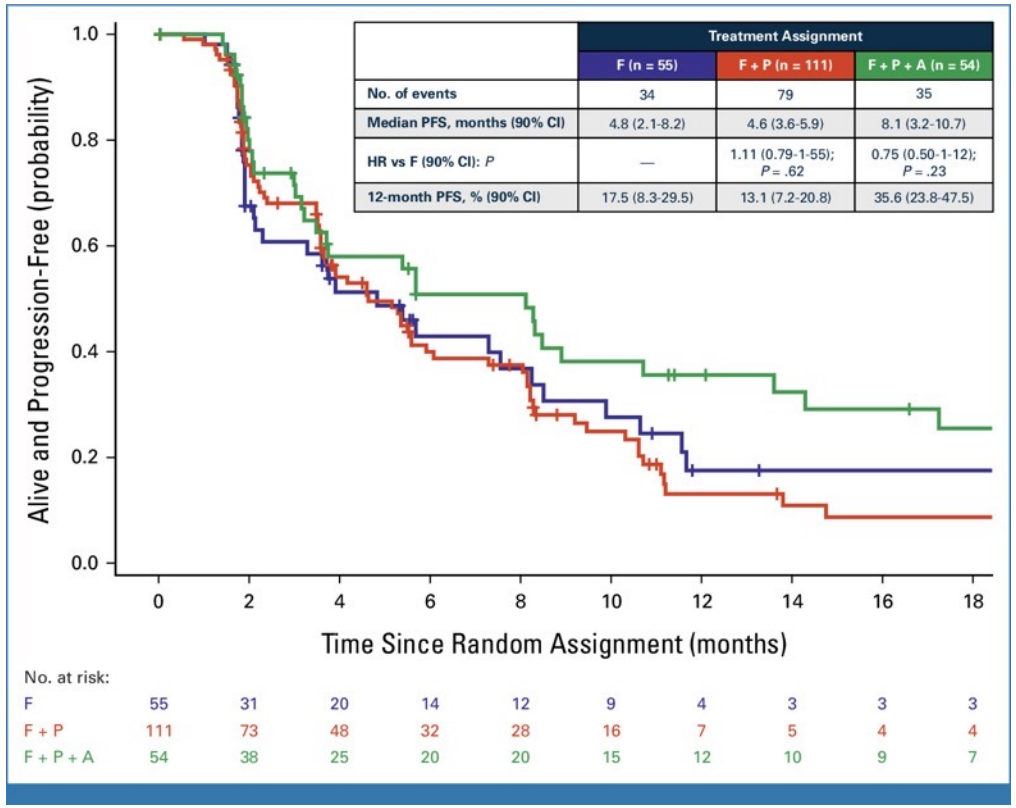
KCSG-BR15-10. ER+, HER2 neg MBC in premenopausal women
Exemestane + GnRH + Palbociclib vs Capecitabine



Number at risk (number censored)													
Palbociclib plus exemestane plus leuprolide group	92 (0)	89 (2)	85 (4)	82 (4)	74 (9)	59 (15)	49 (18)	38 (23)	28 (30)	16 (37)	10 (40)	5 (43)	2 (46)
Capecitabine group	83 (3)	81 (4)	73 (7)	65 (11)	61 (14)	52 (18)	40 (21)	20 (29)	14 (32)	6 (35)	4 (36)	2 (37)	1 (38)

Lancet Oncol 2019;20:1750

PACE: palbo after palbo

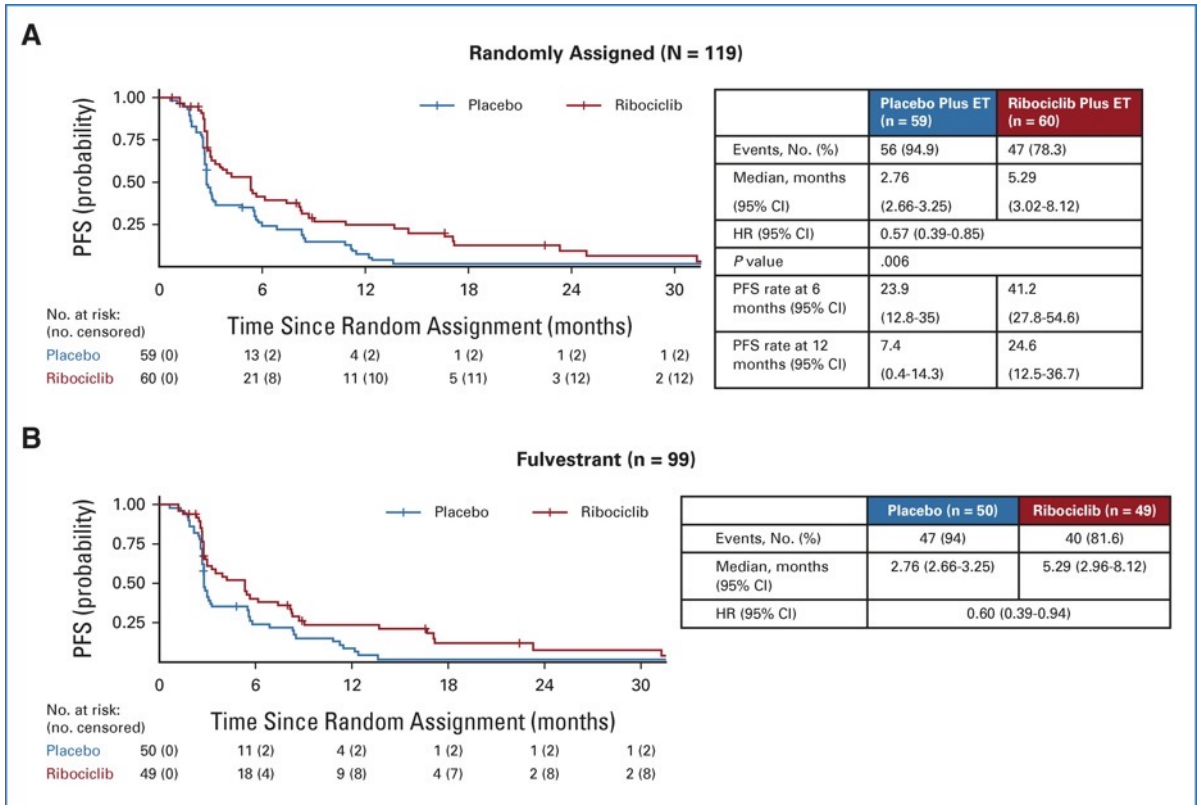


	Treatment Assignment		
	F (n = 55)	F + P (n = 111)	F + P + A (n = 54)
No. of events	34	79	35
Median PFS, months (90% CI)	4.8 (2.1-8.2)	4.6 (3.6-5.9)	8.1 (3.2-10.7)
HR vs F (90% CI): *P*	—	1.11 (0.79-1-55); *P* = .62	0.75 (0.50-1-12); *P* = .23
12-month PFS, % (90% CI)	17.5 (8.3-29.5)	13.1 (7.2-20.8)	35.6 (23.8-47.5)

F = fulvestrant; P = palbociclib; A = avelumab

Mayer EL, et al. JCO 2024

MAINTAIN: ribo after palbo



	Placebo Plus ET (n = 59)	Ribociclib Plus ET (n = 60)
Events, No. (%)	56 (94.9)	47 (78.3)
Median, months (95% CI)	2.76 (2.66-3.25)	5.29 (3.02-8.12)
HR (95% CI)	0.57 (0.39-0.85)	
P value	.006	
PFS rate at 6 months (95% CI)	23.9 (12.8-35)	41.2 (27.8-54.6)
PFS rate at 12 months (95% CI)	7.4 (0.4-14.3)	24.6 (12.5-36.7)

	Placebo (n = 50)	Ribociclib (n = 49)
Events, No. (%)	47 (94)	40 (81.6)
Median, months (95% CI)	2.76 (2.66-3.25)	5.29 (2.96-8.12)
HR (95% CI)	0.60 (0.39-0.94)	

Kalinsky K, et al. JCO 2023

postMONARCH Study Design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

Placebo + Fulvestrant

Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

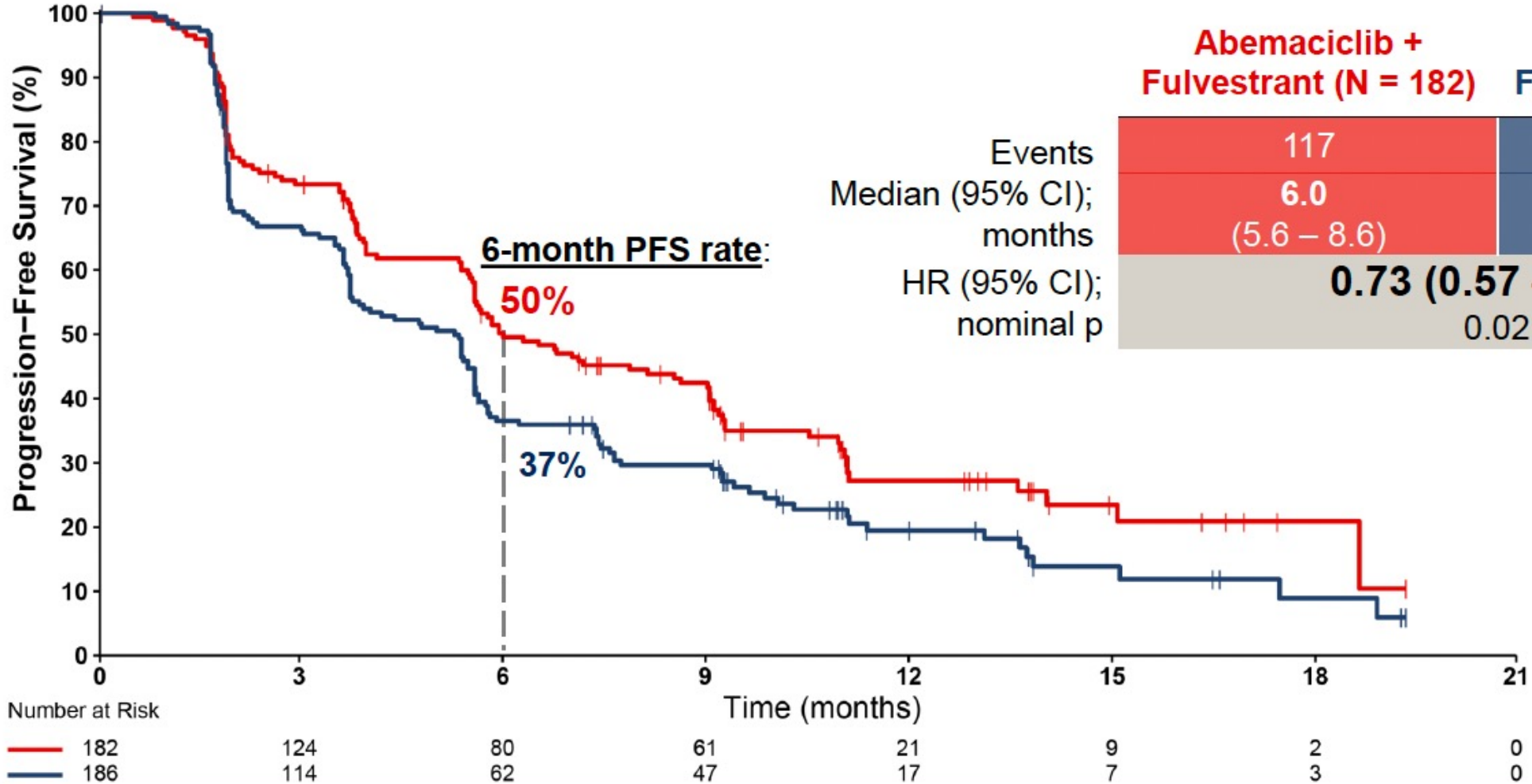
Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

	Abemaciclib + Fulvestrant N = 182	Placebo + Fulvestrant N = 186	Nominal p-value
Measurable disease population	131	127	
ORR by investigator, %	17	7	0.0145
ORR by BICR, %	23	8	0.0008

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22
Median Prior CDK4/6i Duration (mo; range)#	All	19 (2, 110)	21 (3, 87)
	Palbociclib	19	23
	Ribociclib	15	18
	Abemaciclib	26	21

Kalinsky K et al. ASCO 2024;Abstract LBA1001.

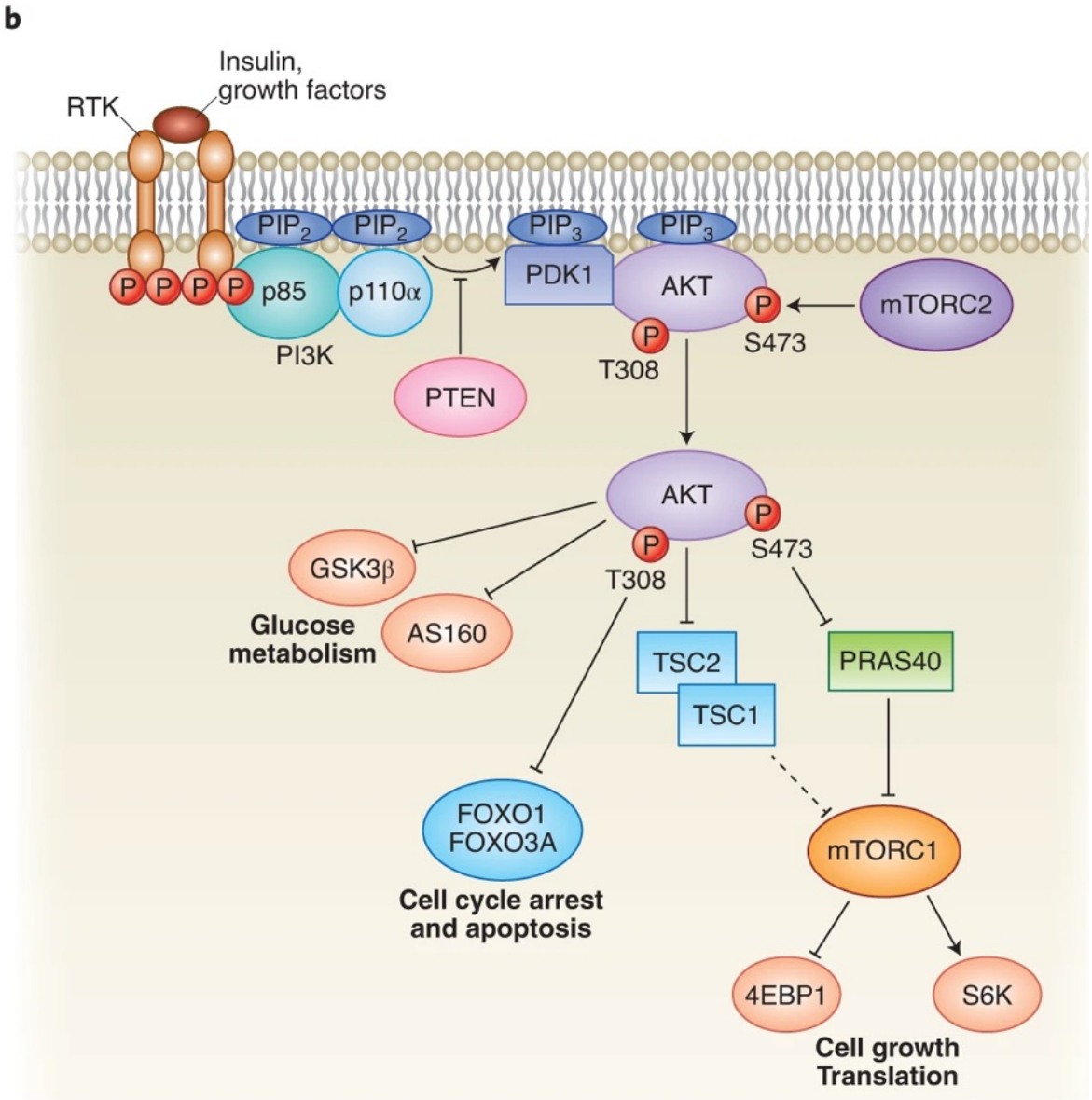
Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS

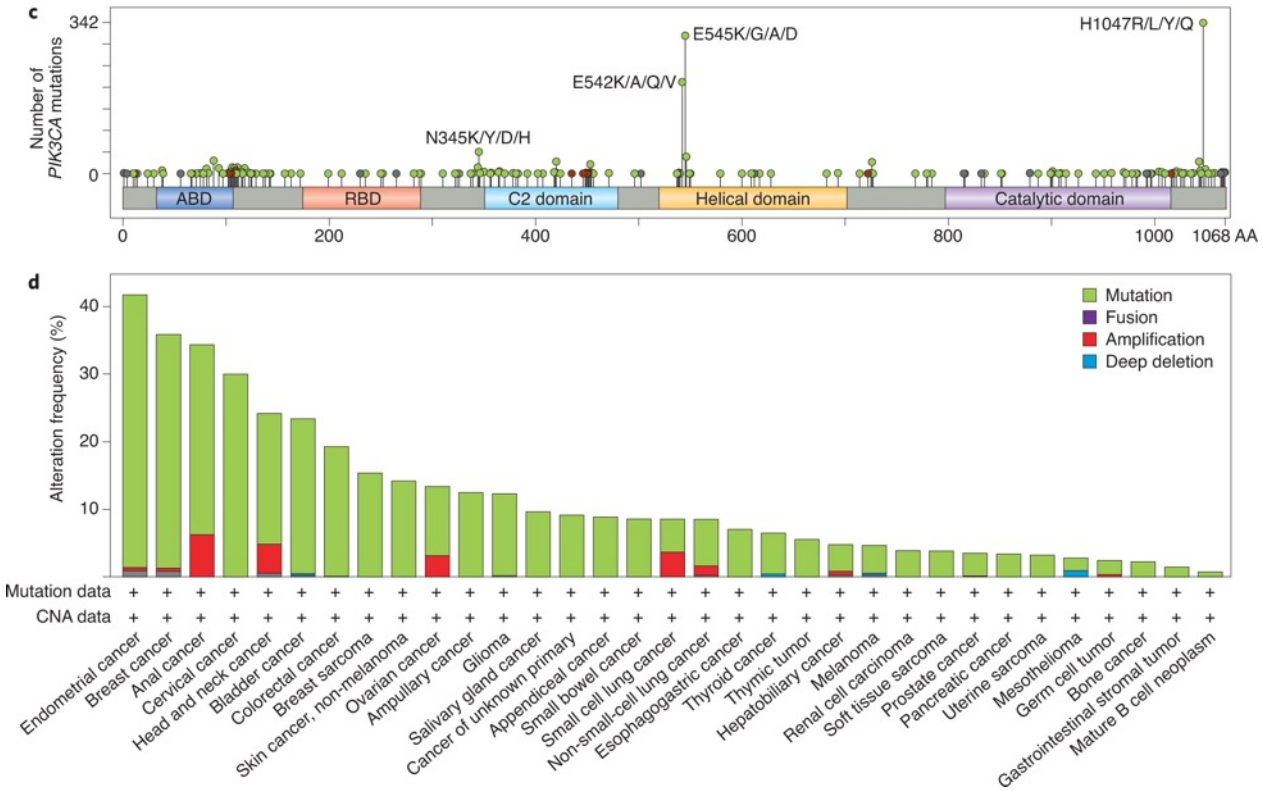


	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	**6.0** (5.6 – 8.6)	**5.3** (3.7 – 5.6)
HR (95% CI); nominal p	**0.73 (0.57 – 0.95)** 0.02	

Abemaciclib led to 27% reduction in the risk of developing PFS event

Kalinsky K et al. ASCO 2024;Abstract LBA1001.

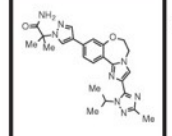
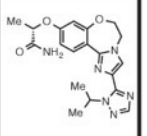
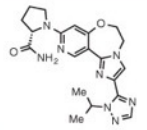
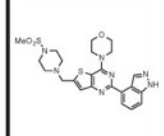
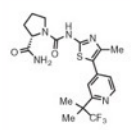
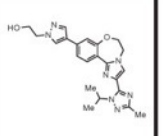
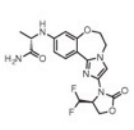




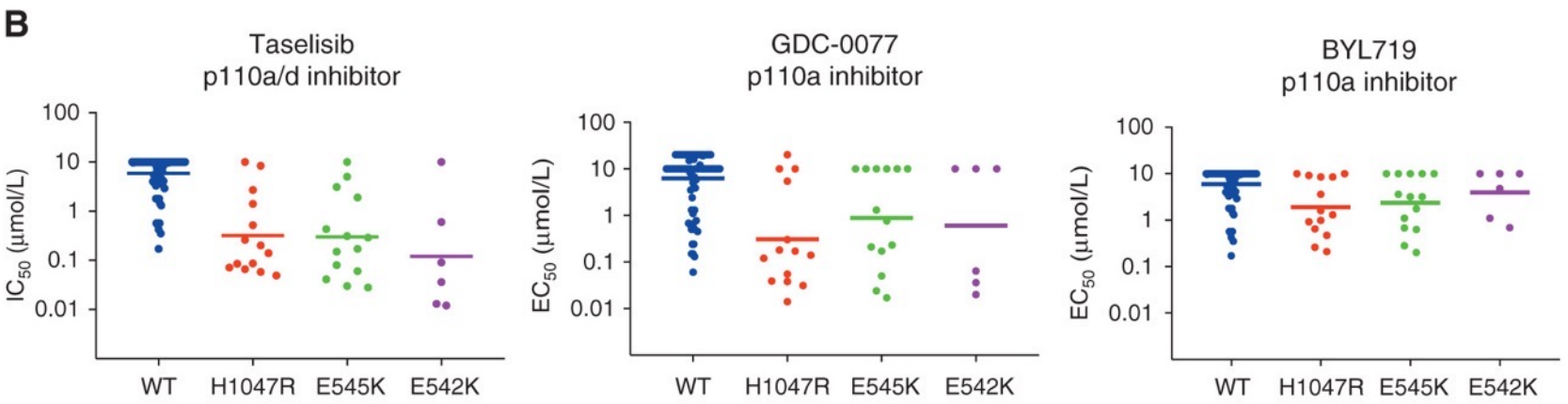
Castel P, et al.
Nature Cancer 2021;2:587.

RTK-Dependent Inducible Degradation of Mutant PI3Kα Drives GDC-0077 (Inavolisib) Efficacy

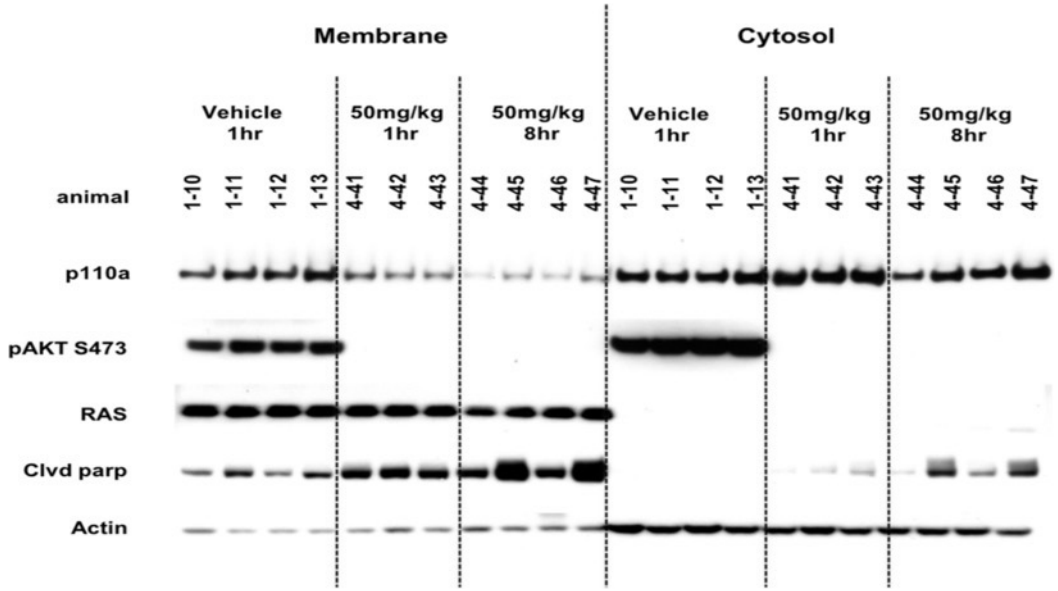
A

	Taselisib GDC-0032	GNE-326	GNE-102	Pictilisib GDC-0941	Alpelisib BYL719	GNE-181	GDC-0077
Structure							
p110a ATP K_i[a]	0.1 nmol/L	0.3 nmol/L	0.2 nmol/L	2.6 nmol/L	2.2 nmol/L	0.4 nmol/L	0.04 nmol/L
Fold a vs. b/d/g[a]	591/0.9/16	502/22/102	1002/34/366	27/0.6/16	424/13/18	119/0.4/2	2676/337/574
Kinetic solubility	33 μmol/L	107 μmol/L	46 μmol/L	37 μmol/L	40 μmol/L	2.1 μmol/L	167 μmol/L
Plasma protein binding[b] (%, H/R/M)	90/97/97	56/69/62	53/48/69	93/93/96	92/91/92	80/98/98	41/39/74
MDCK P_{app} A➔B[c] (B➔A/A➔B)	6.4×10^{-6} cm/s (1.7)	8.5×10^{-6} cm/s (0.9)	2.2×10^{-6} cm/s (2.3)	7.6×10^{-6} cm/s (3.0)	11×10^{-6} cm/s (1.0)	11×10^{-6} cm/s (0.9)	1.9×10^{-6} cm/s (2.5)
Mouse $t_{1/2}$ AUC_{inf} dose[d]	2.1 h 388 μmol/L*h 25 mg/kg	2.4 h 74 μmol/L*h 25 mg/kg	2.6 h 2 μmol/L*h 10 mg/kg	1.4 h 11 μmol/L*h 25 mg/kg	3.1 h 34 μmol/L*h 15 mg/kg	3.1 h 291 μmol/L*h 25 mg/kg	4.3 h 38 μmol/L*h 25 mg/kg

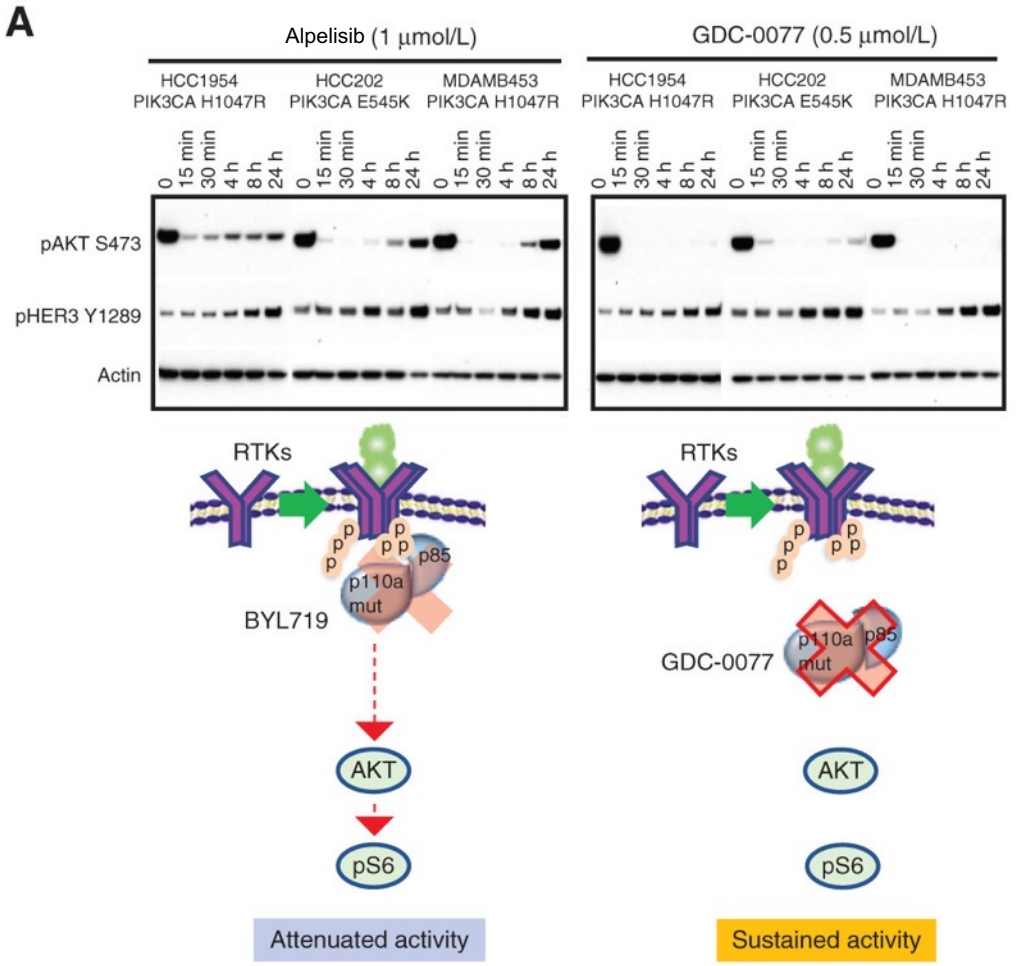
B



Cancer Discov. 2022;12(1):204-219.

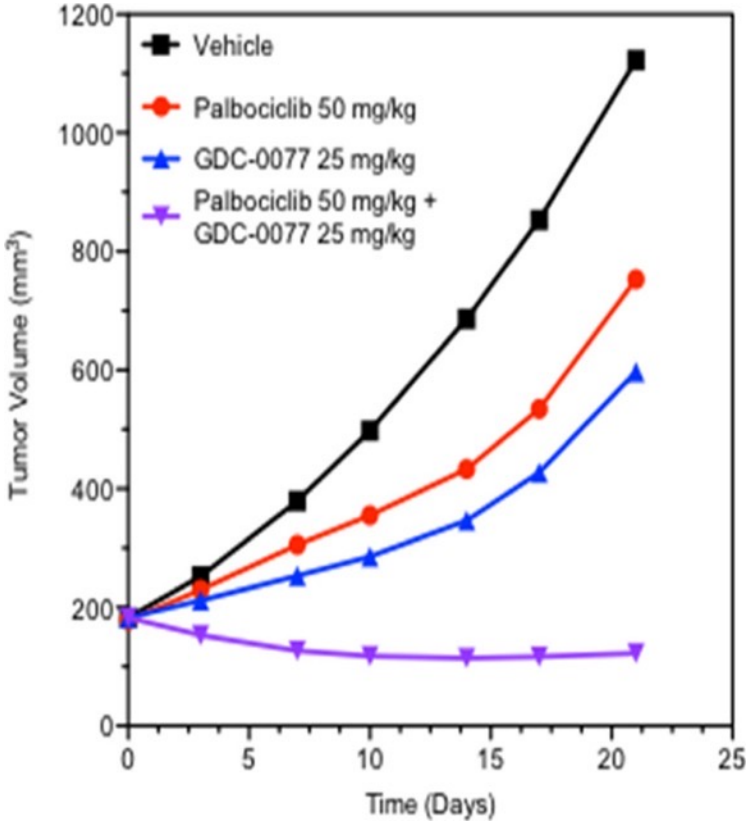


Hanan EJ, et al. J Med Chem 2022;65:16589-16621

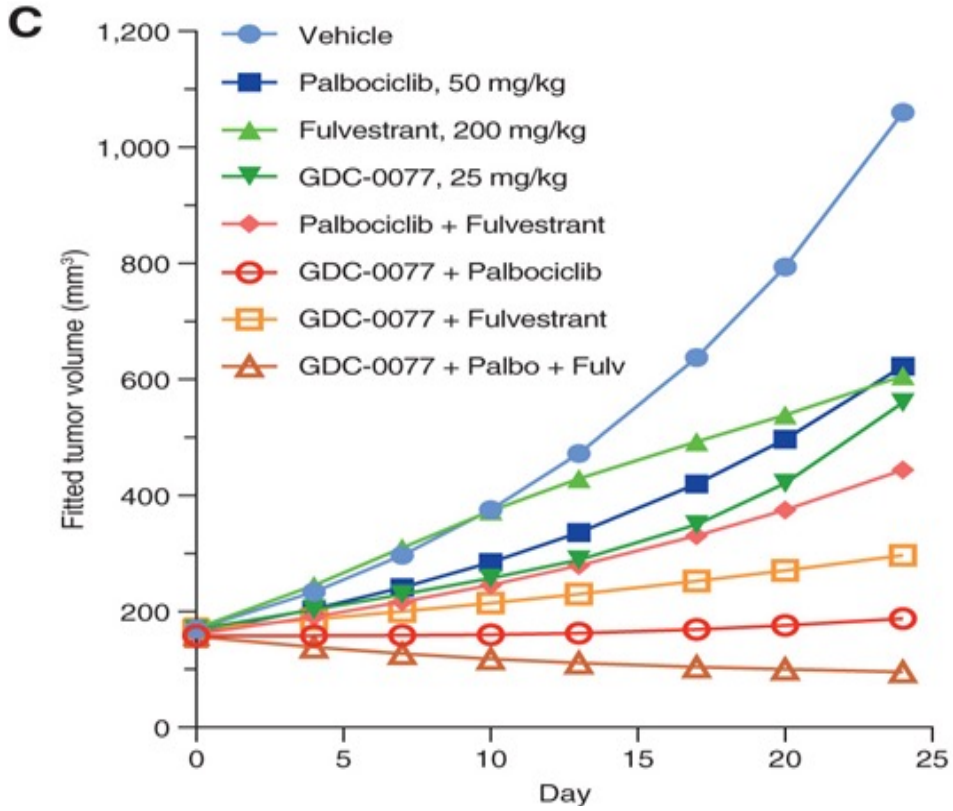


Cancer Discov. 2022;12(1):204-219.

Preclinical models with PIK3CA and CDK4/6 inhibitors in ER+ breast cancer



Hanan EJ, et al. J Med Chem 2022;65:16589-16621



Cancer Discov 2022;12(1):204-219.

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:

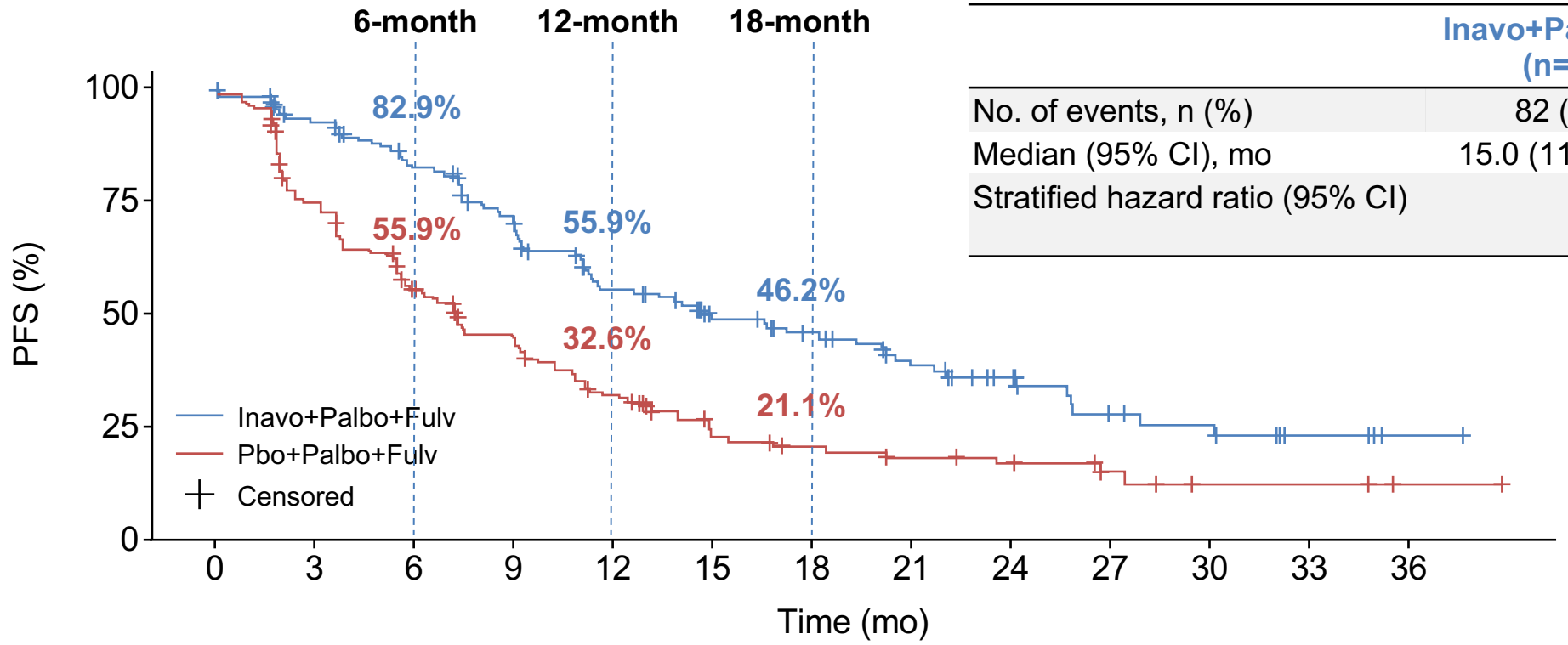
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

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.

Primary endpoint: PFS (investigator assessed)



	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**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

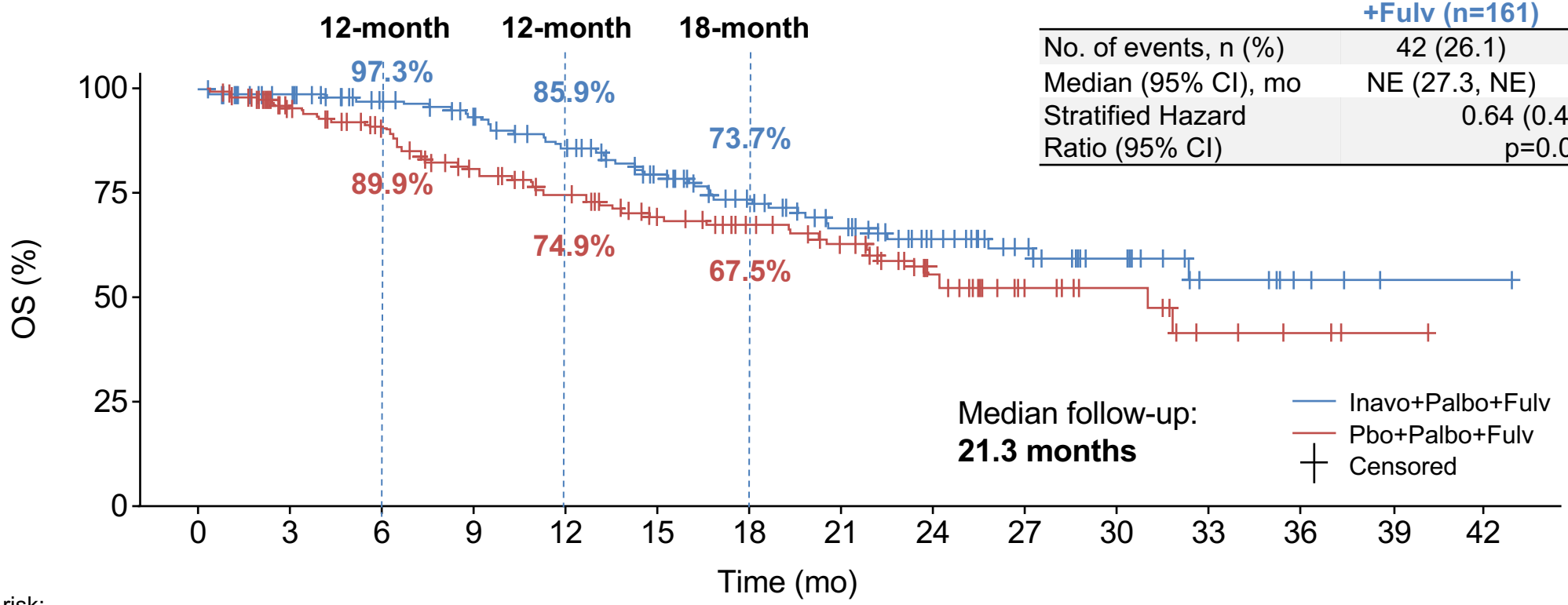
Median follow-up:
21.3 months

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Key secondary endpoint: Overall survival (interim analysis)

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	



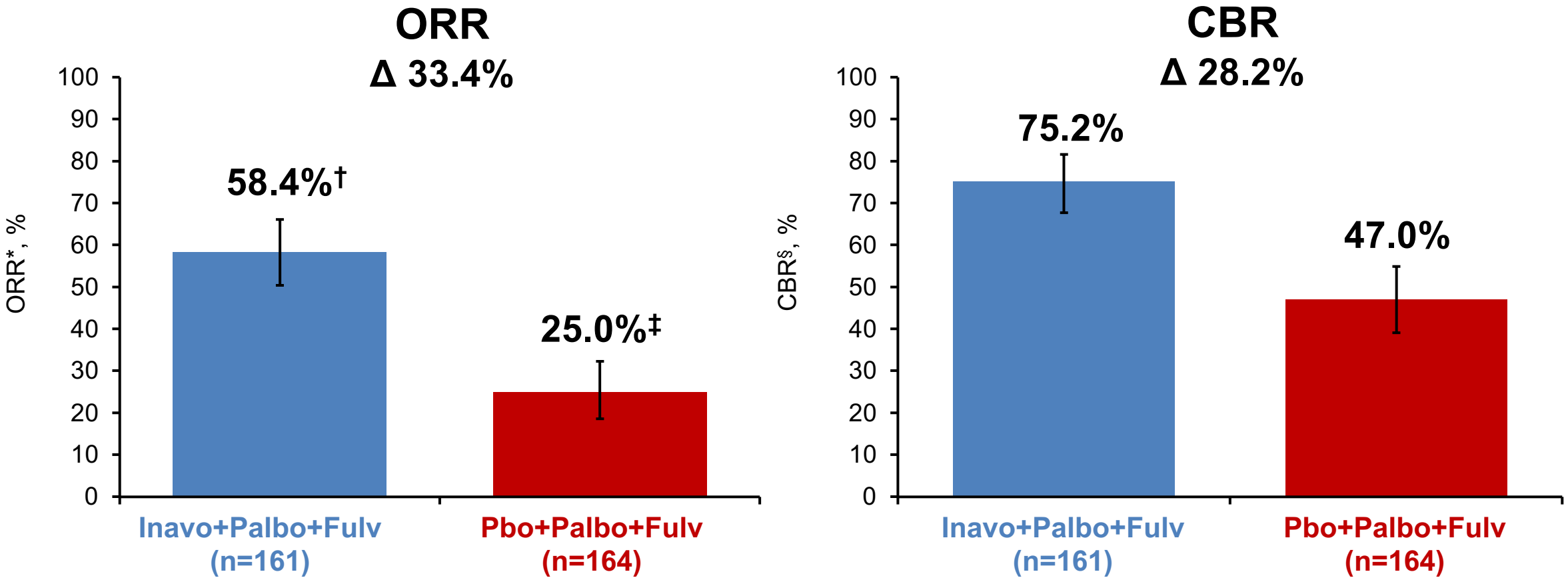
Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS overall survival; Palbo, palbociclib; Pbo, placebo.

Secondary endpoints: ORR and CBR (investigator assessed)



* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR,. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
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/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%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5**.** Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

TABLE 1. Treatment Options According to Prior Endocrine Therapy

Line of Therapy	Tumor Genomic Findings	Prior Endocrine Therapy[a]	
		None, tamoxifen only, or no prior recent AI therapy (anastrozole, exemestane, letrozole)	Recurrence on or within recent exposure to AI therapy
First-line treatment		AI + CDK4/6 inhibitor	Fulvestrant + CDK4/6 inhibitor
Tumor genomic testing[b]			
Second-line treatment	No targetable mutations	Fulvestrant or fulvestrant + everolimus	Fulvestrant + everolimus, or chemotherapy
	ESR1 mutation	Elacestrant, or fulvestrant + everolimus	Elacestrant
	PIK3CA mutation	Fulvestrant + capivasertib, fulvestrant + alpelisib,[d] or fulvestrant	Fulvestrant + capivasertib, or fulvestrant + alpelisib[d]
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib, or fulvestrant	Fulvestrant + capivasertib
Third-line treatment and beyond[c]	No targetable mutations or targeted therapy already given	Chemotherapy or further endocrine-based treatments	Chemotherapy or further endocrine-based treatments
	ESR1 mutation	Elacestrant[e] or chemotherapy	Elacestrant[e] or chemotherapy
	PIK3CA mutation	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib,[e] or chemotherapy	Fulvestrant + capivasertib,[e] or chemotherapy

Burstein HJ, et al. J Clin Oncol 2024

Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Toxicity profiles of PIK3CA inhibitors and selective estrogen receptor degraders; selection and sequencing of new biomarker-based treatment modalities

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Gigi Chen
(Pleasant Hill, California)

QUESTIONS FOR THE FACULTY

What second-line therapy would you most likely recommend for a patient with disease progression 18 months after starting a CDK4/6 inhibitor in combination with an aromatase inhibitor who is found to have a PIK3CA mutation?

How, if at all, would your selection change if the patient also had an ESR1 mutation?

How, if at all, would your selection change if the patient had rapid disease progression after 6 months?

QUESTIONS FOR THE FACULTY

What second-line therapy would you most likely recommend for a patient with disease progression 18 months after starting a CDK4/6 inhibitor in combination with an aromatase inhibitor who is found to have an ESR1 mutation?

How, if at all, would your selection change if the patient had rapid disease progression after 6 months?

QUESTIONS FOR THE FACULTY

Based on what we currently know, how do the various oral SERDs under development, namely camizestrant and imlunestrant, compare to elacestrant in terms of efficacy?

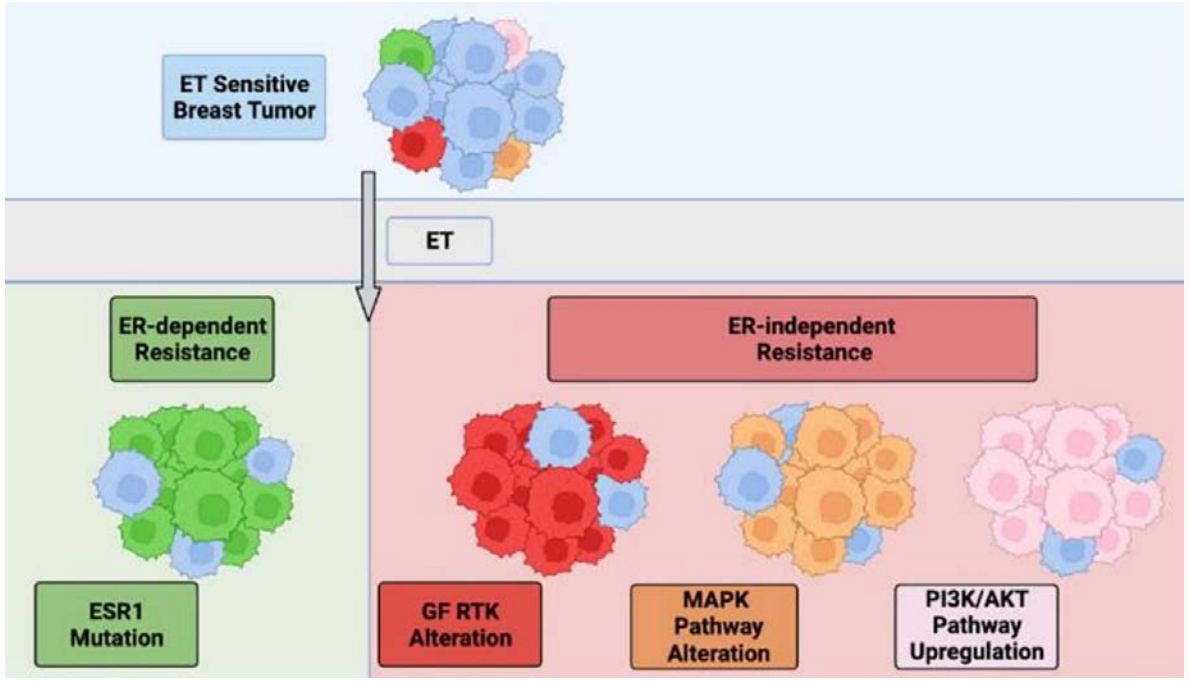
What about tolerability?

UCSF Helen Diller Family Comprehensive Cancer Center

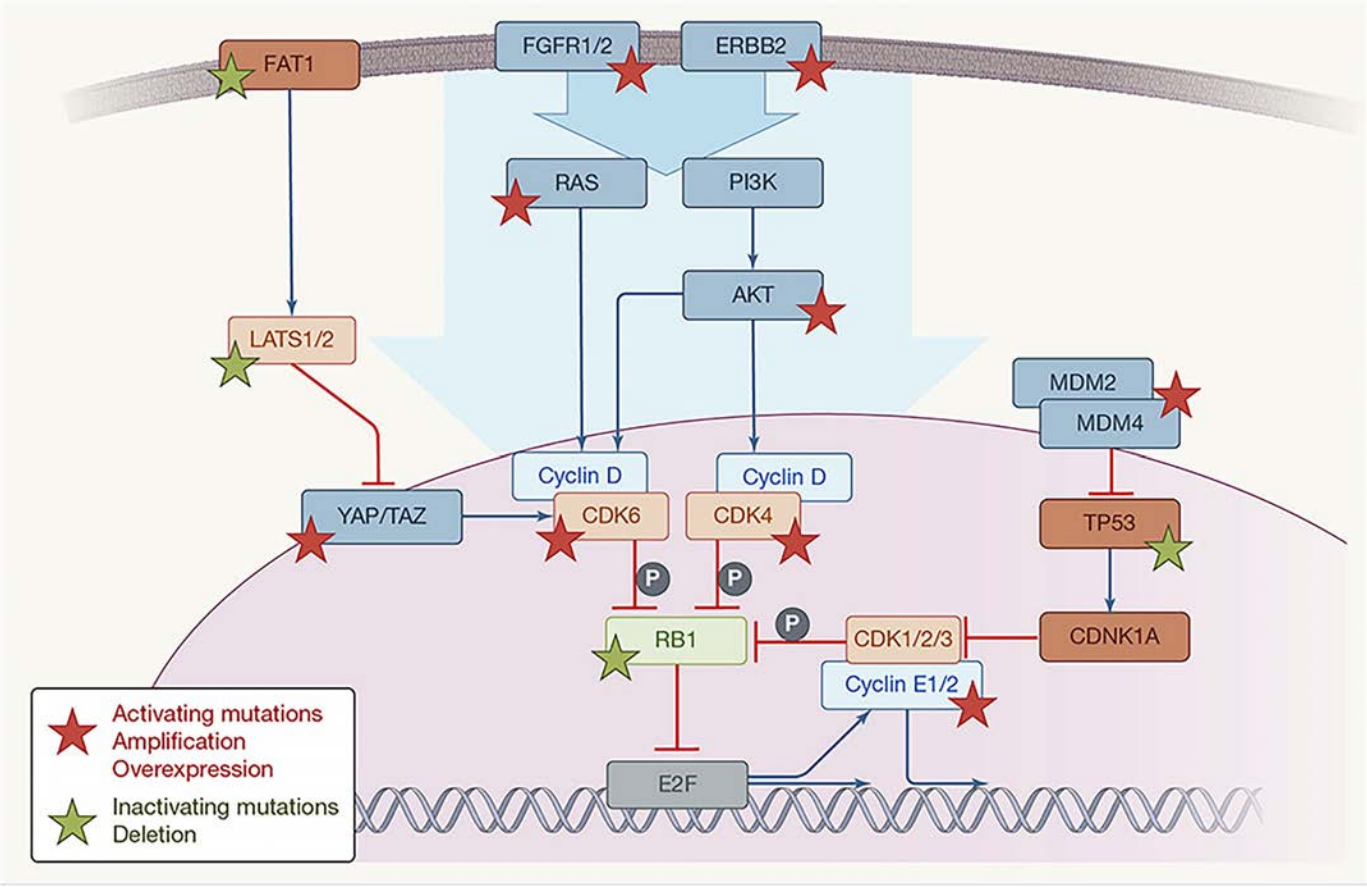
Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition

Hope S. Rugo, MD
Professor of Medicine and Winterhof Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

Resistance to ET + CDK4/6i: A High Unmet Need



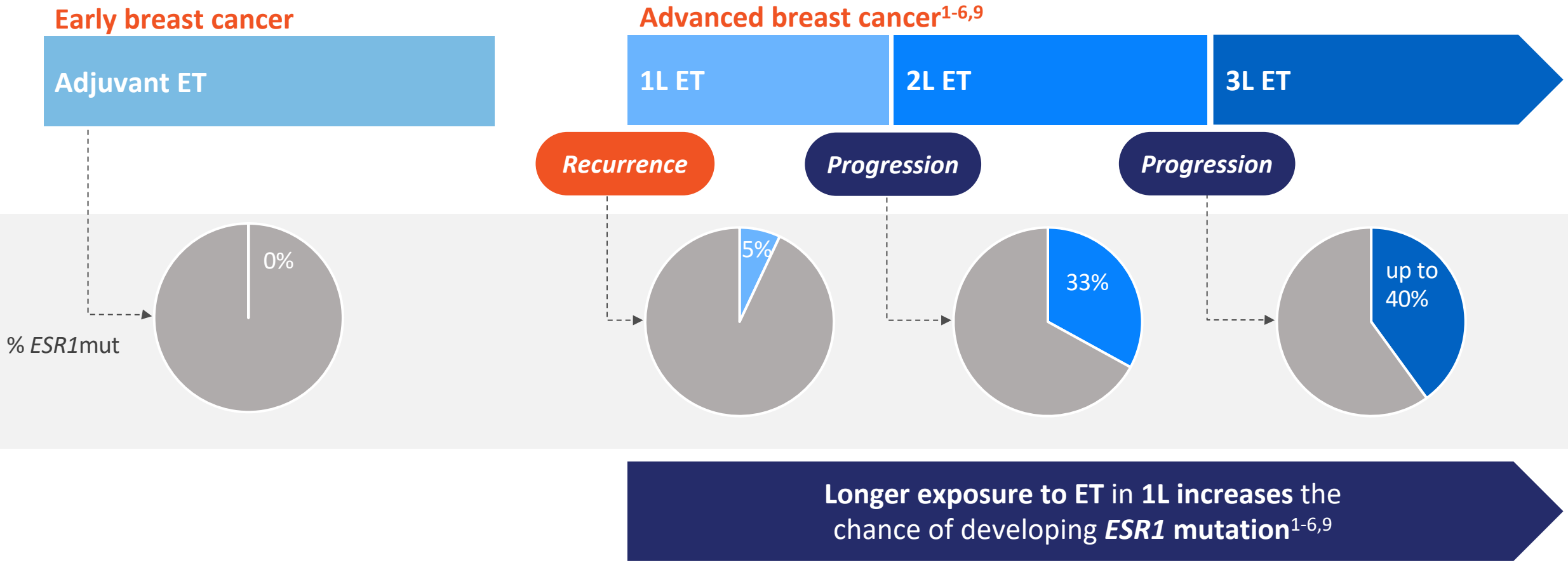
ER dependent and independent mechanism of resistance



Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

Most *ESR1* Mutations Arise After Progression on 1L mBC Therapy[1-9]



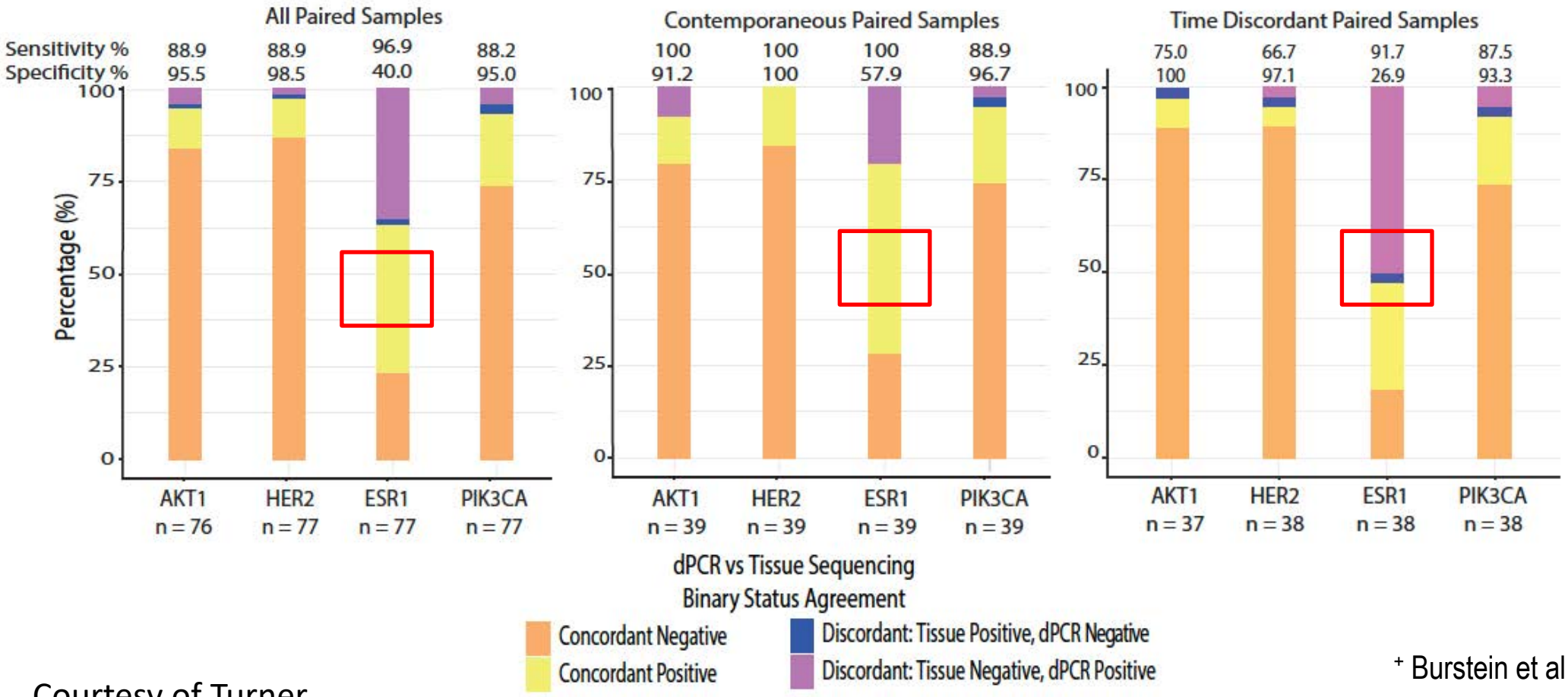
Abbreviations: 1L, first line; 2L, second line; 3L, third line; ESR1, estrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer

1. Jeselsohn R, et al. *Clin Cancer Res.* 2014;20:1757-1767. 2. Jeselsohn R, et al. *Cancer Cell.* 2018;33:173-186. 3. Allouchery V, et al. *Breast Cancer Res.* 2018;20:40; 4. Schiavon G, et al. *Sci Transl Med.* 2015;7;313ra182. 5. Brett JO, et al. *Breast Cancer Res.* 2021;23:85. 6. Callens C, et al. *Anal Chem.* 2022;94:6297-6303. 7. Robinson DR, et al. *Nat Genet.* 2013;45:1446-1451. 8. Reinert T, et al. *Front Oncol.* 2017;7:26. 9. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256.

ctDNA vs paired tumor sequencing

Substantially more *ESR1* mutations identified in liquid biopsy

Overall | Contemporaneous | Discordant | Timing of tissue biopsy



Liquid biopsy preferred to test for *ESR1* mutations⁺

Courtesy of Turner

⁺ Burstein et al ASCO guidance JCO 2023

BIOMARKER TESTING FOR METASTATIC ER+VE BREAST CANCER

Recurrence

First line treatment AI+CDK4/6i

Progression

Proposed testing algorithm

Assuming all currently approved therapies available

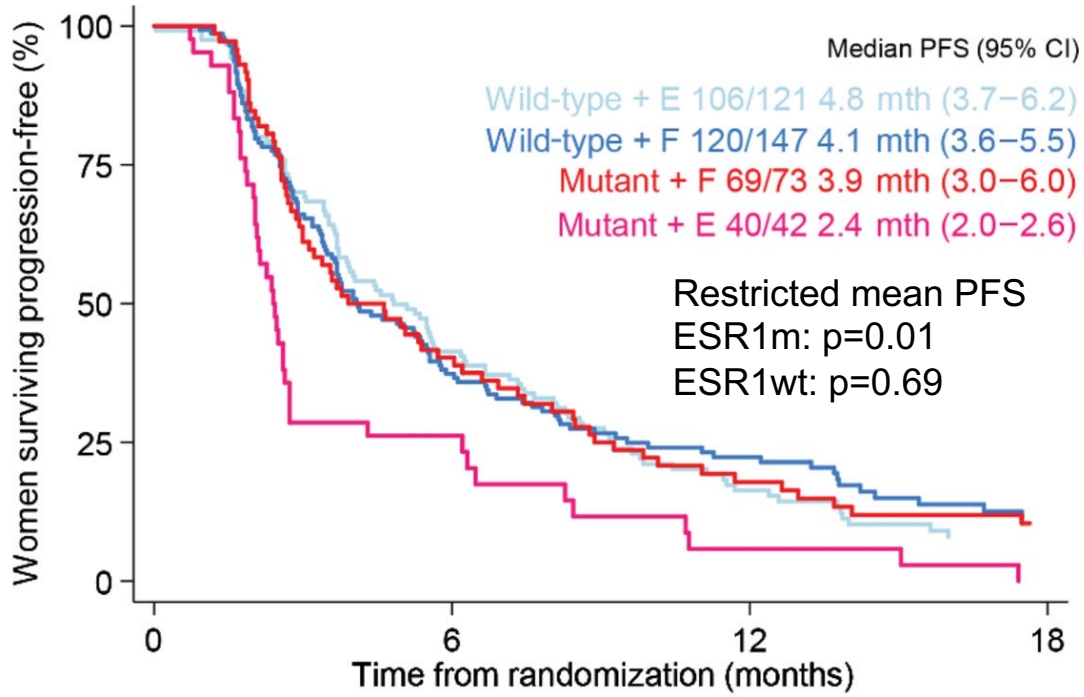
Tissue biopsy
Confirm breast cancer
Receptors including HER2 for 'low'
Molecular testing
PIK3CA/AKT1/PTEN
(including *PTEN* large deletions)

Germline *BRCA1/BRCA2/PALB2*

Liquid biopsy
Test for acquired mutations
ESR1 ~ 40% patients
PIK3CA/AKT1/PTEN mutations acquired since recurrence biopsy 5-10%

Nicholas Turner

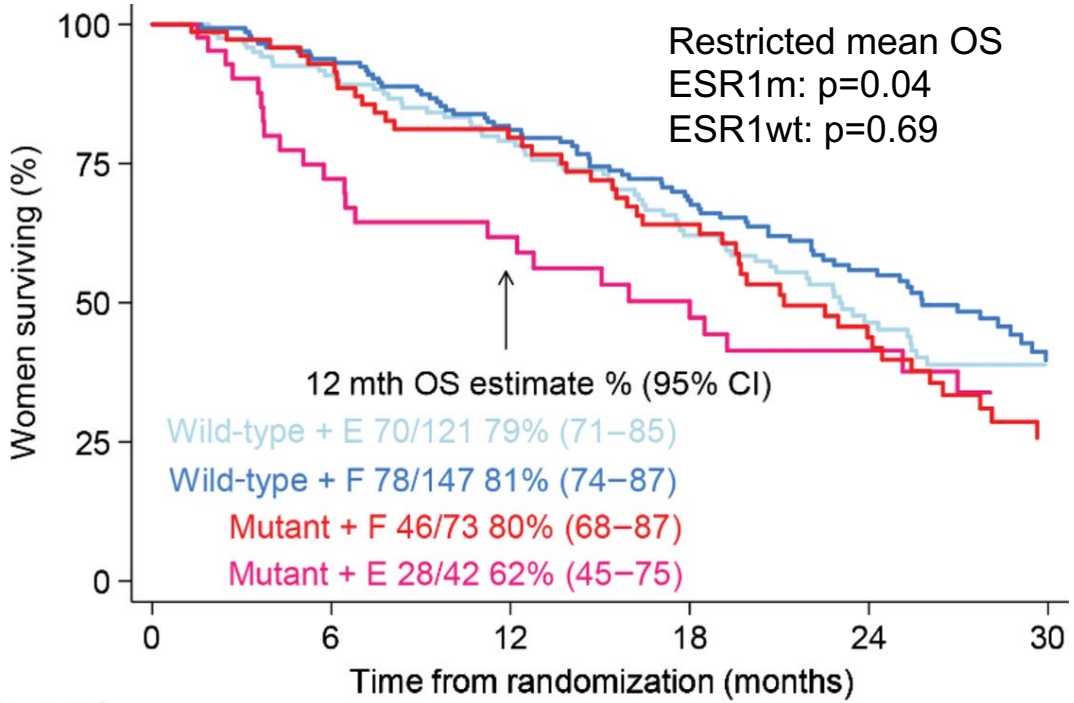
ESR1 Mutations: Fulvestrant vs Exemestane MBC in a Combined Analysis of the Ph III SoFEA and EFECT Trials



N at risk (events)

Wild-type + E	121	(70)	49	(28)	17	(8)	7
Wild-type + F	147	(87)	50	(19)	25	(10)	8
Mutant + E	42	(31)	9	(7)	2	(2)	0
Mutant + F	73	(43)	29	(16)	12	(5)	6

Interaction test p=0.02



N at risk (events)

Wild-type + E	121	(11)	109	(14)	93	(19)	68	(15)	37	(6)	21
Wild-type + F	147	(9)	134	(18)	113	(17)	89	(15)	59	(13)	26
Mutant + E	42	(11)	28	(4)	22	(4)	17	(3)	11	(2)	6
Mutant + F	73	(5)	64	(9)	52	(10)	38	(11)	23	(8)	9

Turner et al. Clin Cancer Res 2020;26:5172-5177

EMERALD Results: Elacestrant vs SOC
PFS by Duration of CDK4/6i in *mESR1* Cohort

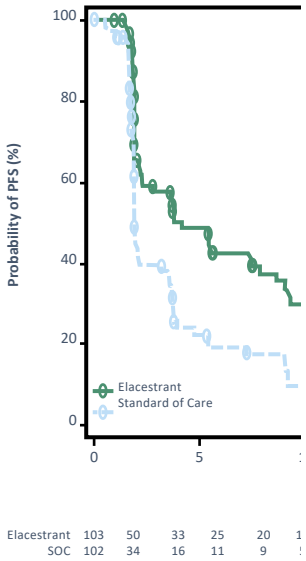
FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

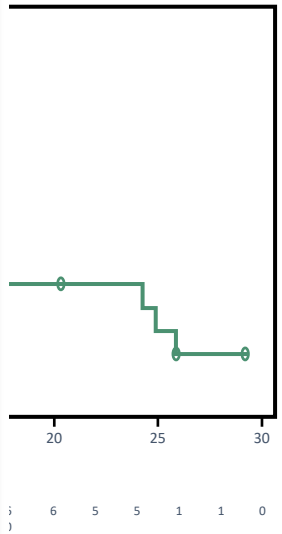
On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant for postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360® CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

≥ 6 M

CDK4/6i





Median PFS, months (95% CI)					**2.10** (1.87 - 3.75)
PFS rate at 12 month (95% CI)	(15.12 - 36.92)	(0.00 - 13.65)	(95% CI)	(21.84 - 49.78)	(0.00 - 17.66)	(95% CI)	(19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)		Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia A et al. SABCS 2022. Abstract GS3-01; Bidard et al, JCO 2022

EMERALD (Phase 3, key subgroup analysis): Elacestrant for *ESR1*-mutated ER+/HER2– advanced/metastatic breast cancer

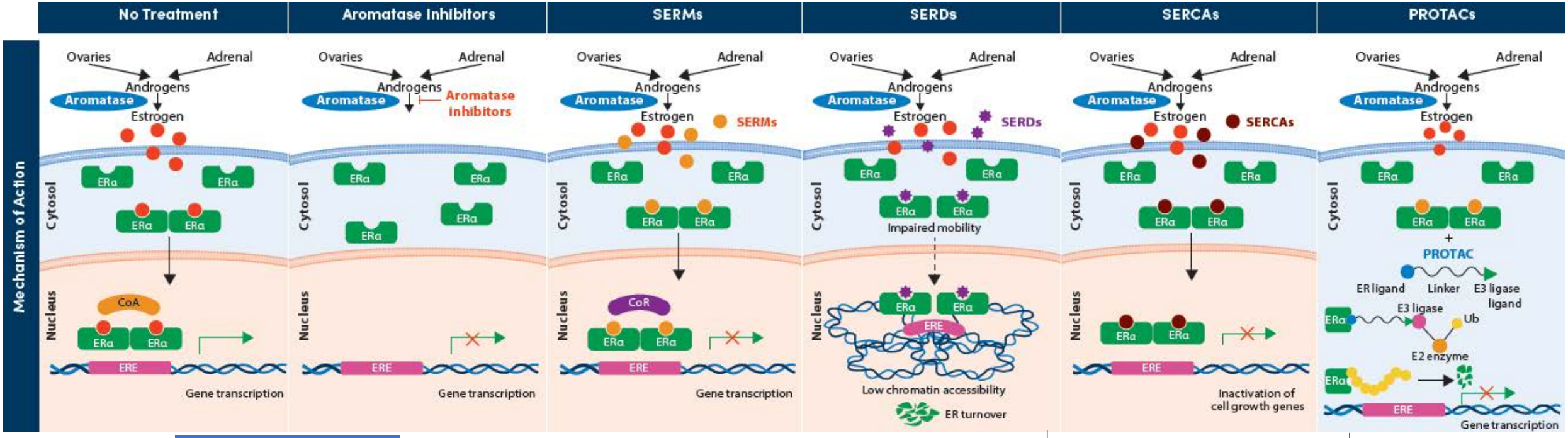
- EMERALD trial reported significantly prolonged PFS with elacestrant vs SOC endocrine therapy in patients with ER+/HER2- ESR1-mutated metastatic breast cancer following progression on prior CDK4/6i and endocrine therapy
- EMERALD is the only oral SERD trial where prior CDK4/6i usage was mandated

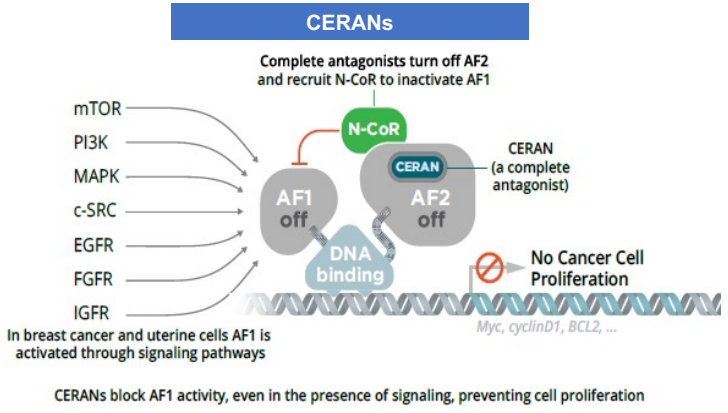
Patient population with exposure to CDK4/6 inhibitor for ≥12 months	% (n)	Median PFS, months (95% CI)		Hazard ratio (95% CI)
		Elacestrant	SOC	
All *ESR1*-mut patients[1]	100 (159)	**8.61** (4.14 – 10.84)	**1.91** (1.87 – 3.68)	**0.410** (0.262 – 0.634)
ESR1-mut and bone metastases[a]	86 (136)	**9.13** (5.49 – 16.89)	**1.91** (1.87 – 3.71)	**0.381** (0.230 – 0.623)
ESR1-mut and liver and/or lung metastases[b]	71 (113)	**7.26** (2.20 – 10.84)	**1.87** (1.84 – 1.94)	**0.354** (0.209 – 0.589)
ESR1-mut and *PIK3CA*-mut[c]	39 (62)	**5.45** (2.14 – 10.84)	**1.94** (1.84 – 3.94)	**0.423** (0.176 – 0.941)
ESR1-mut and HER2-low expression[d]	48 (77)	**9.03** (5.49 – 16.89)	**1.87** (1.84 – 3.75)	**0.301** (0.142 – 0.604)
ESR1-mut and *TP53*-mut	38 (61)	**8.61** (3.65 – 24.25)	**1.87** (1.84 – 3.52)	**0.300** (0.132 – 0.643)

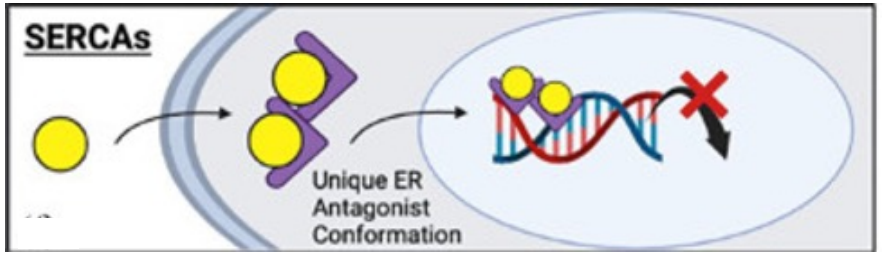
- Benefit of elacestrant is confirmed in patients harboring *ESR1* mutation
- Similar benefit was observed in *PIK3Ca* mutant
- Limited numbers may impact this analysis
- Elacestrant being studied in combination with targeted agents; many new endocrine agents in ongoing trials in metastatic and early-stage disease; early phase combination studies

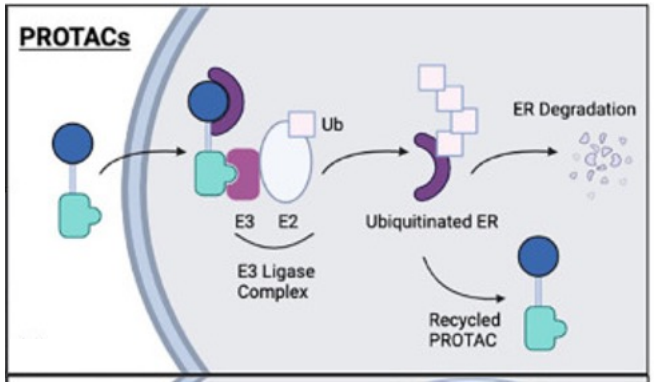
Bardia A, et al. SABCS 2023. Abstract PS17-02

Mechanism of Action of New Endocrine Agents Targeting the ER Domain









1. Hanker AB et al. *Cancer Cell.* 2020;37:496-513 2. Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt:
Inv assessed PFS
of each C arm to F

Post-menopausal ER+/HER2- ABC candidates to receive fulvestrant monotherapy in the ABC setting

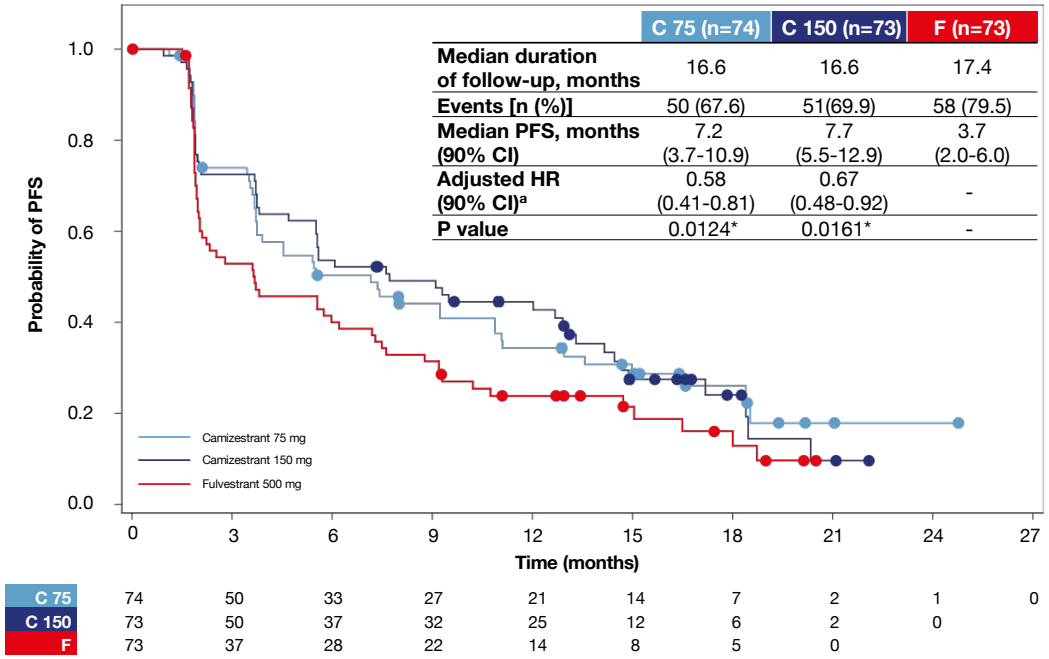
Stratification:
Prior CDK4/6i
Lung/liver mets

R

1:1:1:1
N=240

- camizestrant 300 mg (n=20) (CSP v5 amendment: 16Dec20)
- camizestrant 75 mg (n=74)
- camizestrant 150 mg (n=73)
- fulvestrant (n=73)

Primary endpoint: PFS by investigator assessment



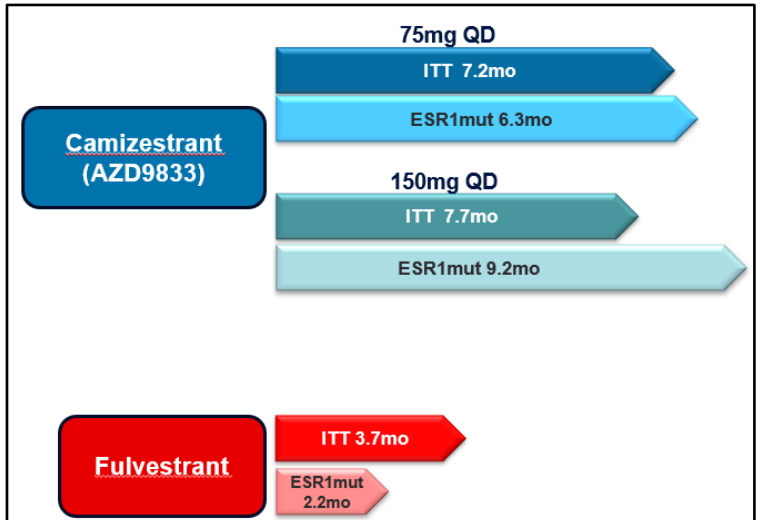
	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

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

Demographics

- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

PFS in pts based on detectable ESR1mut



Oliveira et al, SABCS 2022

Recent Updates In the Novel Endocrine Agents Landscape

	Monotherapy		PI3K Pathway Combinations		CDK4/6i Combinations		
	Imlunestrant	OP-1250 (CERAN)	Imlunestrant + alpelisib	Imlunestrant + everolimus	Vepdegestrant (ARV471/PROTAC) + palbociclib	Palazestrant (OP-1250/CERAN) + palbociclib	Imlunestrant + abemaciclib
N	114	86	21	42	31	19	42
ESR1 mutant	49%	48%	47%	48%	43%	52%	7%
Median Prior Tx	2	2	1	1	4	1	0
% Prior CDK4/6i	93%	97%	100%	100%	87%	72%	0%
% Prior Fulv	52%	66%	43%	31%	80%	11%	5%
% Prior chemo	25%	31% (met)	14%	19%	76% (46% met)	22%	10%
ORR	**8%**	**3%**	**58%**	**21%**	**42%**	**10.5%** (21% incl. uPR)	**32%**
CBR	**42%**	**40%**	**62%**	**62%**	**63%**	**46%**	**71%**
PFS	**4.3** (6.5 2L post CDK4/6i)	**4.6** (7.2 2L/3L)	**9.2**	**15.9**	**11.1**	N/R	**19.2**

N/R = not reported.

Courtesy of Jhaveri

1.Jhaveri et al ASCO 2022; 2. Lin et al ESMO 2023 #382MO, 3. Jhaveri et al ESMO 2023 #383MO, 4. Hurvitz et al SABCS 2023 PS-15-03, 5. Chan et al SABCS 2023 PS-15-04, 6. Jhaveri et al SABCS 2023 PS15-09

Additional Phase III SERD Trials for MBC: Examples

EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

- Imlunestrant 400 mg PO QD (Arm A)
- Investigator's choice ET Fulvestrant or Exemestane (Arm B)
- Imlunestrant 400 mg PO QD + Abemaciclib 150 mg PO BID (Arm C)

Primary Objective:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

R 1:1

- Giredestrant 30mg QD Palbociclib 125mg Letrozole-matched PLA
- Letrozole 2.5mg Palbociclib 125mg Giredestrant-matched PLA

PFS

Recruiting

NCT04546009

SERENA-4

N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

R 1:1

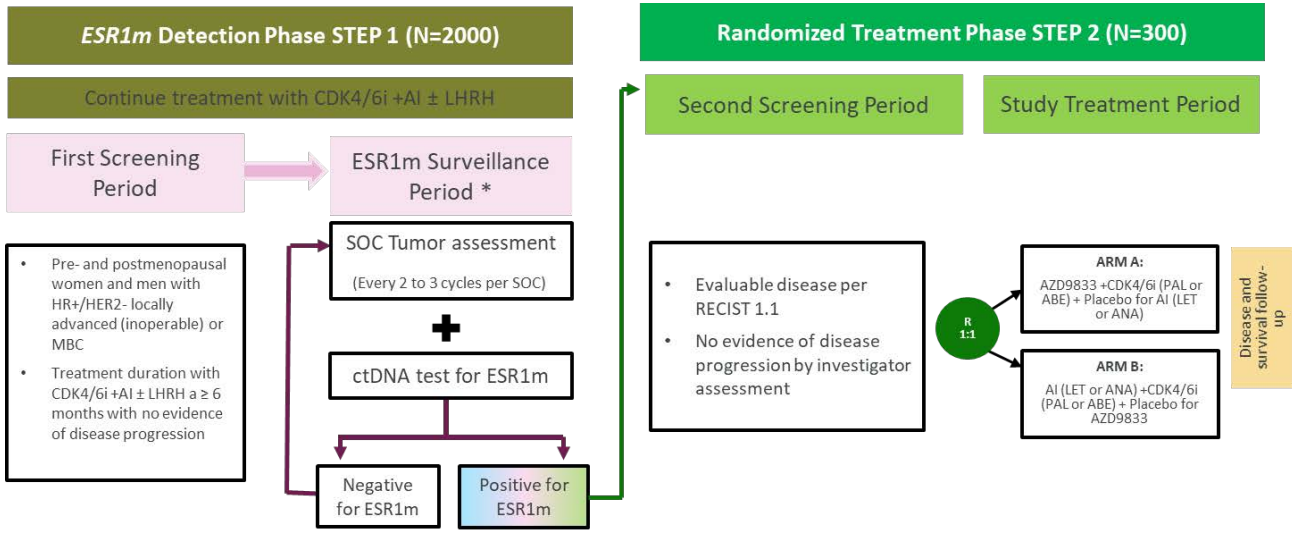
- Camizestrant 75mg QD Palbociclib 125mg Anastrozole-matched PLA
- Anastrozole 1mg Palbociclib 125mg Camizestrant-matched PLA

PFS

Recruiting

NCT04711252

SERENA-6



Select Clinical Trials with ER Targeting Agents

	SERD				PROTAC	CERAN
	Giredestrant	**Camizestrant**	**Imlunestrant**	**Elacestrant**	**Vepdegestrant**	**Palazestrant**
METASTATIC SETTING						
1L: Combination with CDK4/6i	persevERA: NCT04546009 **(Phase 3)**	SERENA-4: NCT04711252 **(Phase 3)**	EMBER-1: NCT04188548 **(Phase 1)**		VERITAC-3 NCT05909397 **(Phase 3)**	
2L: Combination with CDK4/6i	pionERA (NCT06065748) **(Phase 3)**	SERENA-6 NCT04964934 **(Phase 3-ESR1m (switch)**		**ELEVATE (NCT05563220) (Phase 1b/II; also EVE & CAPI**	**TACTIVE-U (phase Ib/II, multiple studies)**	
Post CDK 4/6 inhibitor	evERA NCT05306340 **(Phase 3, EVE)**	SERENA-2: NCT04214288 **(Phase 2)**	EMBER-3: NCT04975308 **(Phase 3)**	EMERALD NCT03778931 **(Phase 3)**	VERITAC-2 NCT05654623 **(Phase 3)**	OPERA-01 NCT06016738 **(Phase 3)**
EARLY-STAGE SETTING						
Pre-operative setting	coopERA: NCT04436744 **(Phase 2)**	SERENA-3: NCT04588298 **(Phase 2)**	EMBER-2: NCT04647487 **(Phase 1)**		TACTIVE-N: NCT05549505 **(Phase 2)**	
Adjuvant setting (upfront)	lidERA NCT04961996 **(Phase 3)**	CAMBRIA-2 NCT05952557 **(Phase 3)**	EMBER-4: NCT05514054 **(Phase 3)**			
Adjuvant setting (switch)		CAMBRIA-1 NCT05774951 **(Phase 3)**				

Results available

Trial completed accrual

*

Adapted from Hamilton

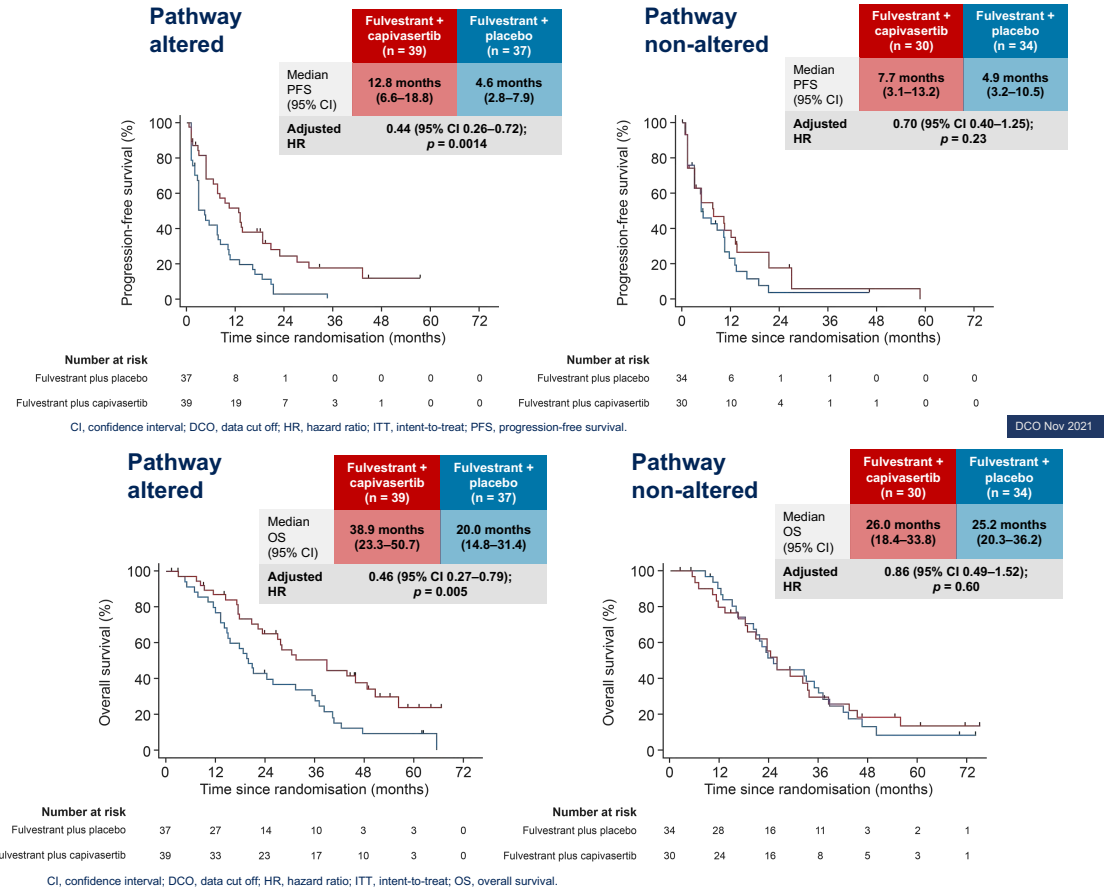
Inhibiting AKT

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*
  - May also occur in cancers without these genetic alterations
  - AKT signalling implicated in development of ET resistance
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)

Turner et al, SABCS 2022; Jones RH, et al. Lancet Oncol 2020; Howell et al, Lancet Oncology 2022

Phase II FAKTION Trial

- Adding Capi to Fulv in PM women with AI resistant HR+ MBC (no prior CDKi) improved PFS and OS, with most benefit in altered population



CAPItello-291:

Phase III, randomized, double-blind, placebo-controlled study

Patients with HR+/HER2– ABC

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

R1:1 (N=708)

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

Capivasertib	400 mg twice daily, 4 days on, 3 days off
43.7% altered	
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
37% altered	
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

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

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, NEJM 2023;388(22):2058-2070.

AKT Pathway Alterations: Tissue Only

Alteration; n (%)			
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Postanalytical failure		9 (2.5)	10 (2.8)

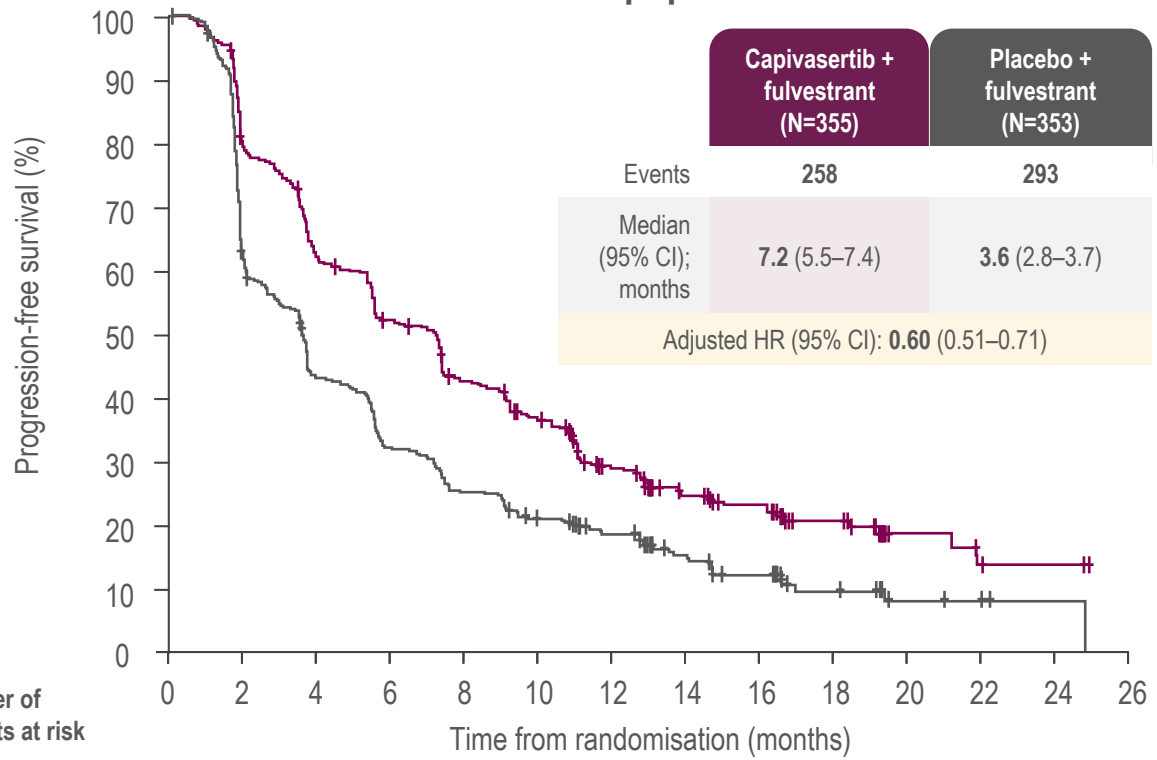
AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al, NEJM 2023;388(22):2058-2070.

Dual primary endpoint: PFS in overall and AKT pathway-altered populations[1]

Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered populations

Overall population

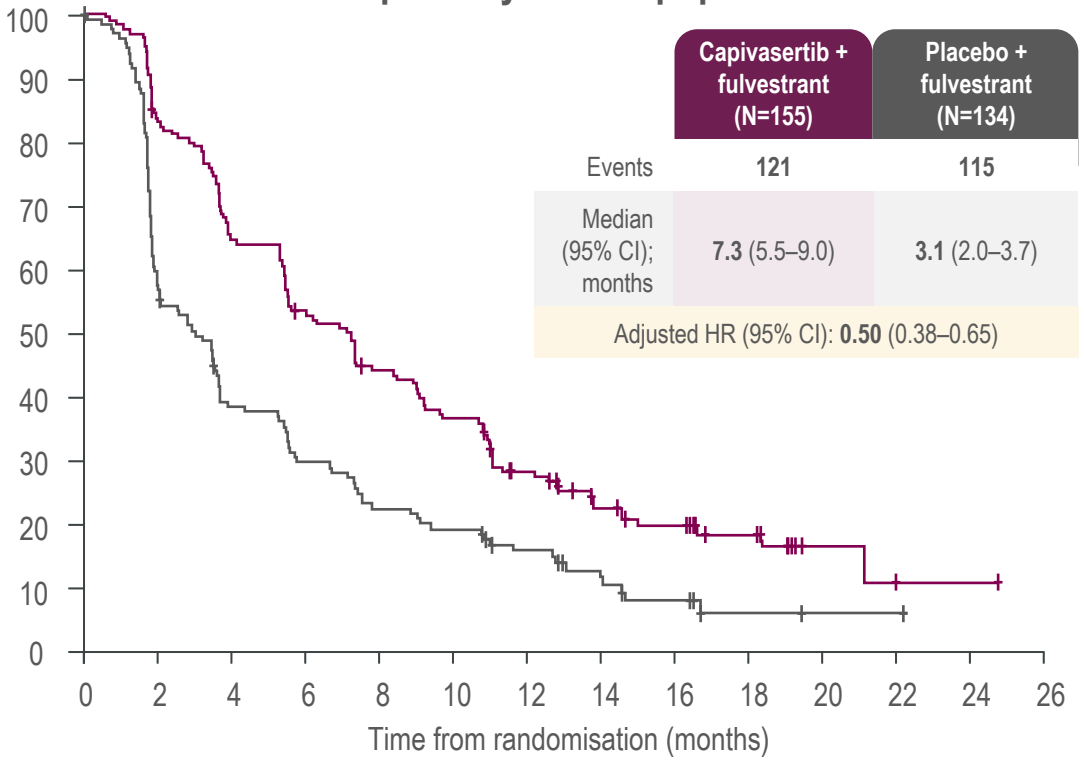


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Events	258	293
Median (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI): **0.60** (0.51–0.71)		

Number of patients at risk

Capivasertib + fulvestrant	355	226	207	172	138	115	78	55	43	25	8	5	2	0
Placebo + fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Events	121	115
Median (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI): **0.50** (0.38–0.65)		

Capivasertib + fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

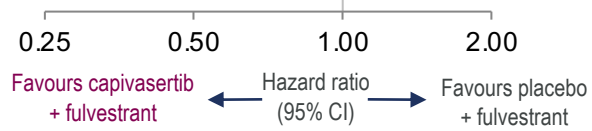
. + indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

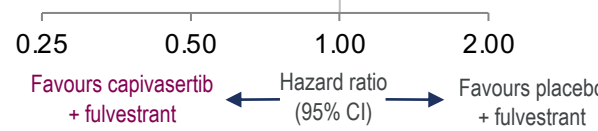
Turner et al, NEJM 2023;388(22):2058-2070

Summary of PFS by subgroups

Consistent clinically meaningful benefit with capivasertib + fulvestrant was observed across clinically relevant subgroups in both the overall population and AKT pathway-altered population

		Overall population				AKT pathway-altered population			
			Median PFS, months				Median PFS, months		
		n	Capivasertib + fulvestrant	Placebo + fulvestrant		n	Capivasertib + fulvestrant	Placebo + fulvestrant	
Overall[a]		708	7.2	3.6		289	7.3	3.1	
Prior CDK4/6 inhibitor[b]	Yes	496	5.5	2.6		208	5.5	2.0	
	No	212	10.9	7.2		81	11.0	7.4	
Prior chemotherapy for ABC[b]	Yes	129	3.8	2.1		53	4.0	2.0	
	No	579	7.3	3.7		236	7.4	3.5	
Liver metastases at baseline[b]	Yes	306	3.8	1.9		123	5.5	1.8	
	No	402	9.2	5.5		166	9.1	3.7	



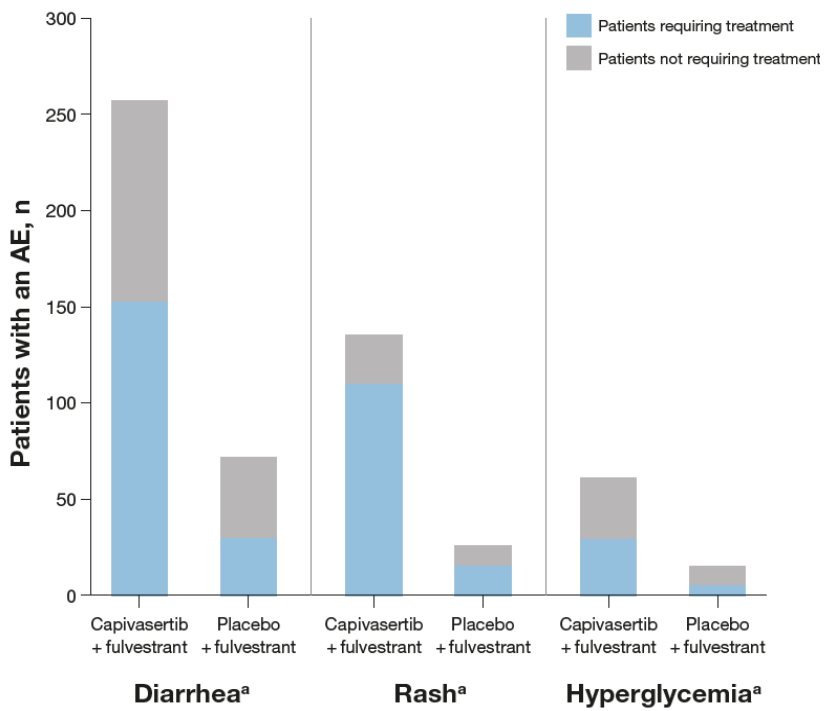


[a]HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region. [b]HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and geographic region (prior CDK4/6 inhibitor subgroup), the presence of liver metastases and prior use of CDK4/6 inhibitor (prior chemotherapy for ABC subgroup [overall population]) and prior use of CDK4/6 inhibitor only (prior chemotherapy for ABC subgroup [AKT pathway-altered population] and liver metastases subgroup).

Oliveira et al, ESMO BC 2023

CAPItello-291: Safety Analysis

AE; n (%)	Capivasertib + fulvestrant (n=355)					Placebo + fulvestrant (n=350)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea[a]	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	71 (20.3)	61 (17.4)	9 (2.6)	1 (0.3)	0
Rash[a]	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Hyperglycemia[a]	60 (16.9)	26 (7.3)	26 (7.3)	7 (2.0)	1 (0.3)	14 (4.0)	8 (2.3)	5 (1.4)	1 (0.3)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0



AEs leading to:

- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

Median time to onset, Days

- Diarrhea: 8 (2-22)
- Rash: 12 (10-15)
- Hyperglycemia: 15 (1-51)

AEs leading to discontinuation

- Diarrhea: 2%
- Rash 4.5%
- Hyperglycemia: 0.3%

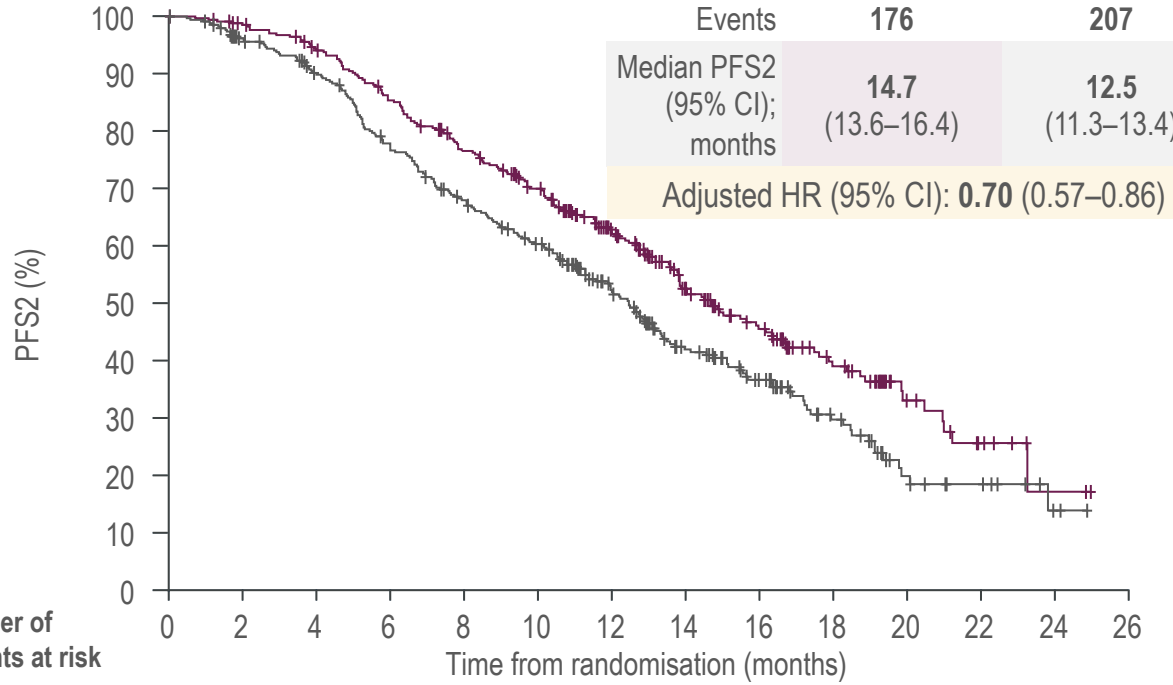
Rugo et al, ASCO 2023

Progression-free survival 2 (PFS2)

Extended treatment benefit (PFS2) with capivasertib-fulvestrant observed in the overall and the *PIK3CA*/*AKT1*/*PTEN*-altered populations

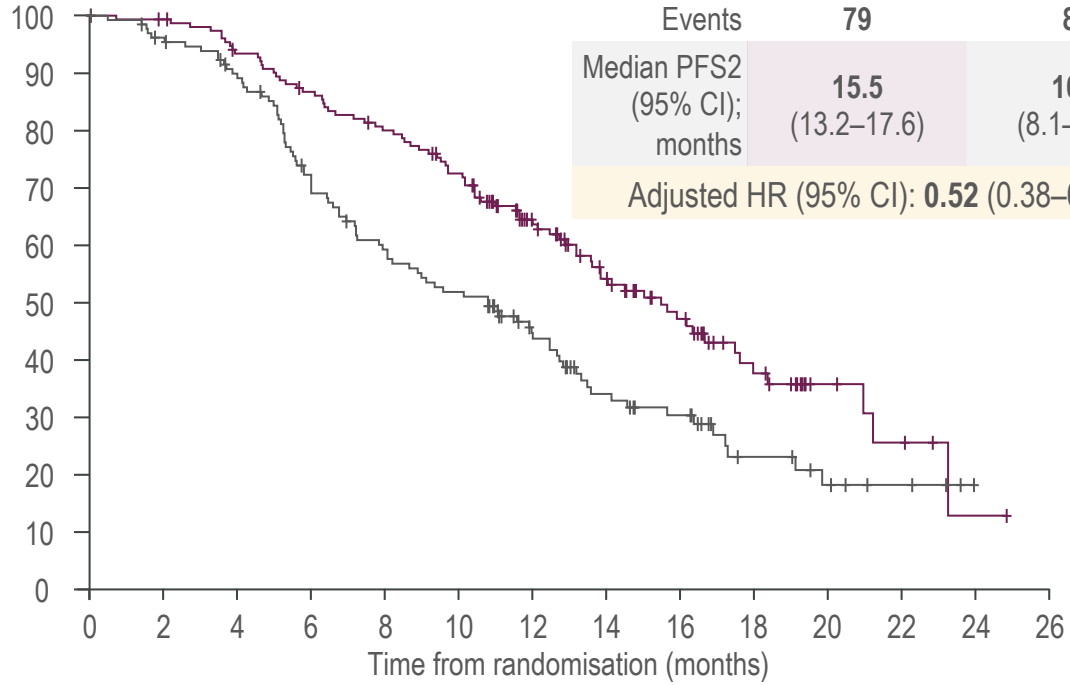
Overall population

	Capivasertib-fulvestrant (N=355)	Placebo-fulvestrant (N=353)
Events	176	207
Median PFS2 (95% CI); months	14.7 (13.6–16.4)	12.5 (11.3–13.4)
Adjusted HR (95% CI): **0.70** (0.57–0.86)		



PIK3CA/*AKT1*/*PTEN*-altered population

	Capivasertib-fulvestrant (N=155)	Placebo-fulvestrant (N=134)
Events	79	87
Median PFS2 (95% CI); months	15.5 (13.2–17.6)	10.8 (8.1–12.7)
Adjusted HR (95% CI): **0.52** (0.38–0.71)		



Number of patients at risk

Capivasertib-fulvestrant	355	334	315	283	248	218	164	108	78	48	20	11	2	0
Placebo-fulvestrant	353	321	294	252	216	185	137	88	63	33	14	9	2	0

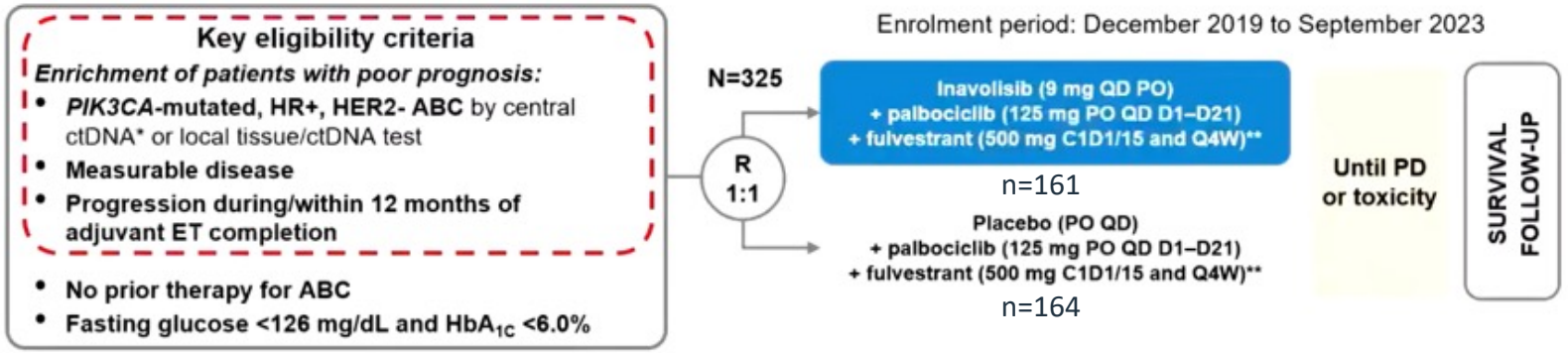
Capivasertib-fulvestrant	155	151	140	129	118	105	76	53	38	22	8	5	1	0
Placebo-fulvestrant	134	124	113	89	72	63	45	29	22	11	7	4	0	0

PFS2 defined as the time from randomisation to second progression (i.e. the earliest of either death or a progression event following treatment start after first progression).
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.

Summary: Capivasertib and Fulvestrant

- Capivasertib/fulvestrant vs Pla/fulvestrant improved PFS in the overall population and in patients with tumor PIK3CA altered population; overall survival immature
- Efficacy in the subset of patients with non-altered tumors encouraging
  - Trial was not powered to look at this subgroup; small group with unknown mutation profile hard to take into account
- Benefit seen across subgroups including those with prior CDK4/6i and with visceral metastases
- Safety
  - Overall well tolerated, low rate of hyperglycemia
- Data to be considered for regulatory approval
- Additional studies
  - **CAPItello-292** (NCT04862663): Fulvestrant/Palbociclib +/- Capi; now being evaluated with ribociclib and abemaciclib combinations
  - Inavolisib: INAVO120! Ongoing comparison with alpelisib
  - Dual inhibitor of mTOR and PIK3CA: Gedatolisib (VIKTORIA-1)
  - New mutation specific PIK3CA inhibitors: LOX783, RLY-2608 and more!

INAVO120 (Phase 3): Inavolisib + palbociclib and fulvestrant for PIK3CA-mutated HR+, HER2– metastatic breast cancer



Patients remaining on treatment
- Inavolisib/palbociclib/fulvestrant, n=67 (42%)
- Placebo, palbociclib/fulvestrant, n=49 (30%)

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

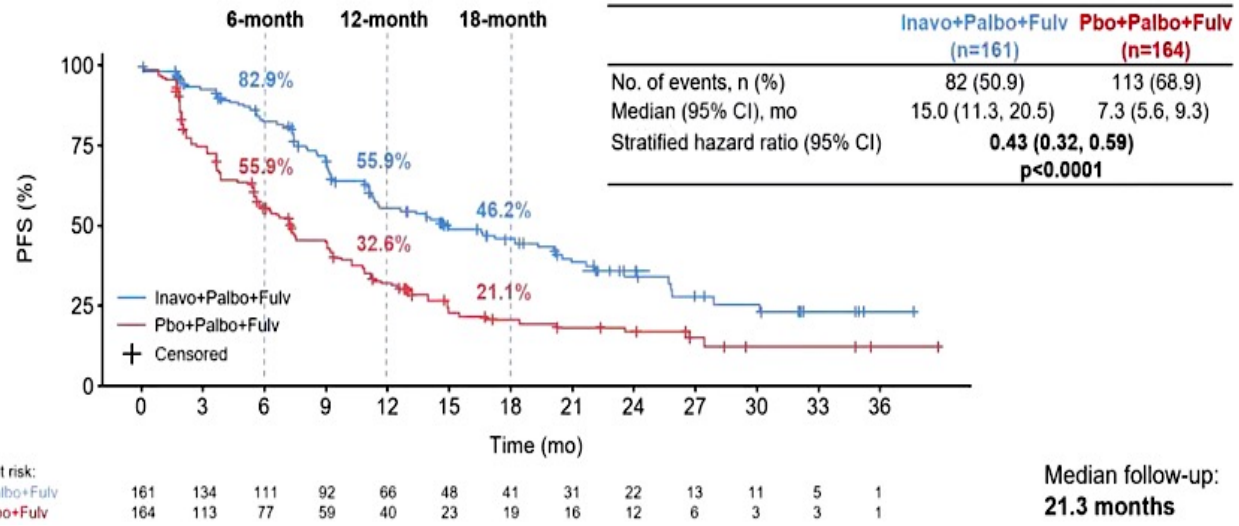
Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**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%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

Jhaveri KL, et al. SABCS 2023. Abstract GS03-13

INAVO120: Efficacy

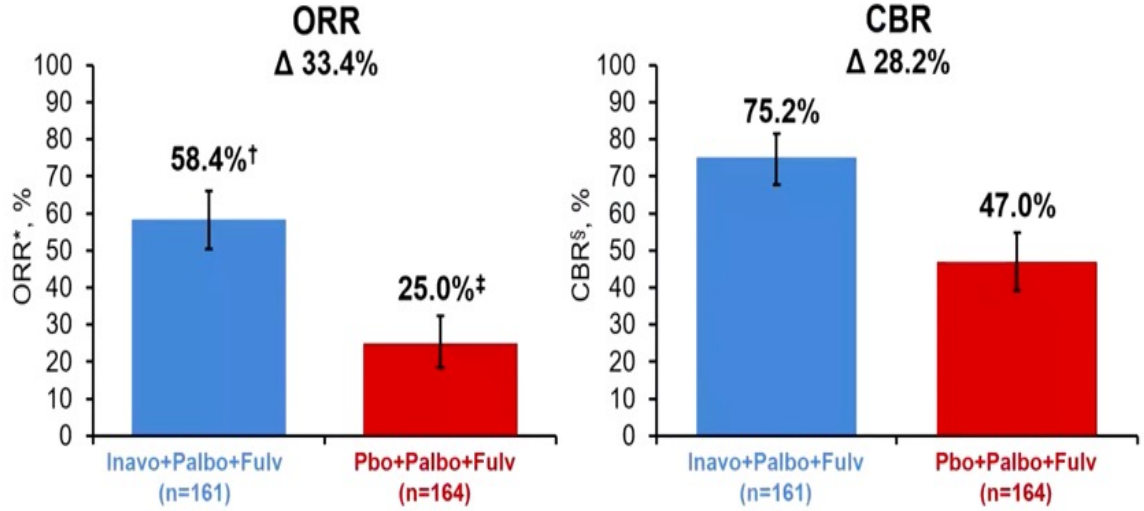
Primary endpoint: PFS (investigator-assessed)



	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**	

Median follow-up: **21.3 months**

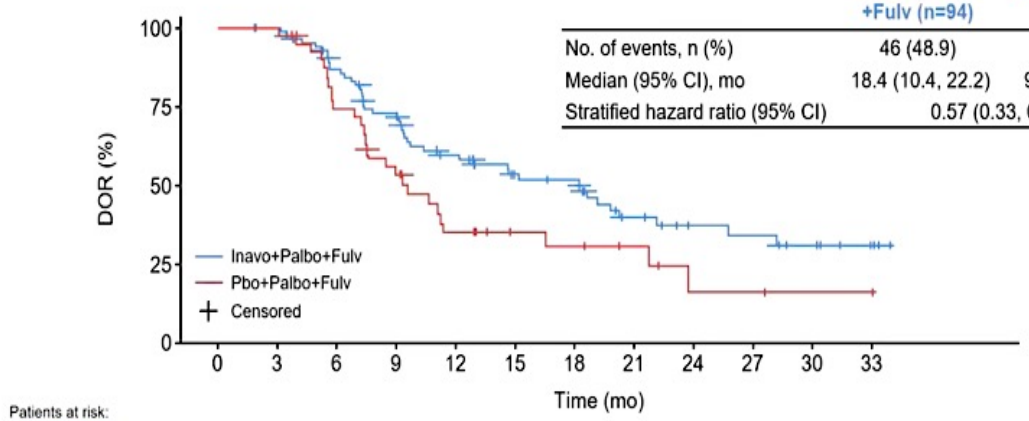
ORR and CBR (investigator-assessed)



OS, interim analysis, immature (median follow-up 21.3 months)

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

DOR (investigator-assessed)



	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	

Median follow-up: **21.3 months**

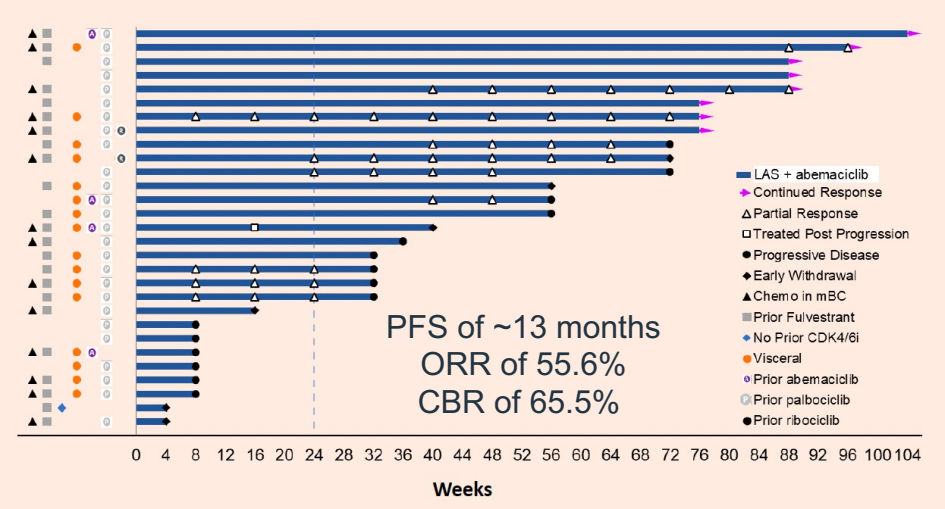
Jhaveri KL, et al. SABCS 2023. Abstract GS03-13

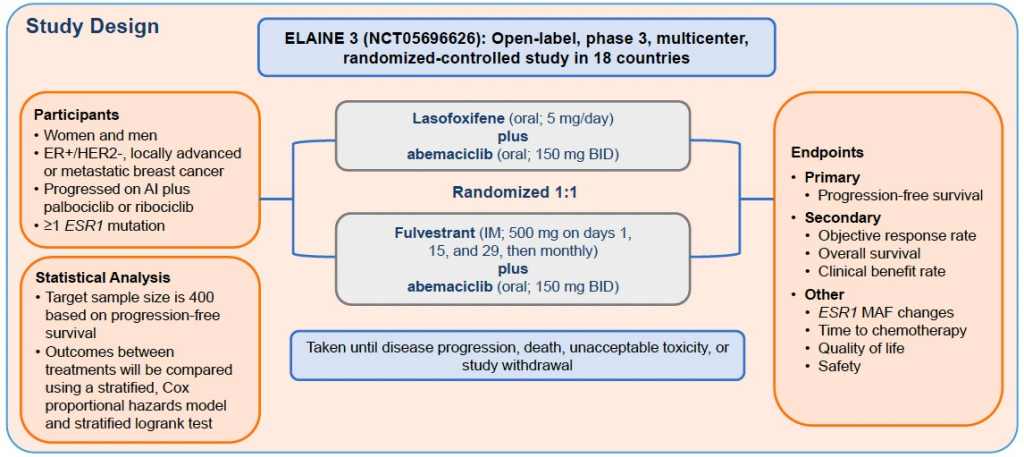
Novel SERM and CDK after CDK

Lasofoxifene

– oral, next-generation ET and breast ER antagonist

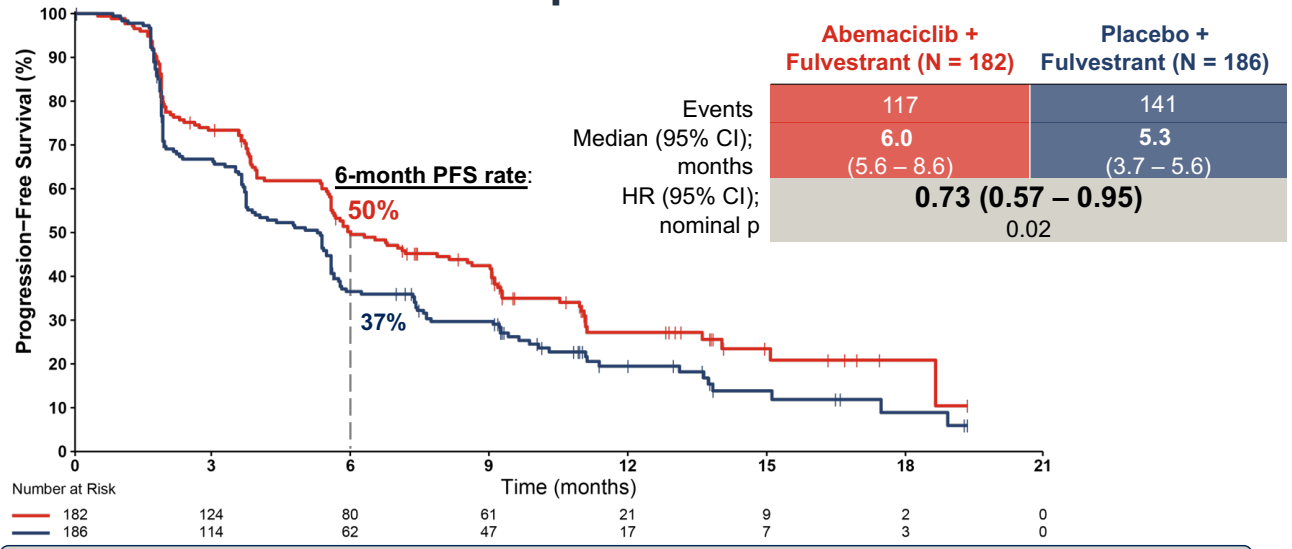
Patient response in ELAINE 2
(PD on ET/CCK4/6i, ESR1 mutation)





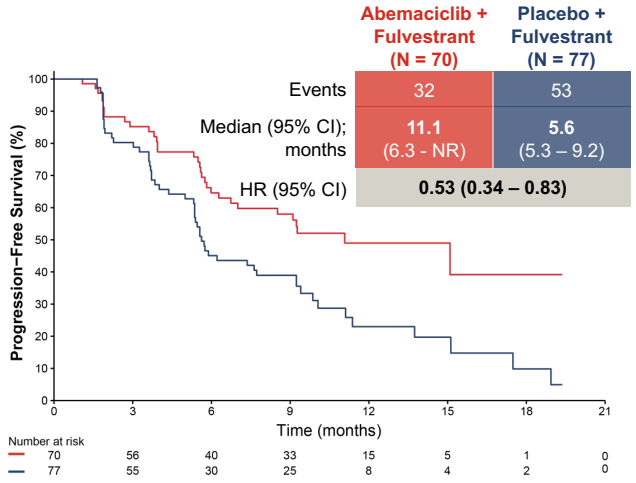
Goetz et al, SABCS 2023

Phase 3 postMONARCH trial

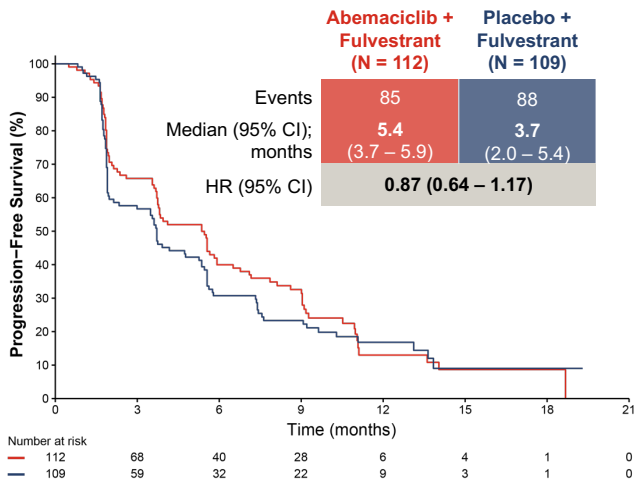


Abemaciclib led to 27% reduction in the risk of developing PFS event

No visceral metastasis



Visceral metastasis



Kalinsky et al, ASCO 2024

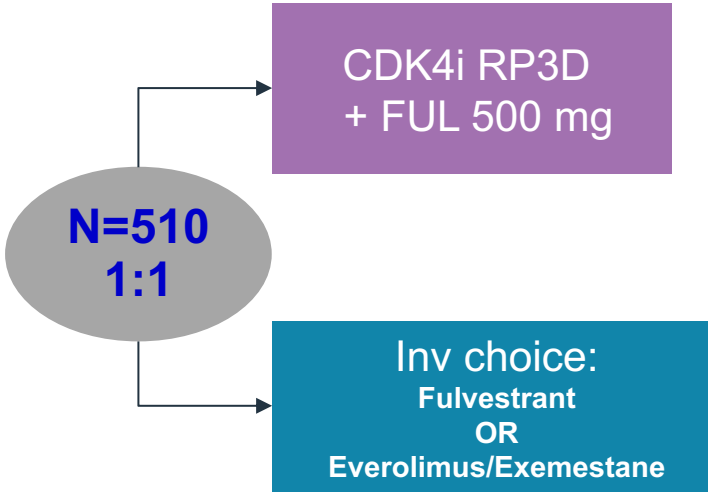
Other Targeted Agents: CDK4 (PF-07220060)

Phase 3 mBC post CDK4/6i

(NCT06105632)

Patients with HR+/HER2- mBC

- Pre/Post menopausal women and men
- Post CDK4/6i either from MBC or EBC as most recent treatment
- No prior Chemo, SERD, mTOR, PI3Ki or AKTi in mBC



Phase 3 first line mBC

Patients with HR+, HER2- mBC

Key eligibility criteria

- Pre/Post menopausal women and men with HR+/HER2- ABC/mBC
- No prior systemic anti-cancer therapy for ABC/mBC
- Measurable disease or bone only disease
- ECOG PS ≤2
- Adequate organ and bone marrow function

Study Endpoints

Co-Primary endpoints

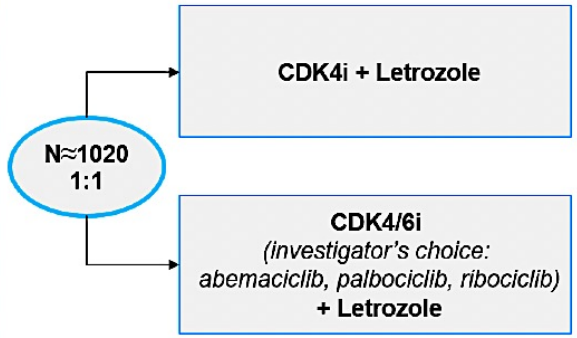
- PFS by BICR
- OR by BICR

Secondary endpoints

- OS [Key Secondary]
- PFS, OR by investigator, CBR, DOR
- Safety/Tolerability
- PRO
- Biomarkers

Exploratory endpoints

- PK



Major Progress
A long way to go…

Thank you!

Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Selection of first-line treatment for patients with triple-negative breast cancer and metastatic recurrence after completion of the KEYNOTE-522 regimen

Dr Laila Agrawal (Louisville, Kentucky)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you typically approach patients with TNBC who have received adjuvant immunotherapy and experienced disease progressed?

Do you generally rechallenge with an anti-PD-1/PD-L1 agent?

How does the disease-free interval affect your thinking in this regard? Is there a minimum amount of time off of adjuvant therapy that you typically look for before rechallenging?

QUESTIONS FOR THE FACULTY

For a patient initially found to have HER2 IHC 1+ disease but on later biopsy is found to have HER2 IHC 0 disease, would you offer T-DXd?

Does HR status affect your approach?

QUESTIONS FOR THE FACULTY

How do you generally sequence T-DXd and sacituzumab govitecan for patients with HER2-low disease?

Does HR status affect your approach?

QUESTIONS FOR THE FACULTY

How was HER2-ultralow defined in DESTINY-Breast06?

Based on the results of this trial, will you be offering your patients with HER2-ultralow disease treatment with T-DXd when you return to the clinic?

Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2 Ultralow Disease

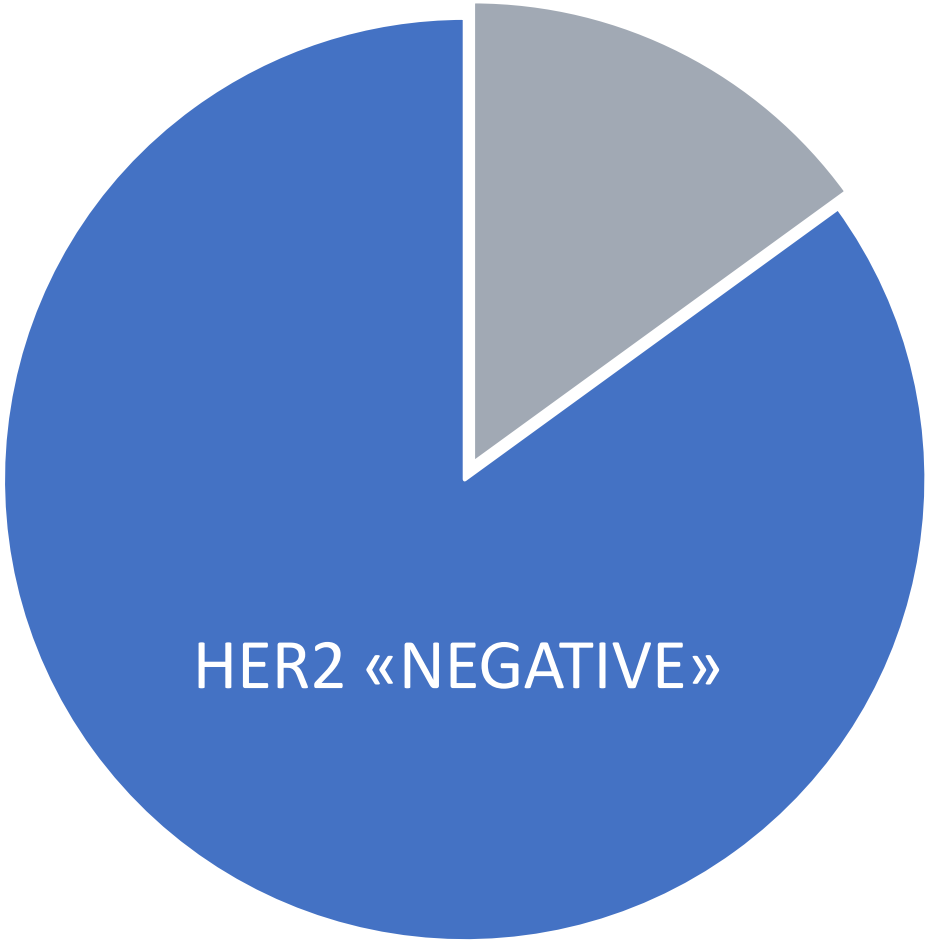
Giuseppe Curigliano, MD, PhD
University of Milano and Istituto Europeo di Oncologia
Milano, Italia

UNIVERSITÀ DEGLI STUDI DI MILANO

IEO Istituto Europeo di Oncologia

New HER2 low segment

The “traditional” HER2 pie chart



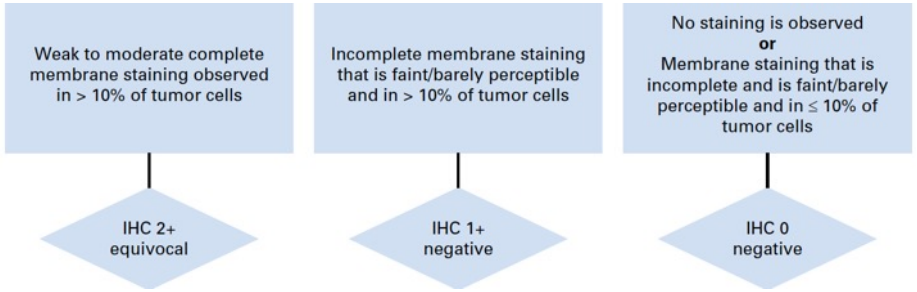
Conversely, those patients lacking ERBB2 amplification are collectively defined **HER2-negative**

ERBB2=Erb-B2 Receptor Tyrosine Kinase 2; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridisation.

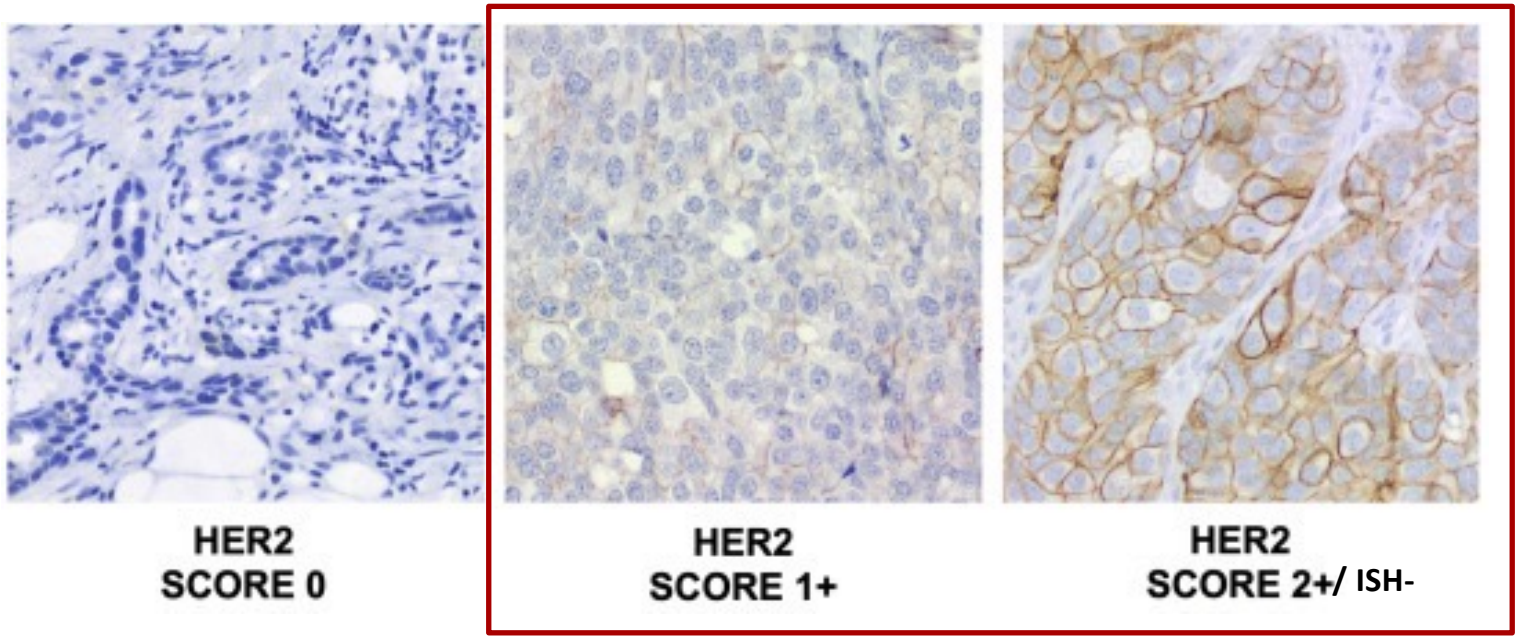
1. Adapted from Wolff A et al. *J Clin Oncol.* 2018 10;36(20):2105-2122.

HER2 « negative »

- 1. Adapted from Marchiò C et al. *Semin*



10,000–1,000,000
HER2 receptors per cell



2020 - Proposal of a new pie chart for HER2

- About 50% of breast cancers are HER2-low according to the current definition

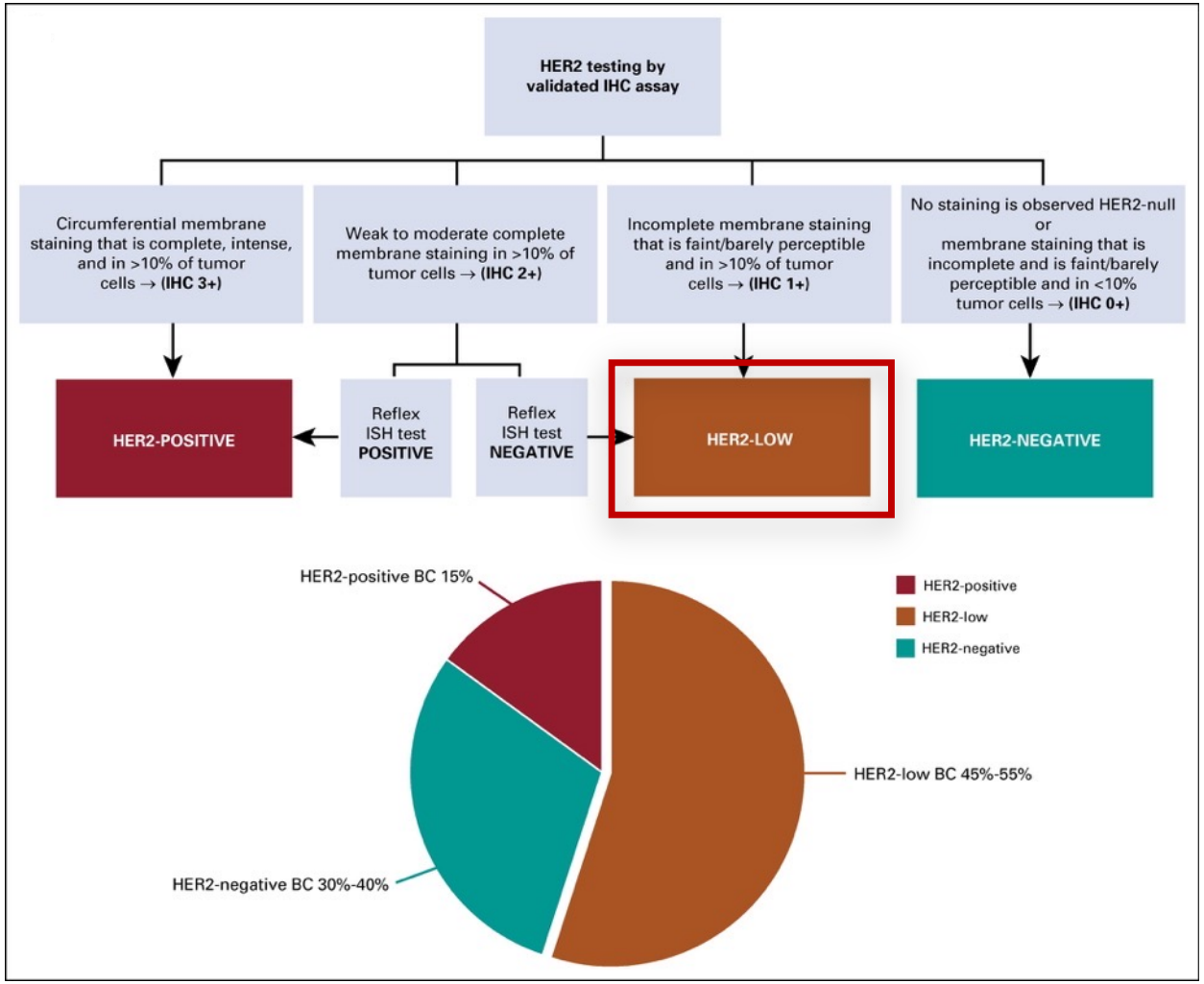
Hormone receptors expressed?

YES

NO

HR+
HER2-LOW
(~60% of HR+ tumours)

TNBC
HER2-low
(~40% of TNBCs)



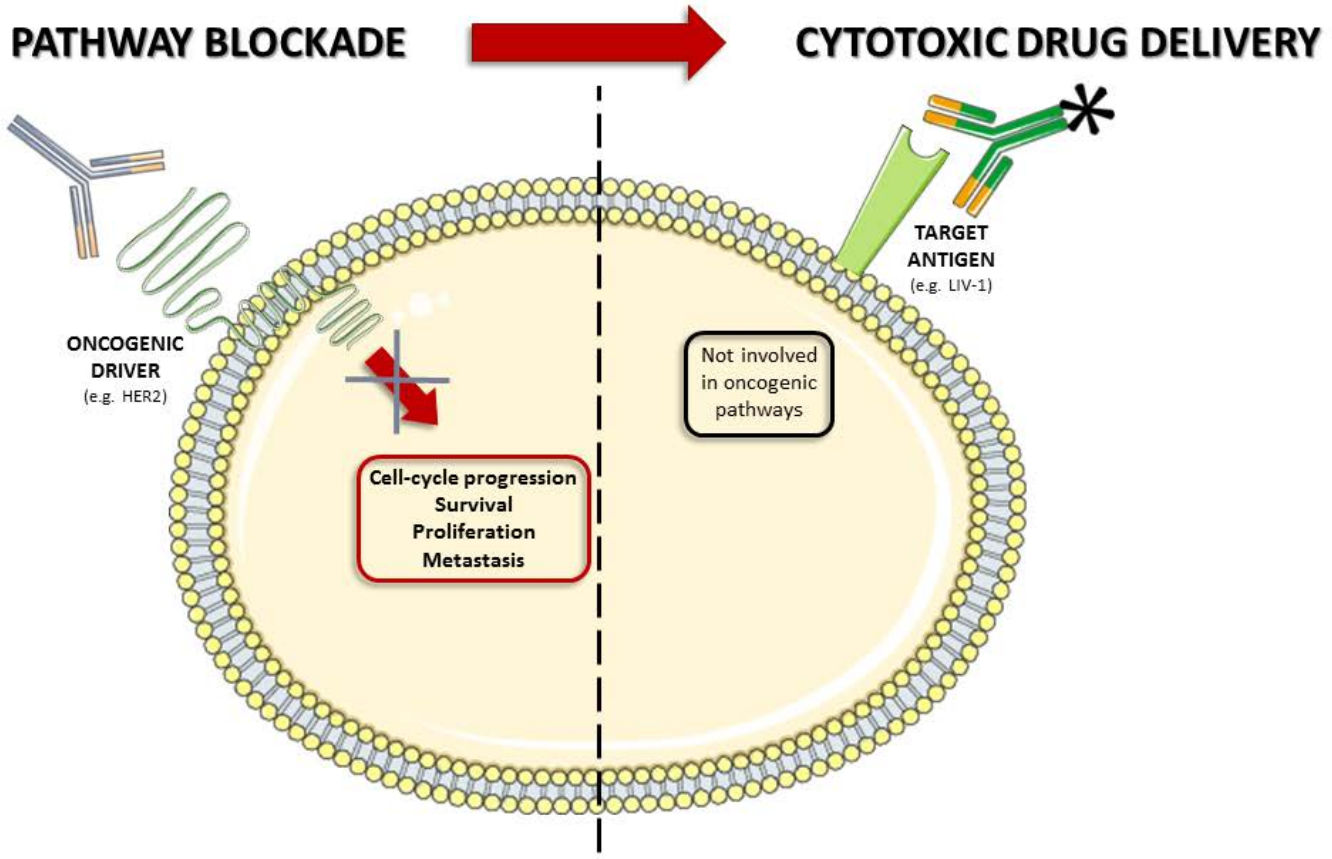
Tarantino P et al. *J Clin Oncol.* 2020;38(17):1951–1962.

HER2-low: distinct entity?

No distinct biology
No distinct prognosis
No benefit with HER2-blockade

But encouraging activity with the delivery of cytotoxic payloads through ADCs.

A randomized trial was needed to confirm this paradigm.



Tarantino P et al. Exp Opin Biol Ther 2020

DESTINY-Breast04 Study Design:

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

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

R 2:1

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

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

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

Primary endpoint
- PFS by BICR (HR+)

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

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

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

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Modi S et al. ESMO 2023;Abstract 376O.

Patient characteristics

60% HER2 1+, 40% HER2 2+ /ISH-

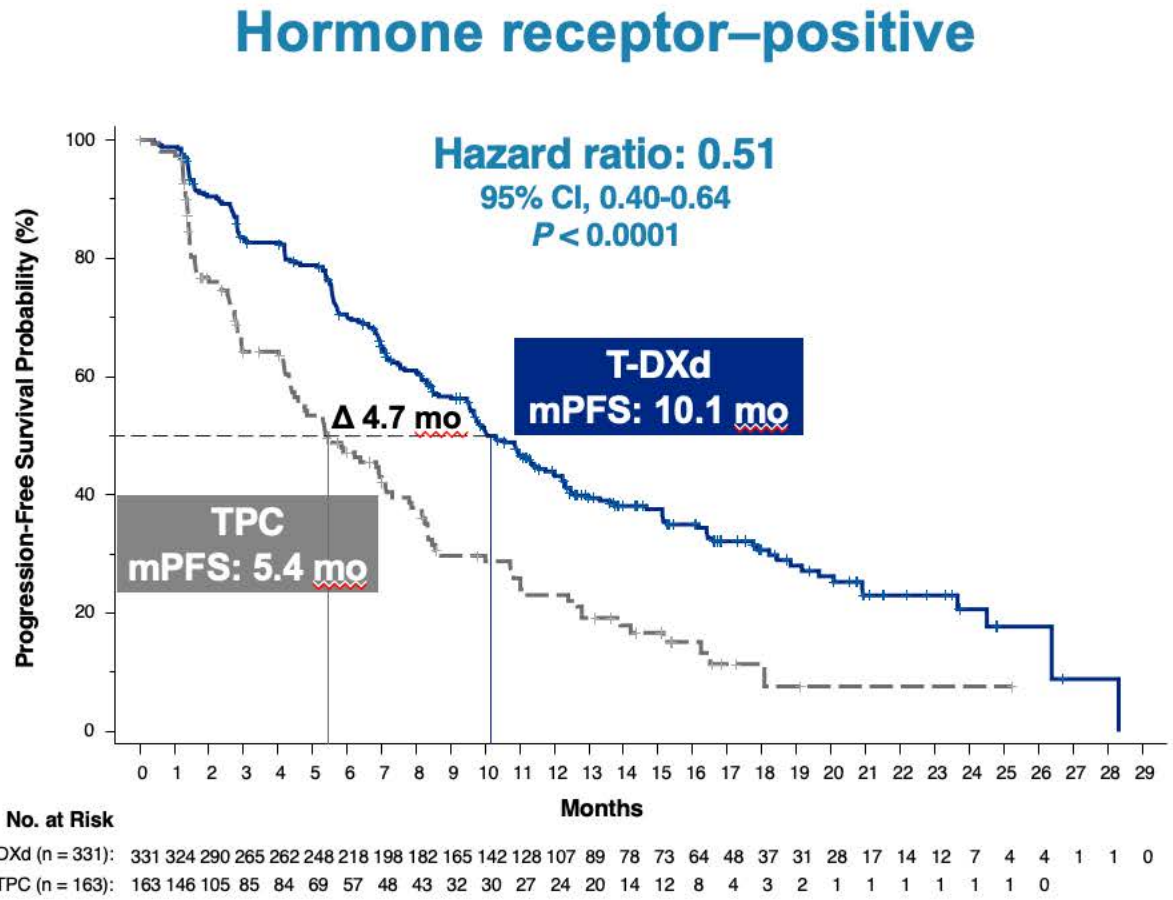
90% HR+ (n=499), 10% TNBC (n=58)

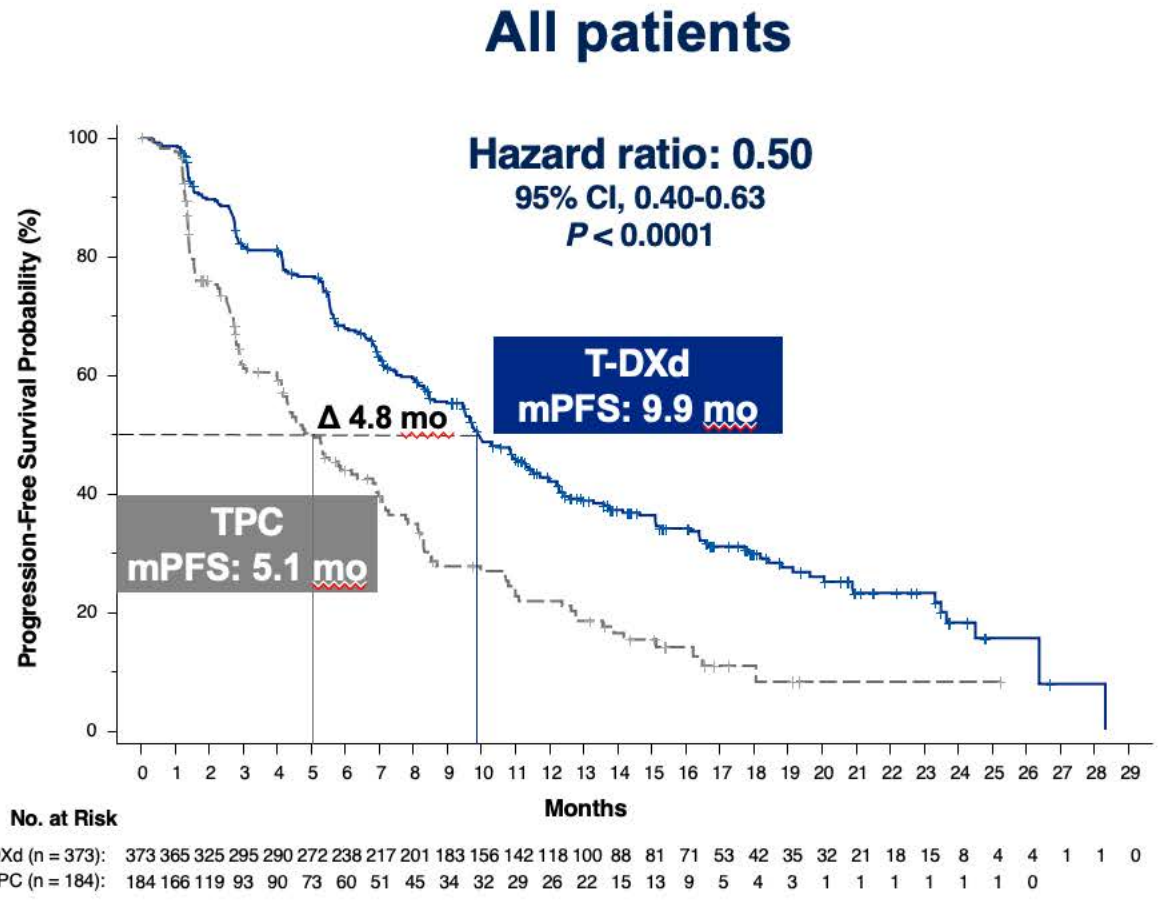
Median of 2 prior lines of ET and 1 chemo

70% of HR+ received prior CDK4/6 inh

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

PFS in HR+ and in All Patients

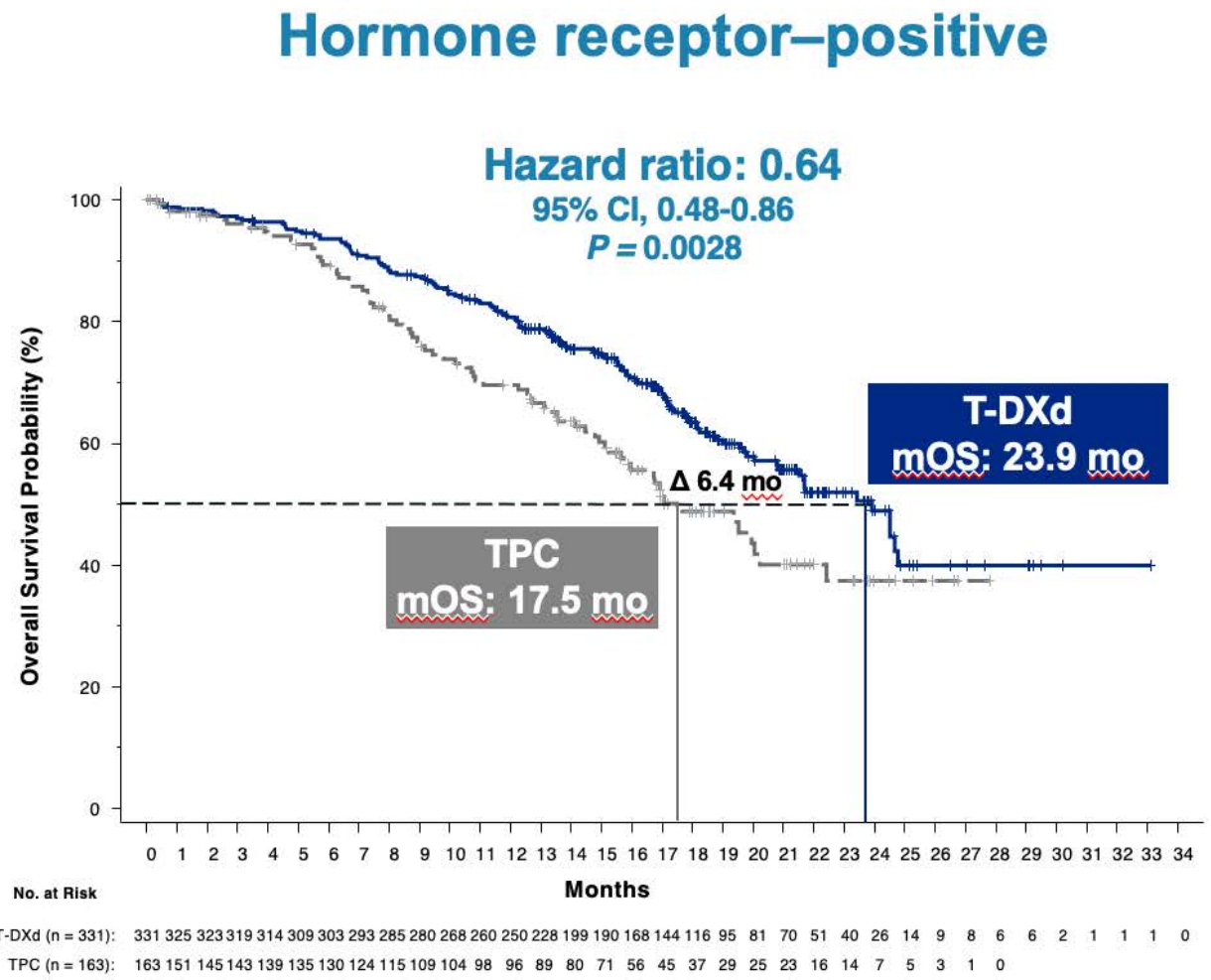


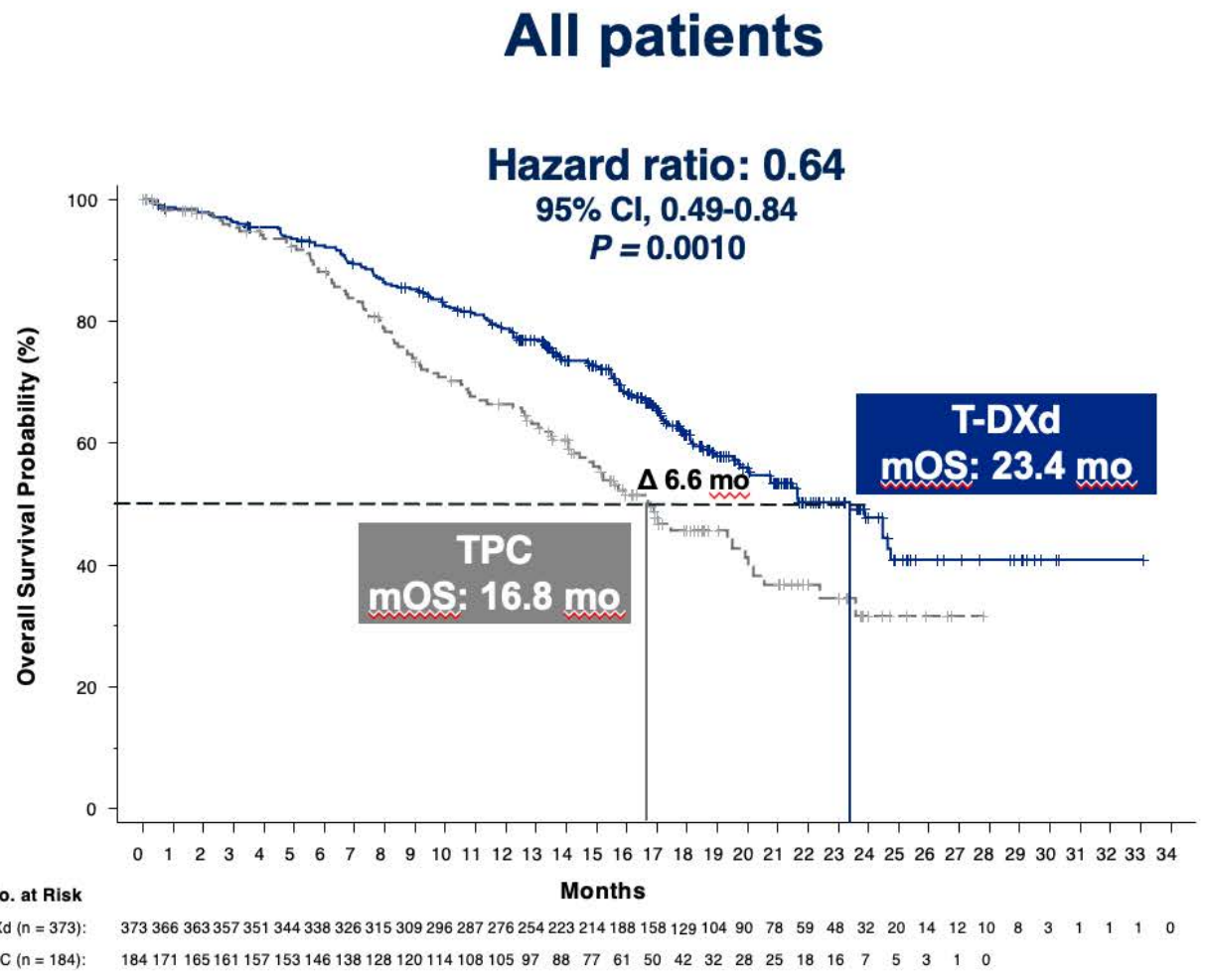


TPC: eribulin (51.1%), capecitabine (20.1%), nab-paclitaxel (10.3%), gemcitabine (10.3%), or paclitaxel (8.2%)

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. NEJM 2022;387(1):9-20.

OS in HR+ and in All Patients

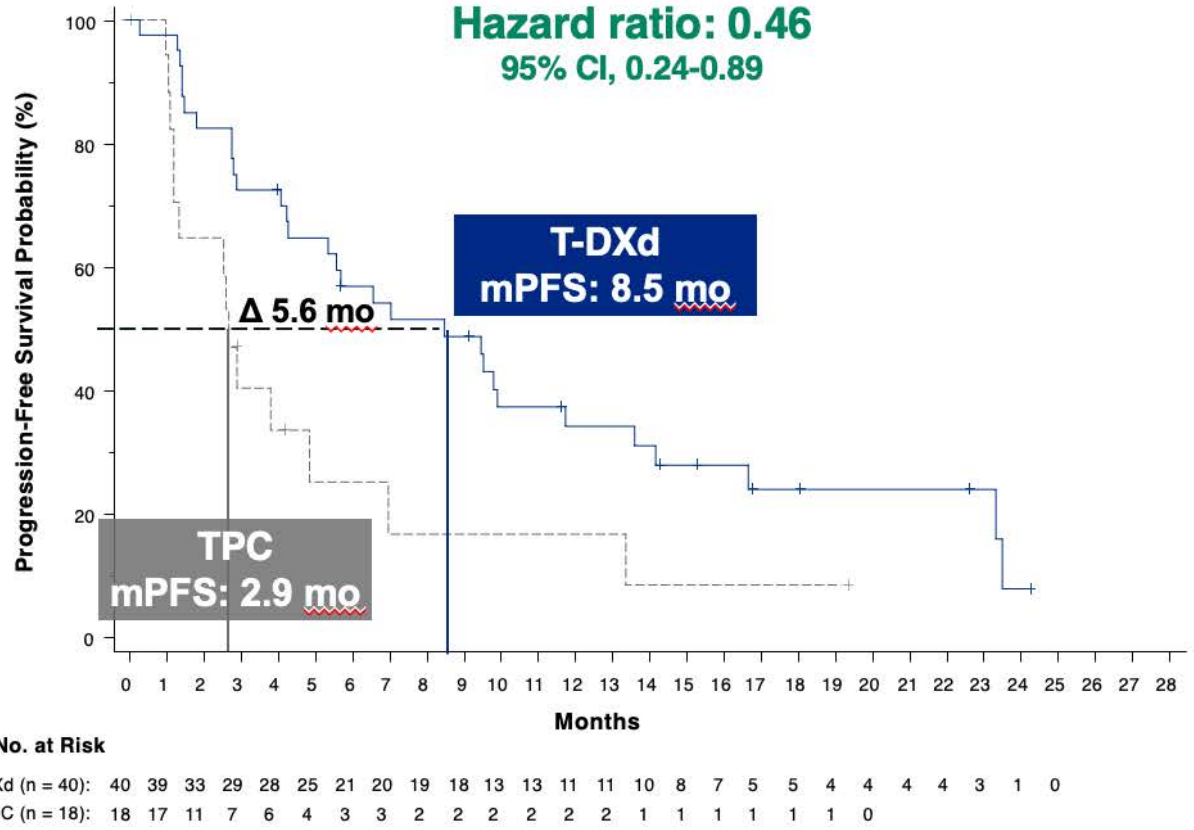




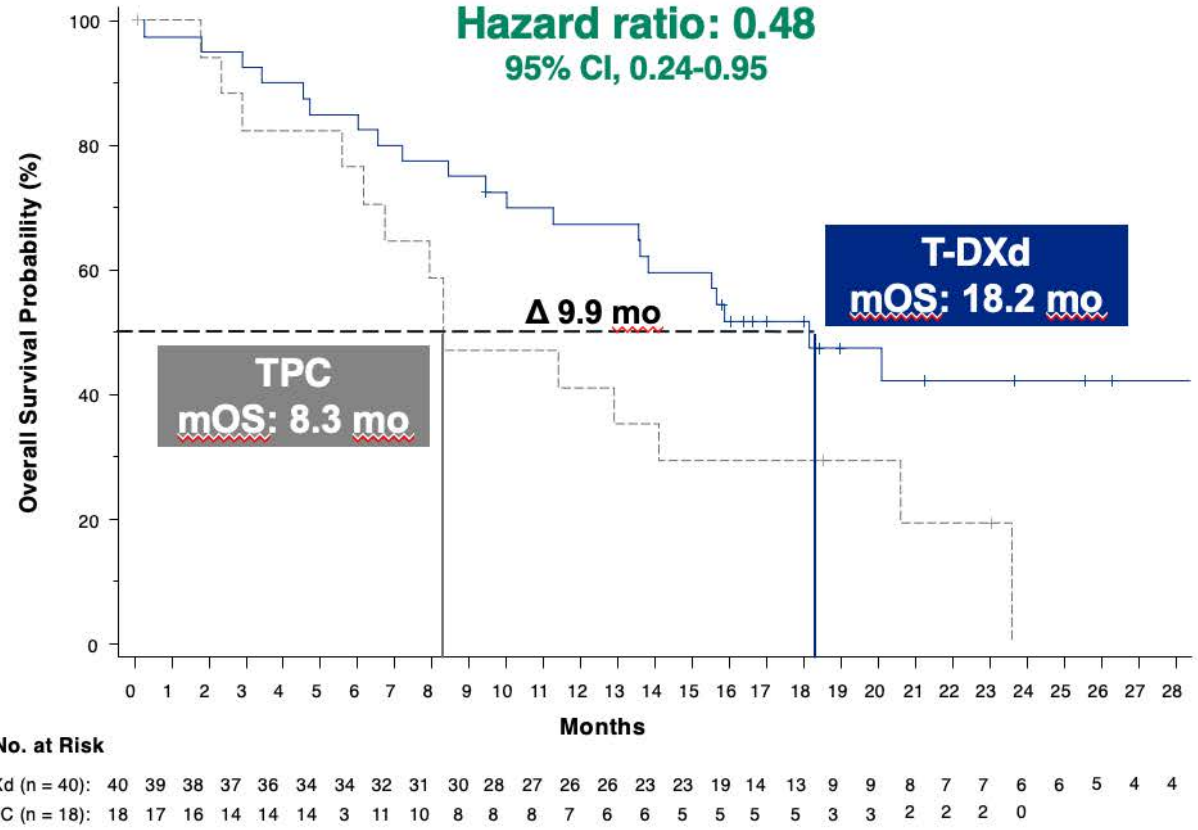
Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. NEJM 2022;387(1):9-20.

PFS and OS in HR– (Exploratory Endpoints)

PFS

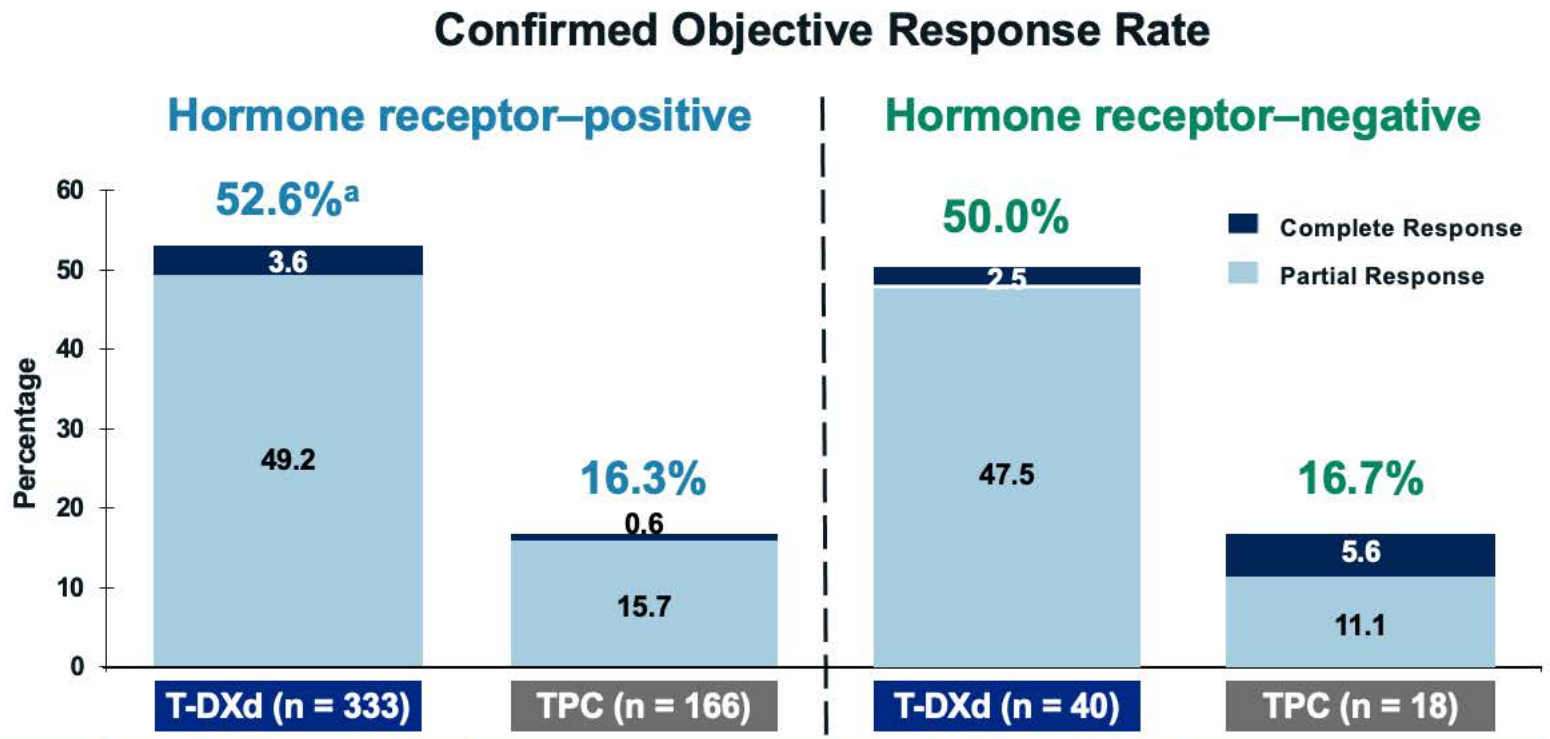


OS



Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. NEJM 2022;387(1):9-20.

ORR in HR+ and HR-

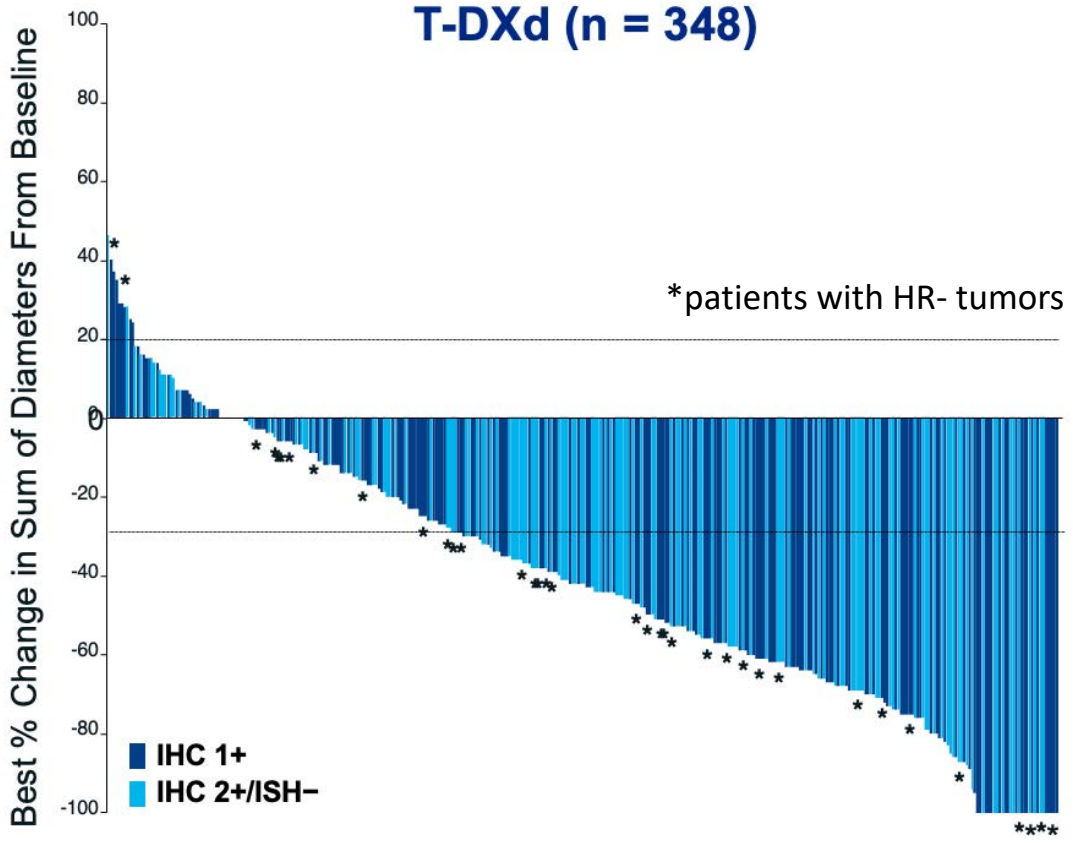


Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. NEJM 2022;387(1):9-20.

Activity in IHC 1+ vs 2+/ISH-

Similar activity in terms of response rate and duration of PFS was observed in patients with IHC 1+ and 2+/ISH- disease



Subgroup Analysis: PFS in HR+

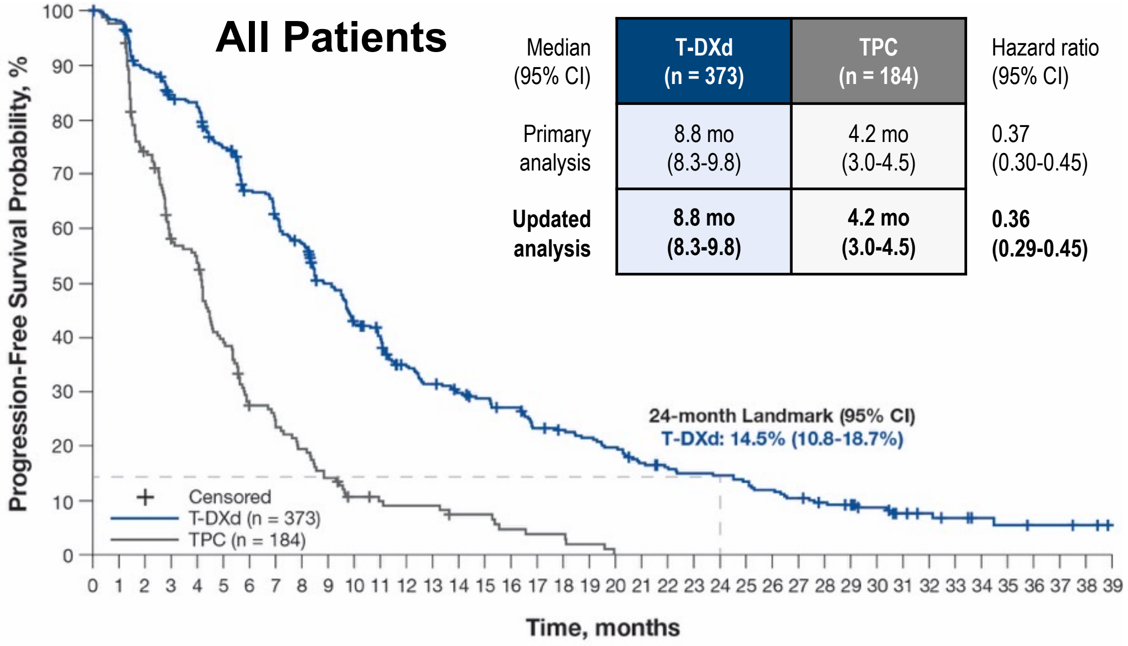
	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. NEJM 2022;387(1):9-20.

Progression-Free Survival

All Patients

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



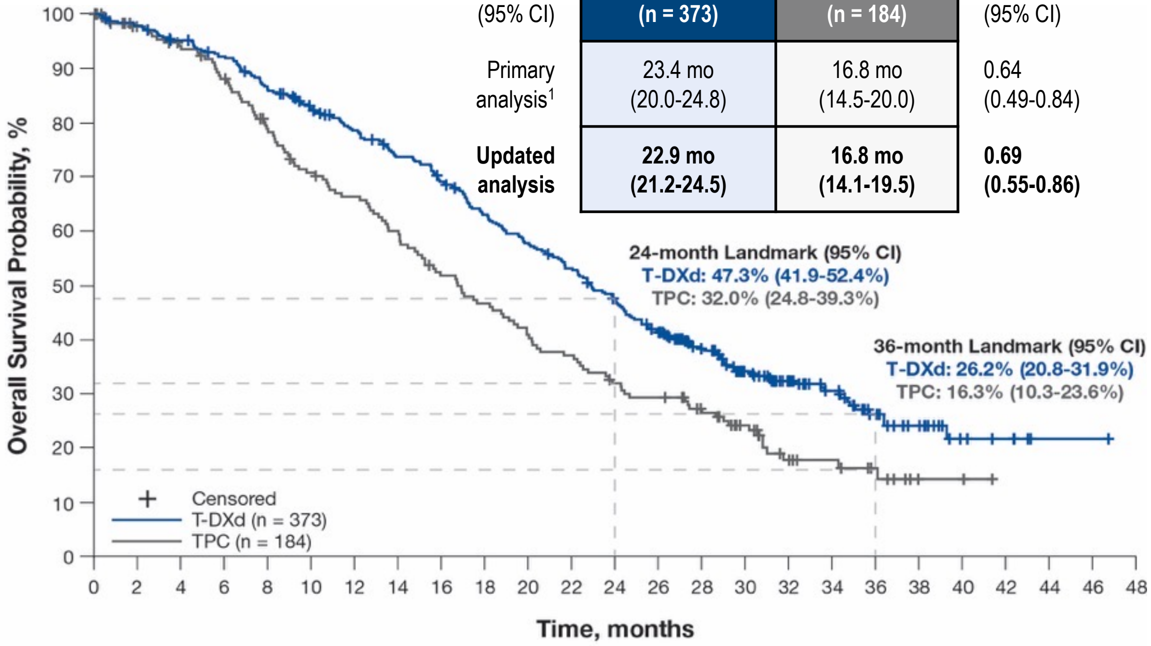
Patients still at risk:

T-DXd (n = 373)	373	364	327	304	297	267	234	216	198	166	140	130	107	97	90	85	79	67	64	60	55	46	42	39	38	35	31	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 184)	184	163	121	92	85	61	41	35	29	21	14	12	11	11	8	8	5	4	4	2	0																			

Overall Survival

All Patients

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



Patients still at risk:

T-DXd (n = 373)	373	366	363	355	350	342	337	325	314	308	295	285	276	269	257	254	240	231	217	205	199	191	182	168	160	148	137	122	107	94	81	75	62	52	48	39	28	21	18	11	7	6	5	3	1	1	1	0
TPC (n = 184)	184	170	165	160	156	152	145	137	127	119	113	107	105	100	95	88	81	76	73	69	64	59	58	53	49	45	45	44	37	33	27	18	15	12	12	10	8	5	2	2	2	1	0					

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

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

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

Overall Safety Summary

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

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

Safety analysis set[a]

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

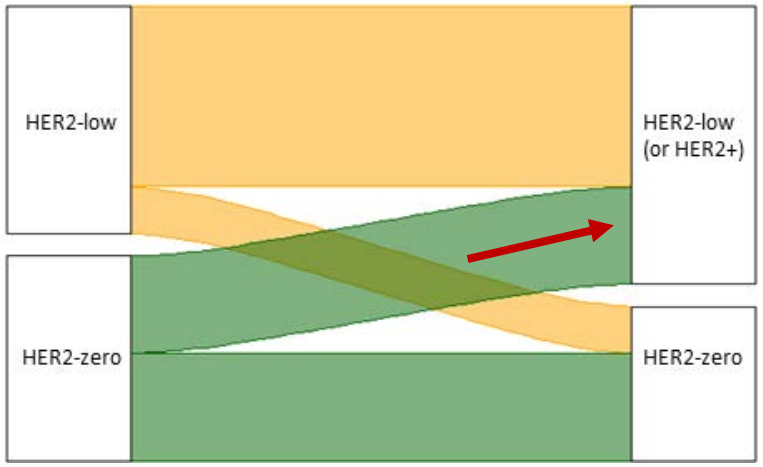
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death that occurred any time from date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

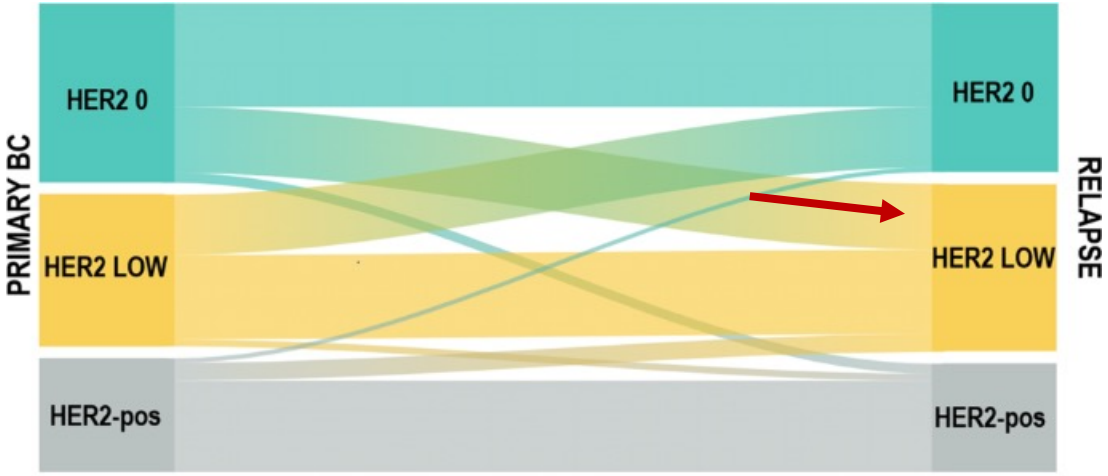
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

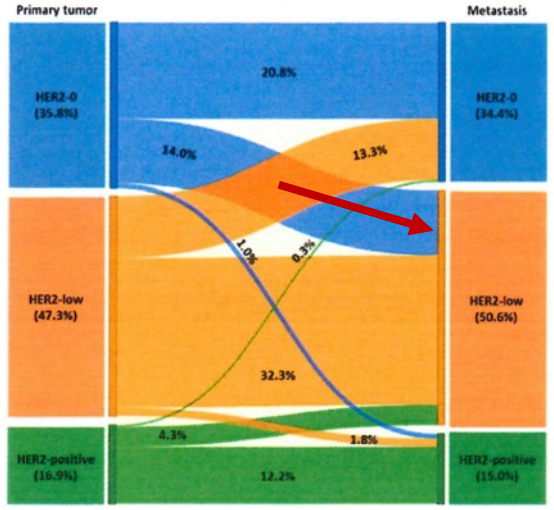
Modi S et al. ESMO 2023;Abstract 376O.

HER2-low is unstable

- **Multiple studies have confirmed the instability of HER2-low expression.** The reason is unclear, but may be multifactorial: (pre)analytical factors, HER2 expression heterogeneity, biologic evolution of the disease



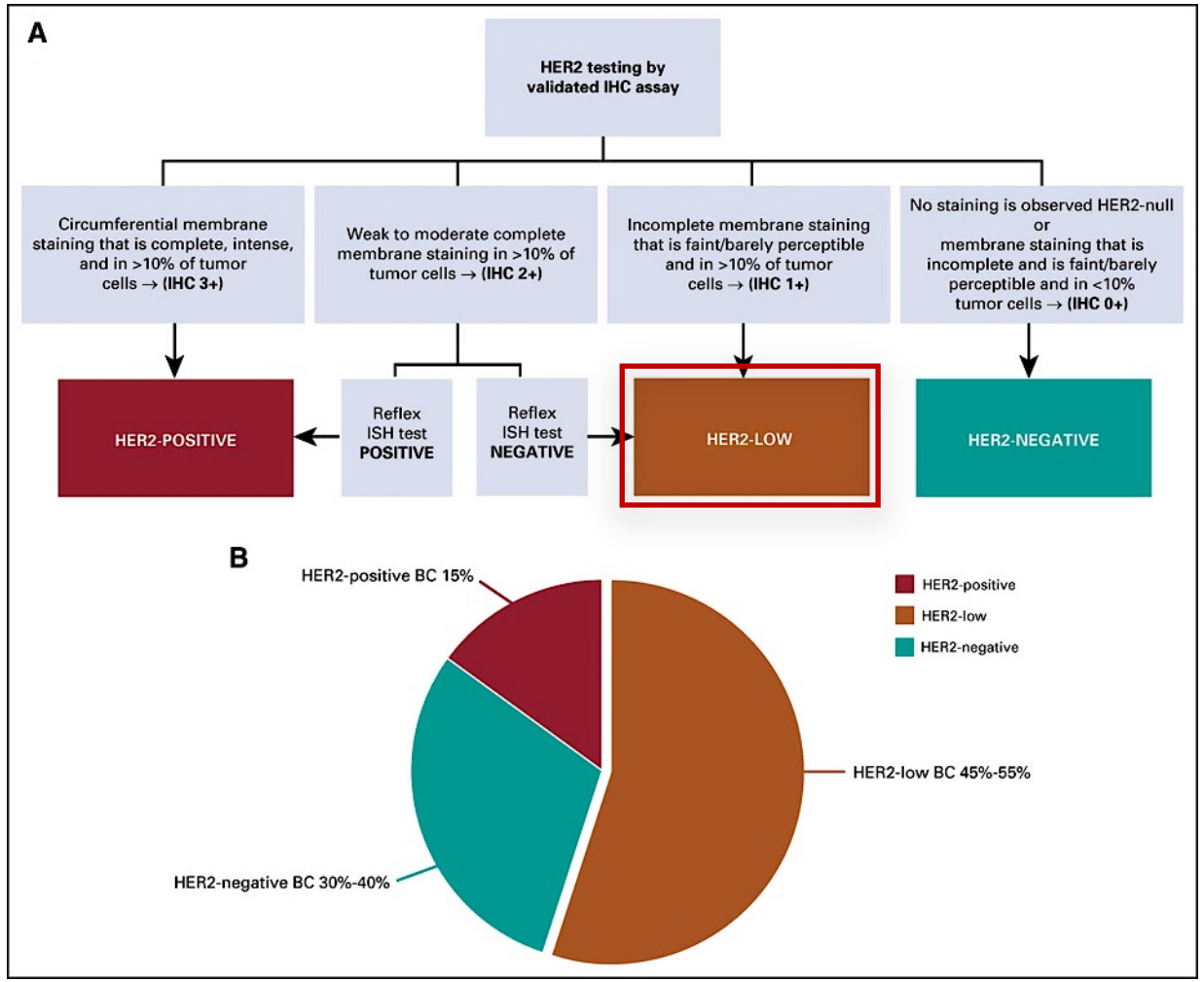




Tarantino P, et al *Eur J Cancer*. 2022;163:35–43; Miglietta F, et al. *NPJ Breast Cancer*. 2021;7(1):137; Bergeron A. et al. Presented at USCAP 2022.

How to define HER2-low breast cancer?

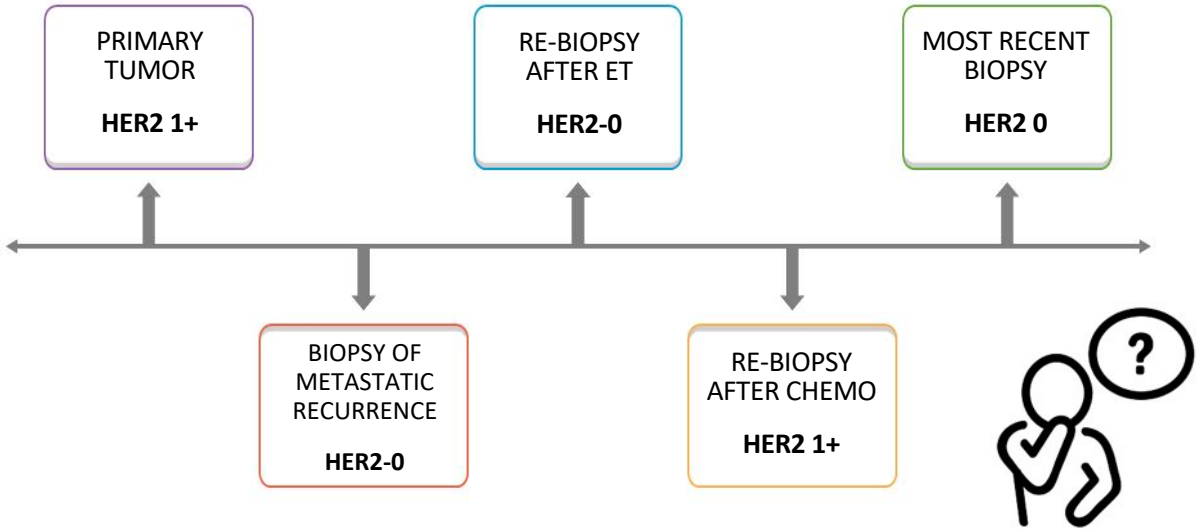
Static definition (for books)



Dynamic definition (real life)

HER2-low status changes over time

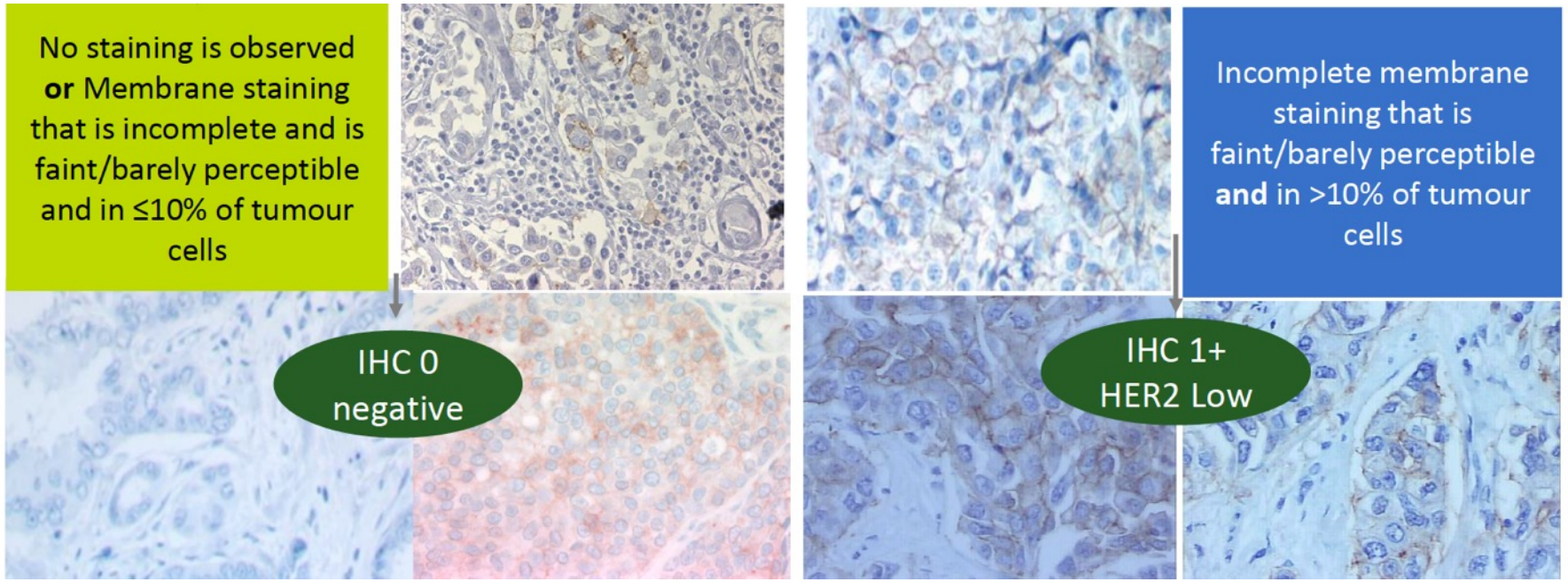
Which timepoint to use to define a tumor HER2-low?



Low concordance among pathologists for HER2-0 vs HER2-low

In a recent study, among 18 experienced pathologists there was **only 26% concordance** between the diagnoses of HER2-0 and HER2 1+. Current IHC assays were developed to identify overexpressing cases, and are **unsuitable to distinguish HER2-0 from HER2-low**

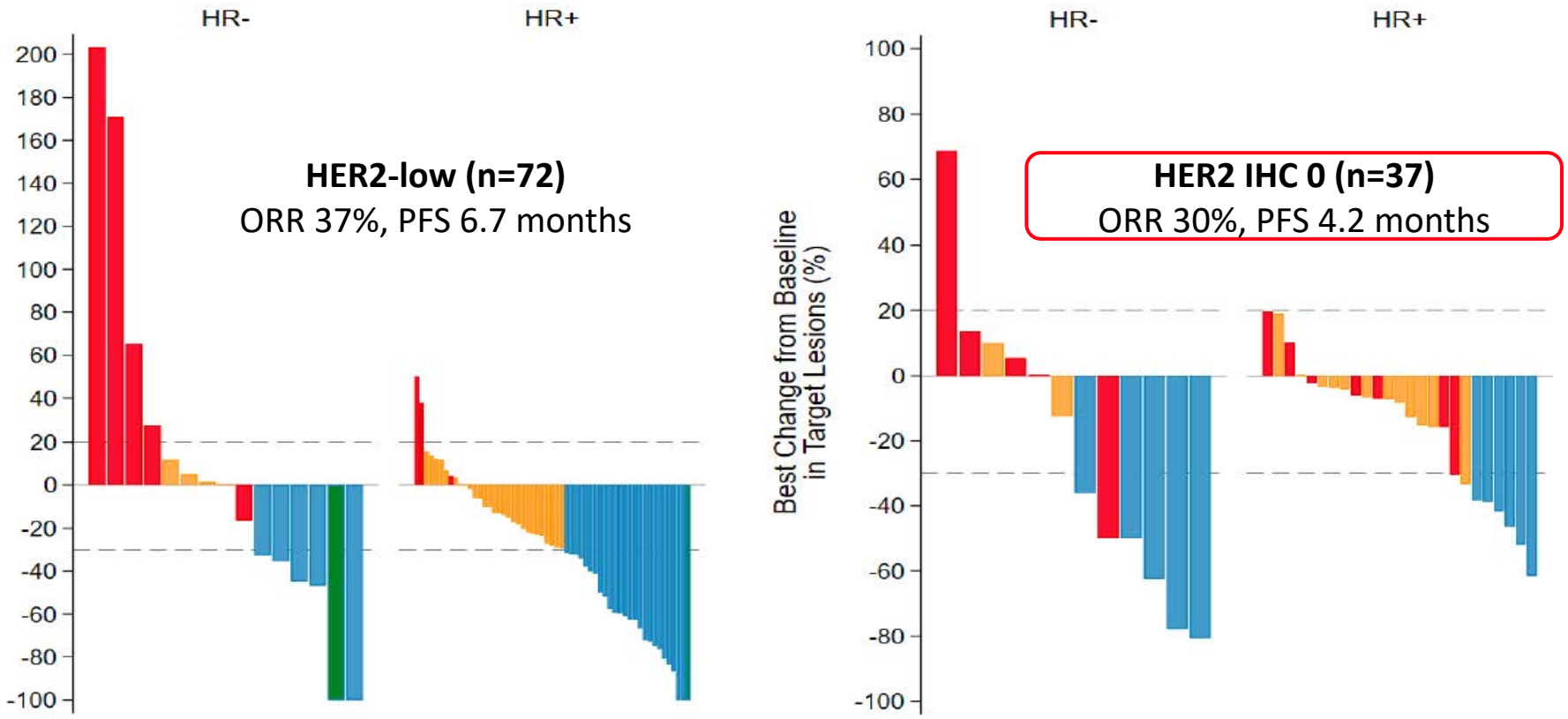
Importantly, HER2-0 does not mean absence of HER2, but also includes tumors with "ultralow" expression



Fernandez A. et al. *JAMA Onc.* 2022

Do we really **need** HER2-low expression?

Recently presented data suggest meaningful activity of HER2 ADC even in mBC with HER2 IHC 0



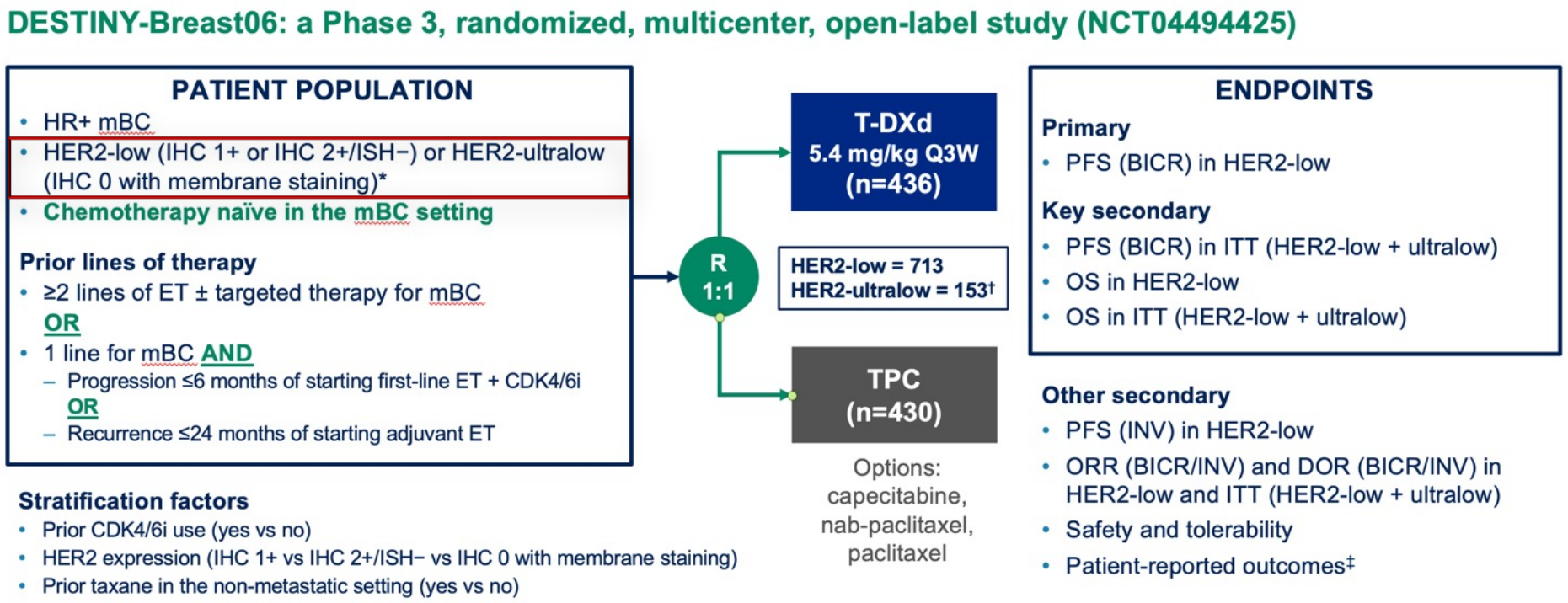
Dieras V, et al. Presented at SABCS 2021.

How will HER2-low evolve?

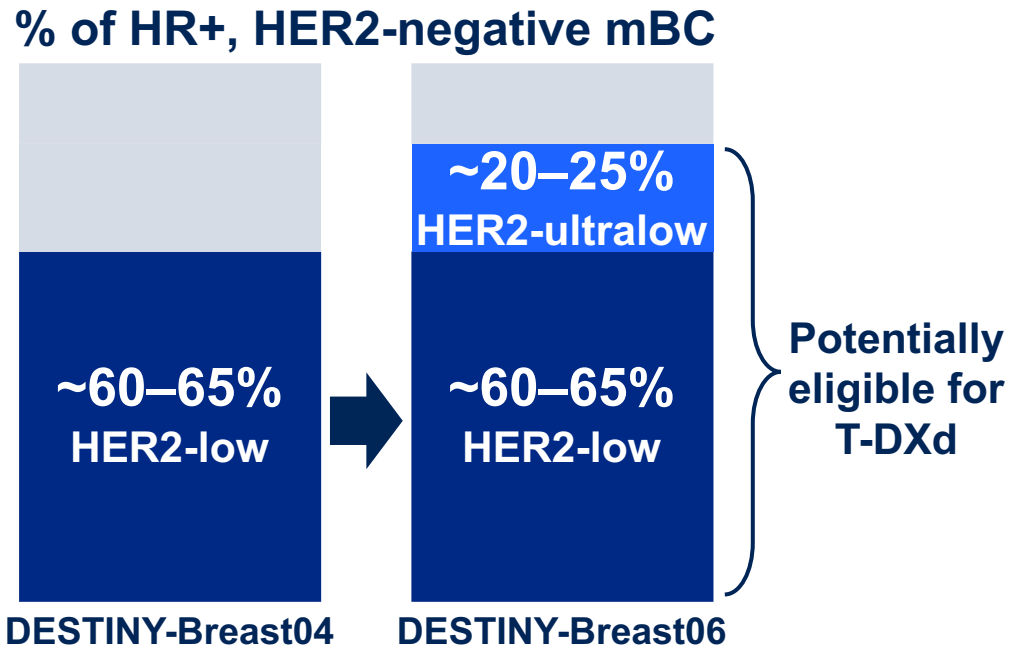
- DESTINY-Breast06 Phase 3 includes IHC0 with «ultralow» expression

Key differences with DB-04:

- Includes IHC0 (ultralow)
- Larger (n=866)
- Restricted to HR+ disease
- Chemo-naïve patients



DESTINY-Breast06: key takeaways

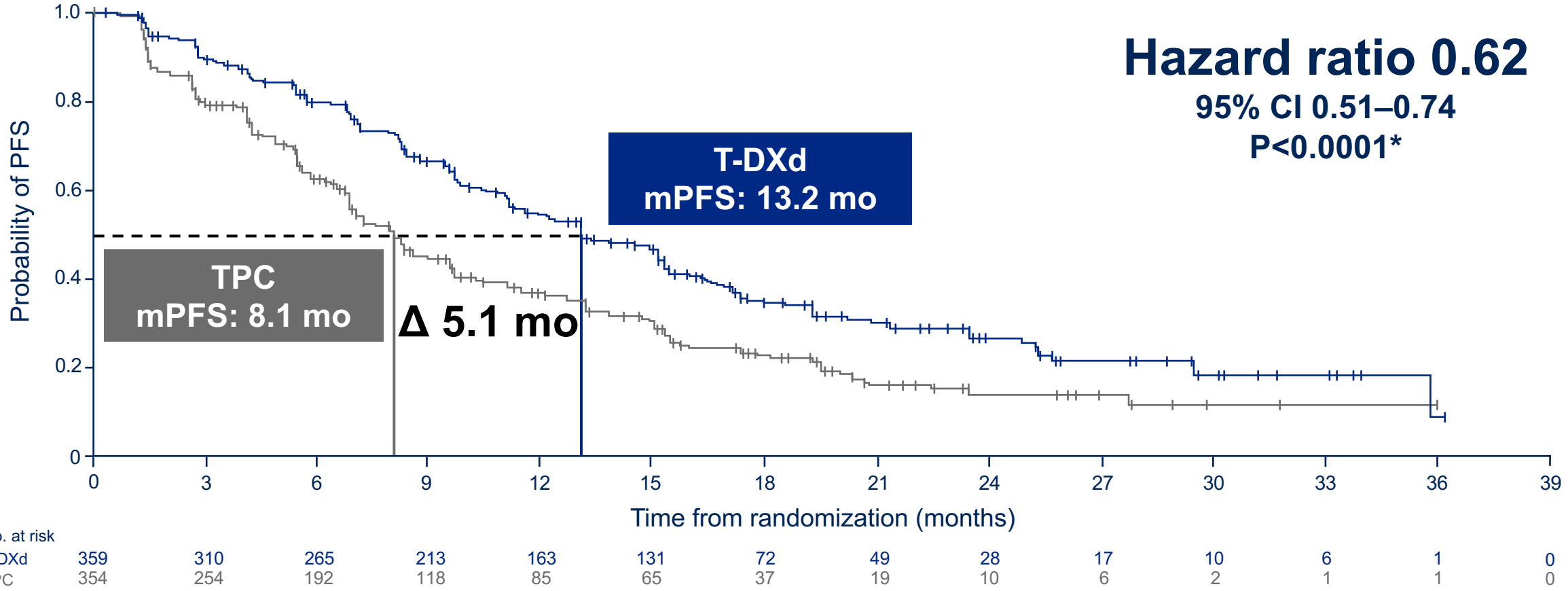


- T-DXd demonstrated efficacy in **HER2-low mBC** in an **earlier line of treatment** to DESTINY-Breast04
- Including HER2-ultralow, the proportion of patients who could benefit from T-DXd is **~85% of HR+, HER2-negative mBC** after DESTINY-Breast06

In DESTINY-Breast06, T-DXd demonstrated a statistically significant and clinically meaningful PFS benefit vs TPC (chemotherapy) in HR+, HER2-low mBC after ≥1 endocrine-based therapy, with consistent results in HER2-ultralow mBC

HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS (BICR) in HER2-low: primary endpoint



Hazard ratio 0.62
95% CI 0.51–0.74
P<0.0001*

No. at risk

T-DXd	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0

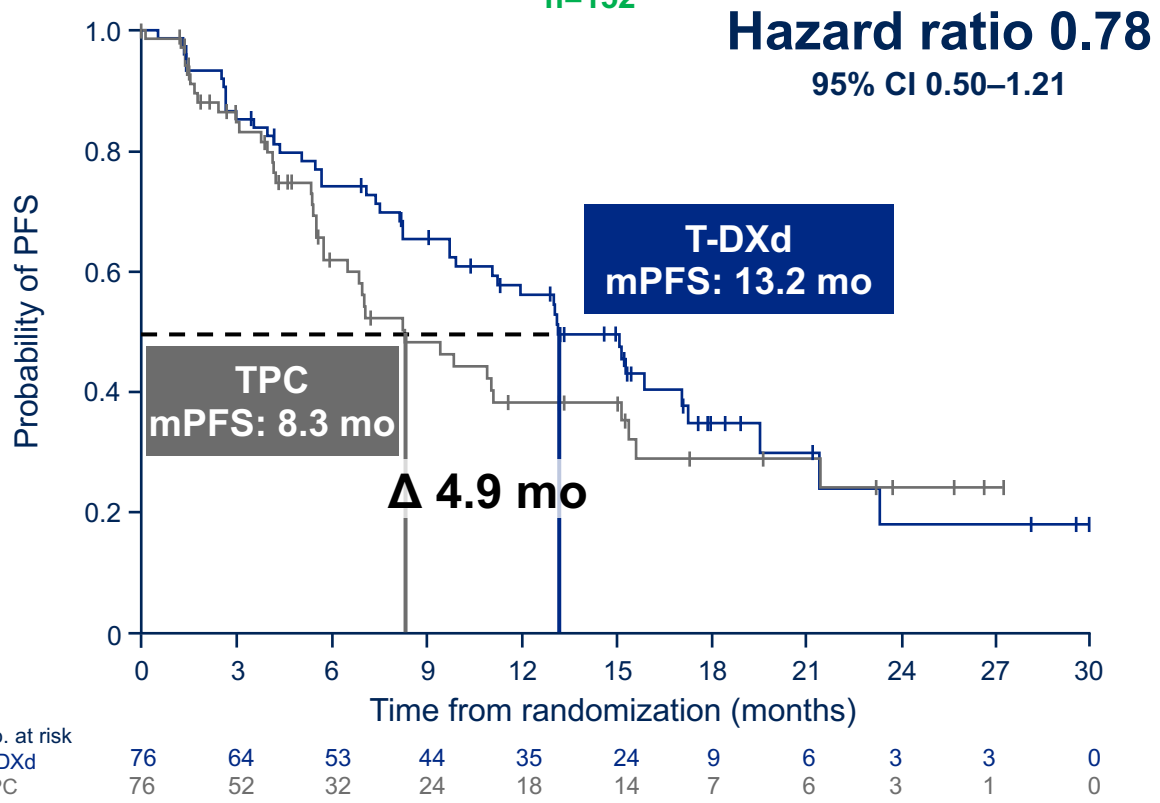
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS and OS in HER2-ultralow: prespecified exploratory analyses

PFS (BICR)

n=152

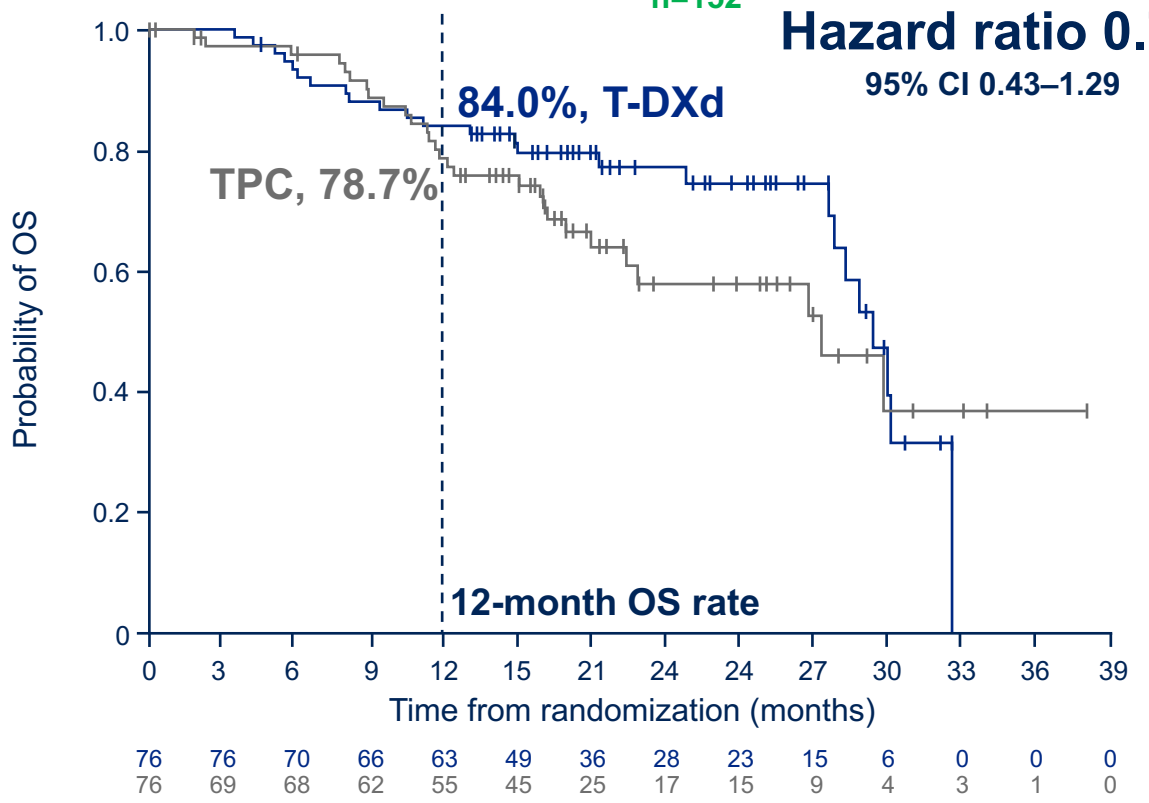


No. at risk

T-DXd	76	64	53	44	35	24	9	6	3	3	0
TPC	76	52	32	24	18	14	7	6	3	1	0

OS*

n=152



76	76	70	66	63	49	36	28	23	15	6	0	0	0
76	69	68	62	55	45	25	17	15	9	4	3	1	0

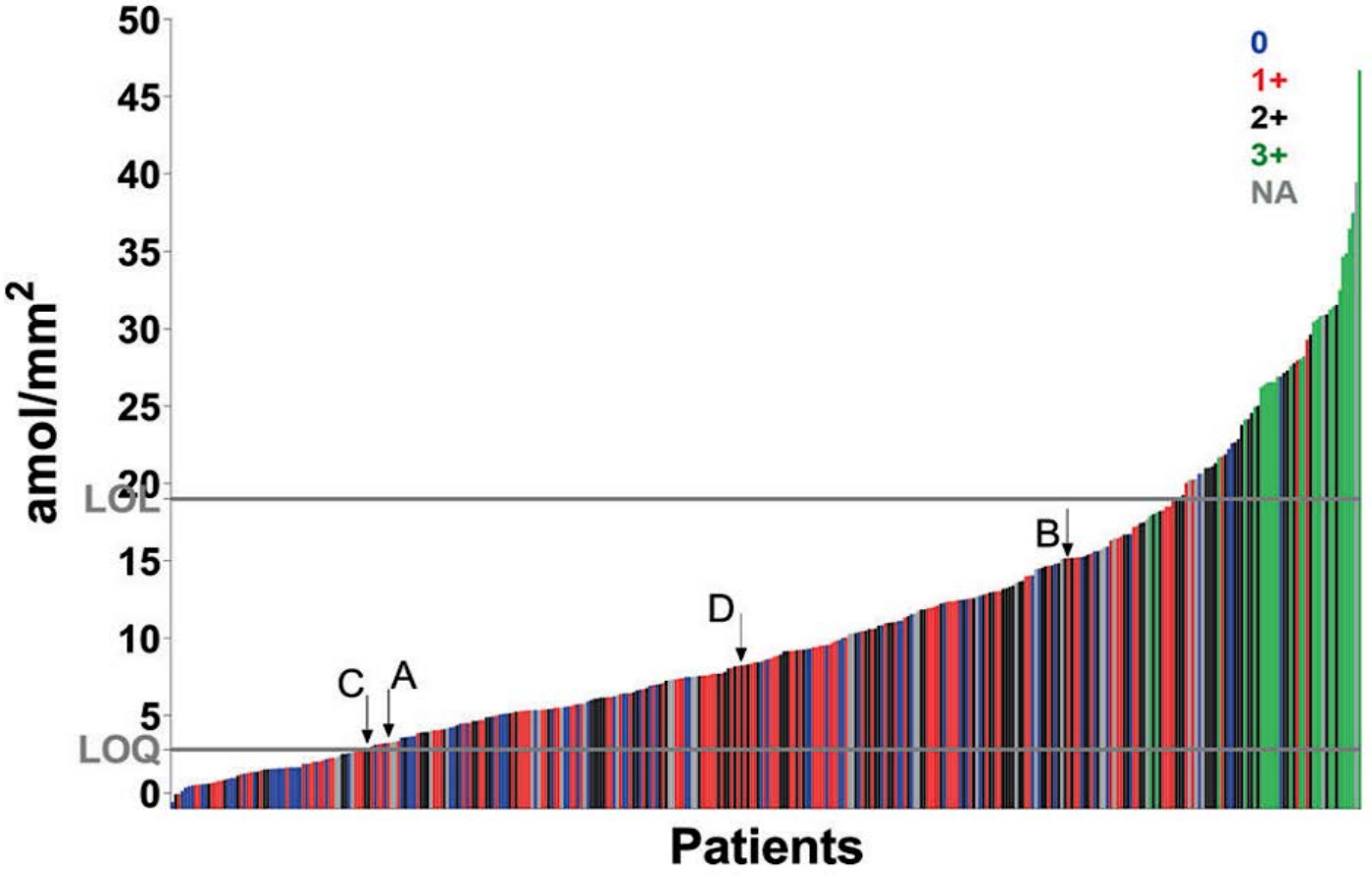
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

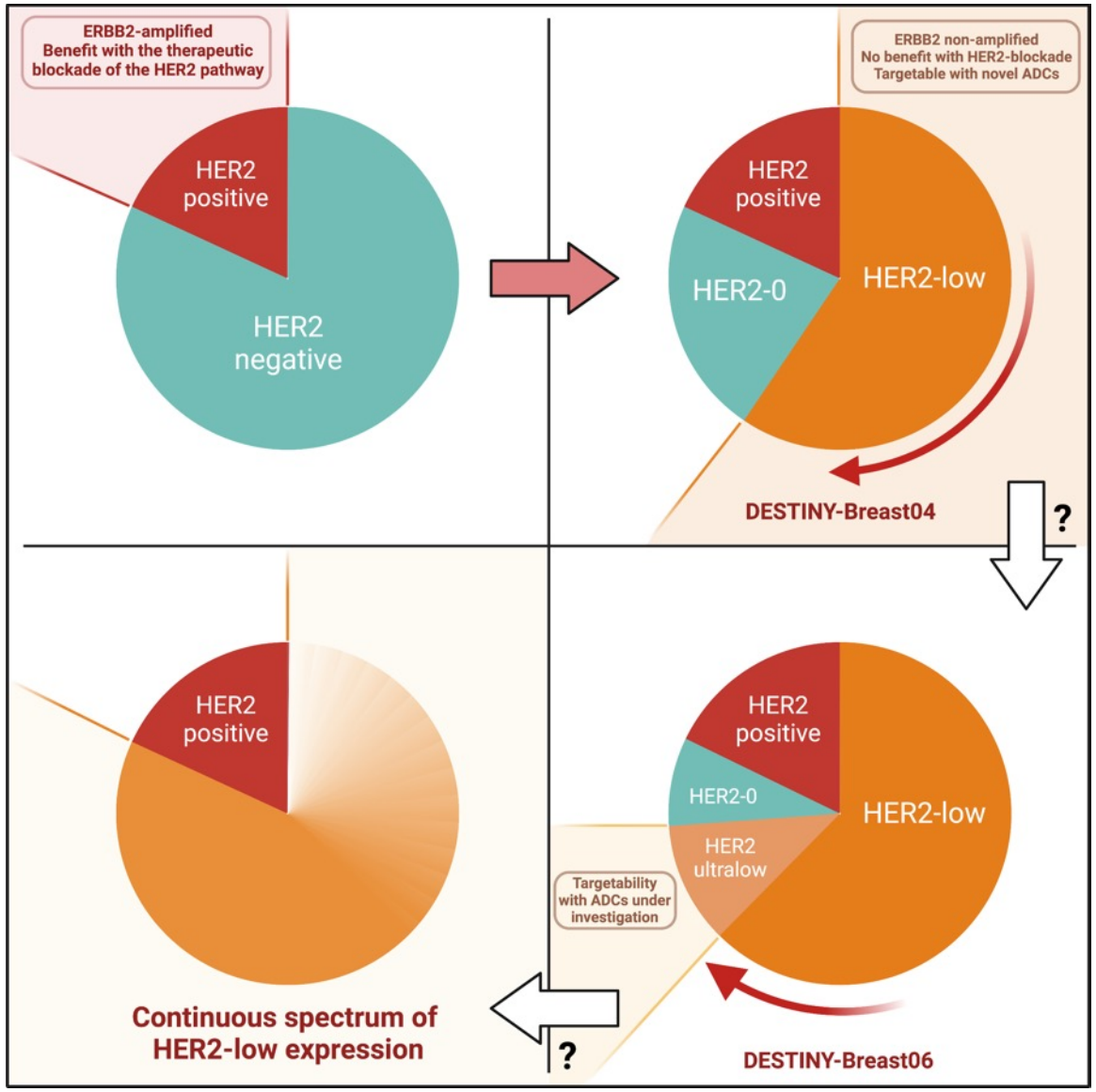
How will HER2-low evolve?

Novel **quantitative HER2 testing assays** may improve our capabilities to predict the activity of anti-HER2 ADCs, unlocking the full spectrum of HER2 expression



Moutafi M. et al, Lab Invest 2022

The future pie-chart of HER2-low breast



Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Potential role of trastuzumab deruxtecan for TNBC with a HER2 mutation

Dr Shaachi Gupta (Lake Worth, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How would you approach treatment for a young, male patient with de novo metastatic TNBC who is found to have a HER2 exon 20 mutation?

Would you consider the use of T-DXd in this situation?

QUESTIONS FOR THE FACULTY

In general, how do you approach endocrine therapy for male patients with breast cancer?

How do you approach the management of the primary for a male patient with metastatic breast cancer?

Consulting Faculty Comments

Management of side effects associated with sacituzumab govitecan

Dr Gigi Chen (Pleasant Hill, California)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you approach the issue of neutropenia for patients receiving sacituzumab govitecan?

How do you approach the use of growth factors for patients receiving the drug?

Selection and Sequencing of Therapy for Patients with Metastatic TNBC

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
Sarah Cannon Cancer Institute
Dallas TX

Approach to Therapy for Metastatic TNBC

	PD-L1+ BRCA1/2 WT	PD-L1- BRCA1/2 WT	PD-L1- BRCA1/2 mut	PD-L1+ BRCA1/2 mut
1st Line	Chemotherapy + Pembrolizumab	Taxane or Platinum	Olaparib or Talazoparib	Chemotherapy + Pembrolizumab
2nd Line	Sacituzumab Govitecan			Olaparib or Talazoparib
3rd Line +	HER2 low: T-DXd Platinum, Eribulin, Capecitabine, Gemcitabine, Vinorelbine			

Future Strategies

- PARPi in somatic BRCA mut or germline PALB2
- Datopotamab Deruxtecan, Sacituzumab Tirumotecan, Patritumab Deruxtecan

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

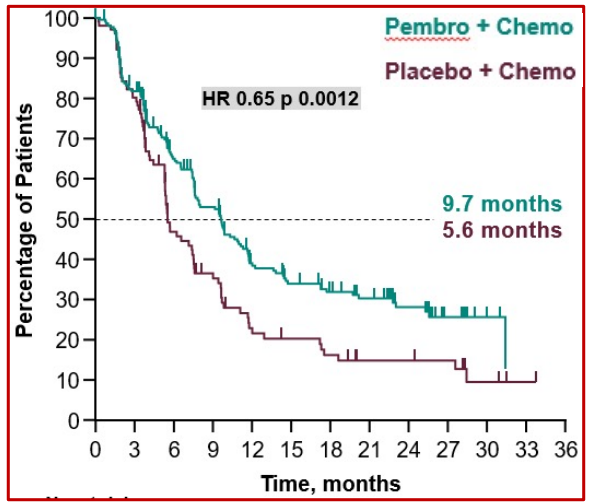
R 2:1

- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

→ Progressive disease[e]/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

PFS: PD-L1 CPS ≥10

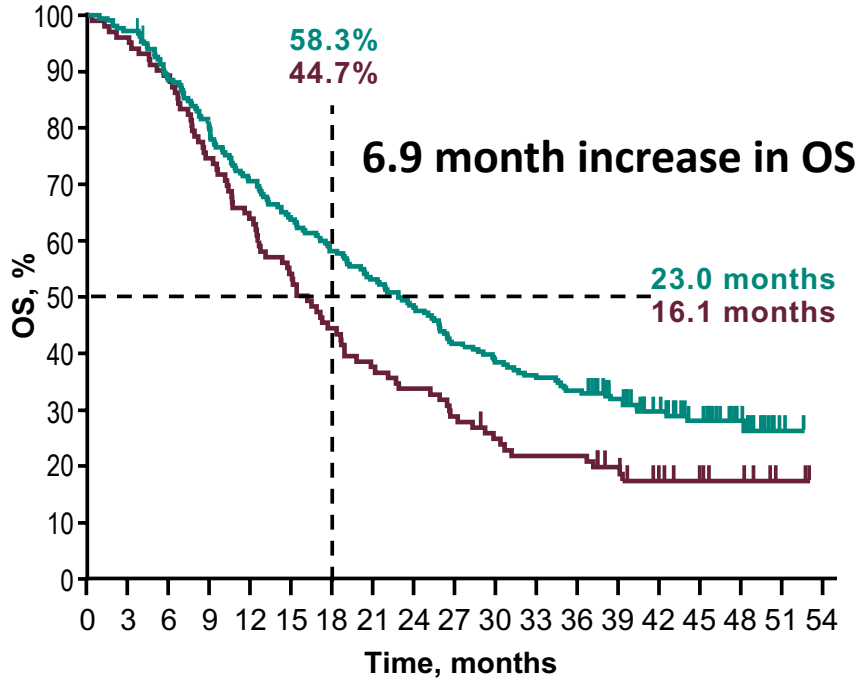


Prespecified *P* value boundary of 0.00411 met

38% of pts

OS: PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		

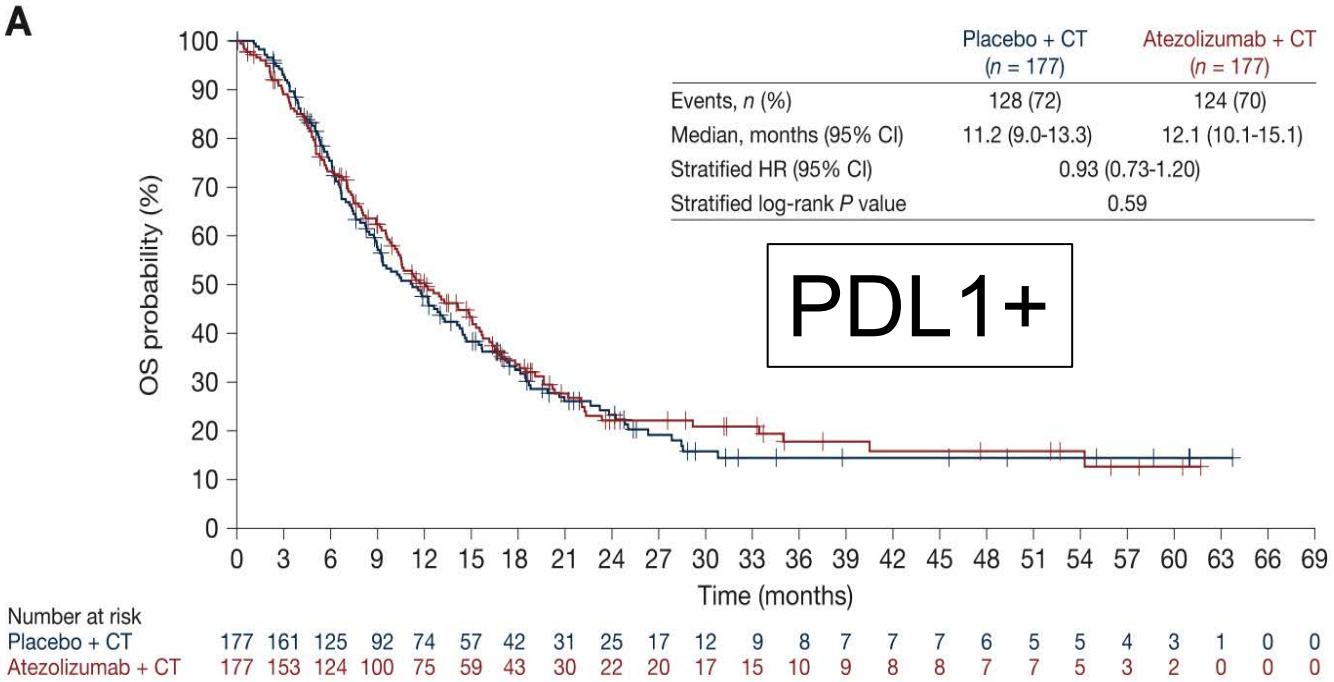


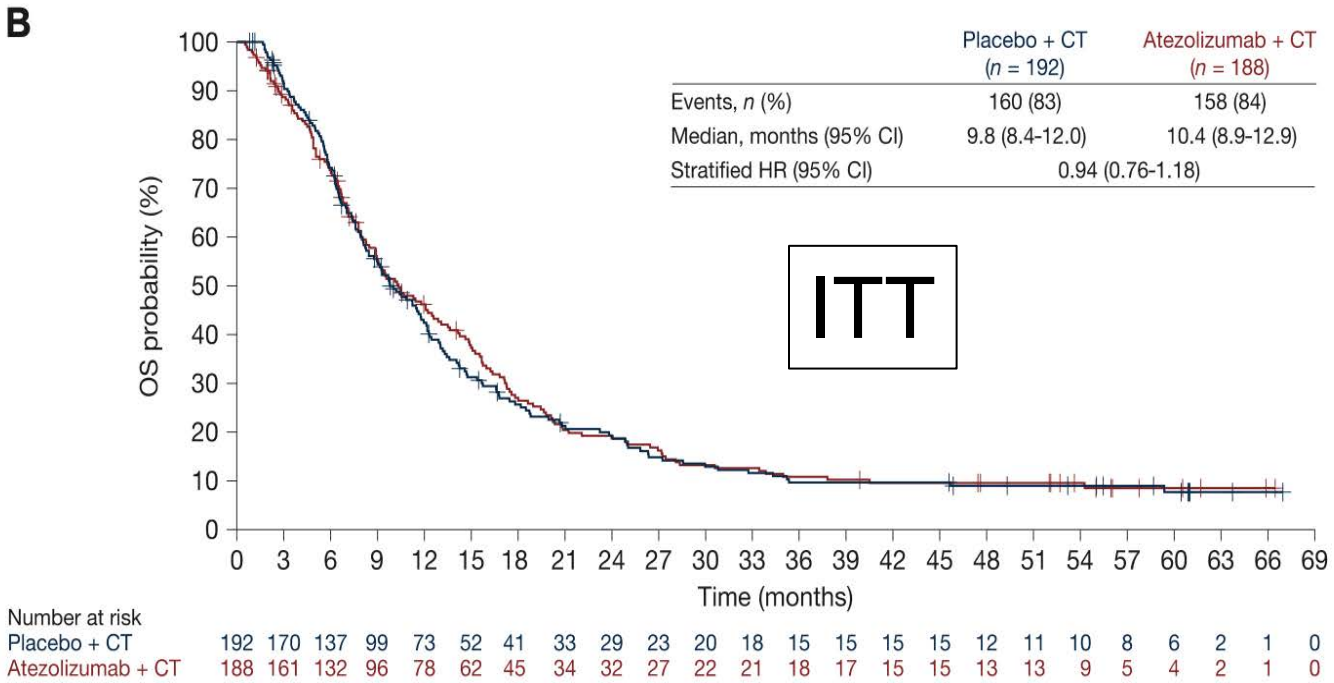
No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Cortes et al, Lancet 2020; Rugo et al, ESMO 2021; Cortes et al, NEJM 2022

IMpassion132 Phase III of 1L Chemotherapy +/- Atezolizumab in Early-Relapsing mTNBC





- Recurrence < 12 mos post-neo/adjuvant chemoRx or surgery
- Neo/adjuvant A/T therapy required
- Chemotherapy: Gem/carbo or capecitabine
- **No improvement in OS with atezolizumab in PDL1+**

Dent R et al. Ann Oncol 2024

OlympiAD

Patient Population
- HER2– MBC
  - ER+ and/or PR+ or
  - TNBC
- Deleterious or suspected deleterious g*BRCA*m
- ≤2 prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ patients who have progressed on ≥1 endocrine therapy, or not suitable
- If patients had received platinum
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

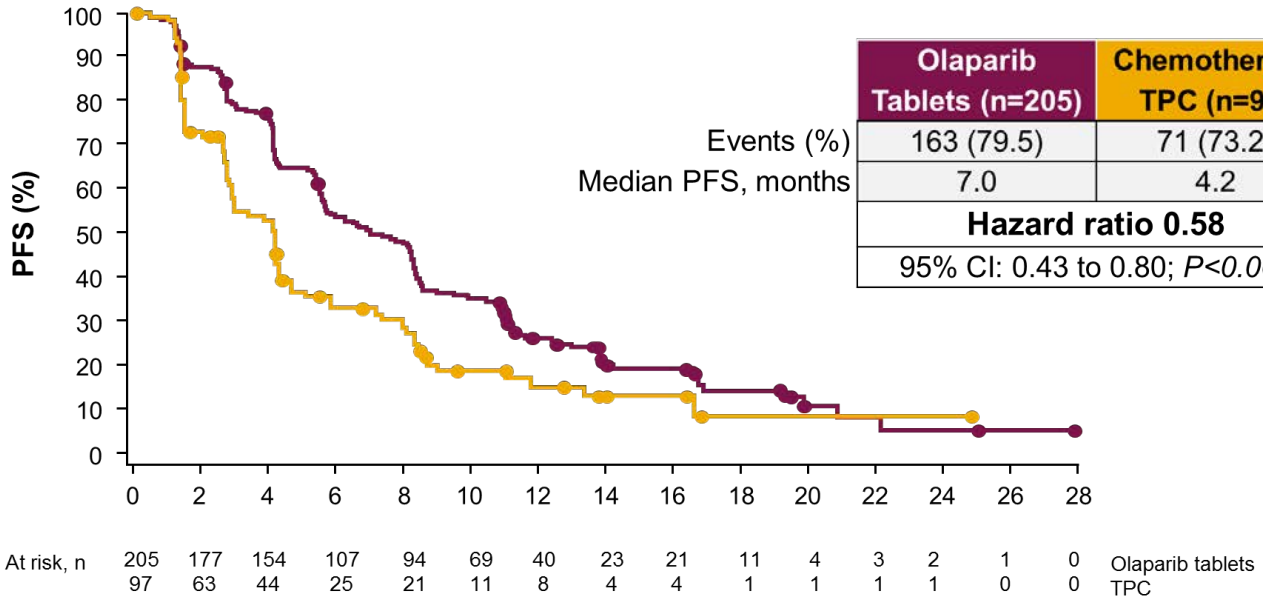
Randomized 2:1 (N=302)

Olaparib tablets 300 mg BID

Chemotherapy TPC
- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

Primary Endpoint	Secondary Endpoints
PFS (RECIST 1.1, BICR)	• OS • Time to second progression or death • ORR • Global HRQoL (EORTC-QLQ-C30) • Safety and tolerability



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

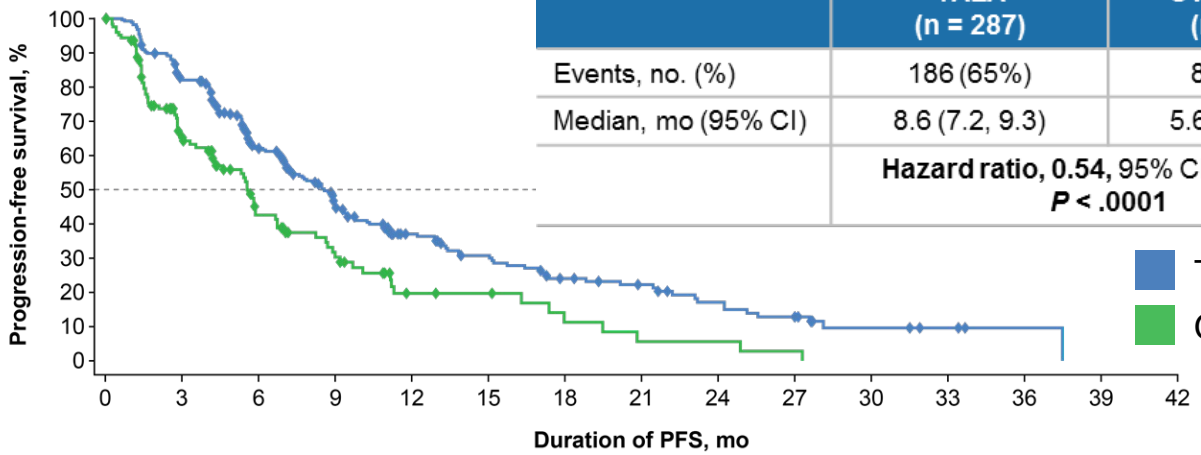
R 2:1

Talazoparib 1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

No. at risk (events/cumulative events)

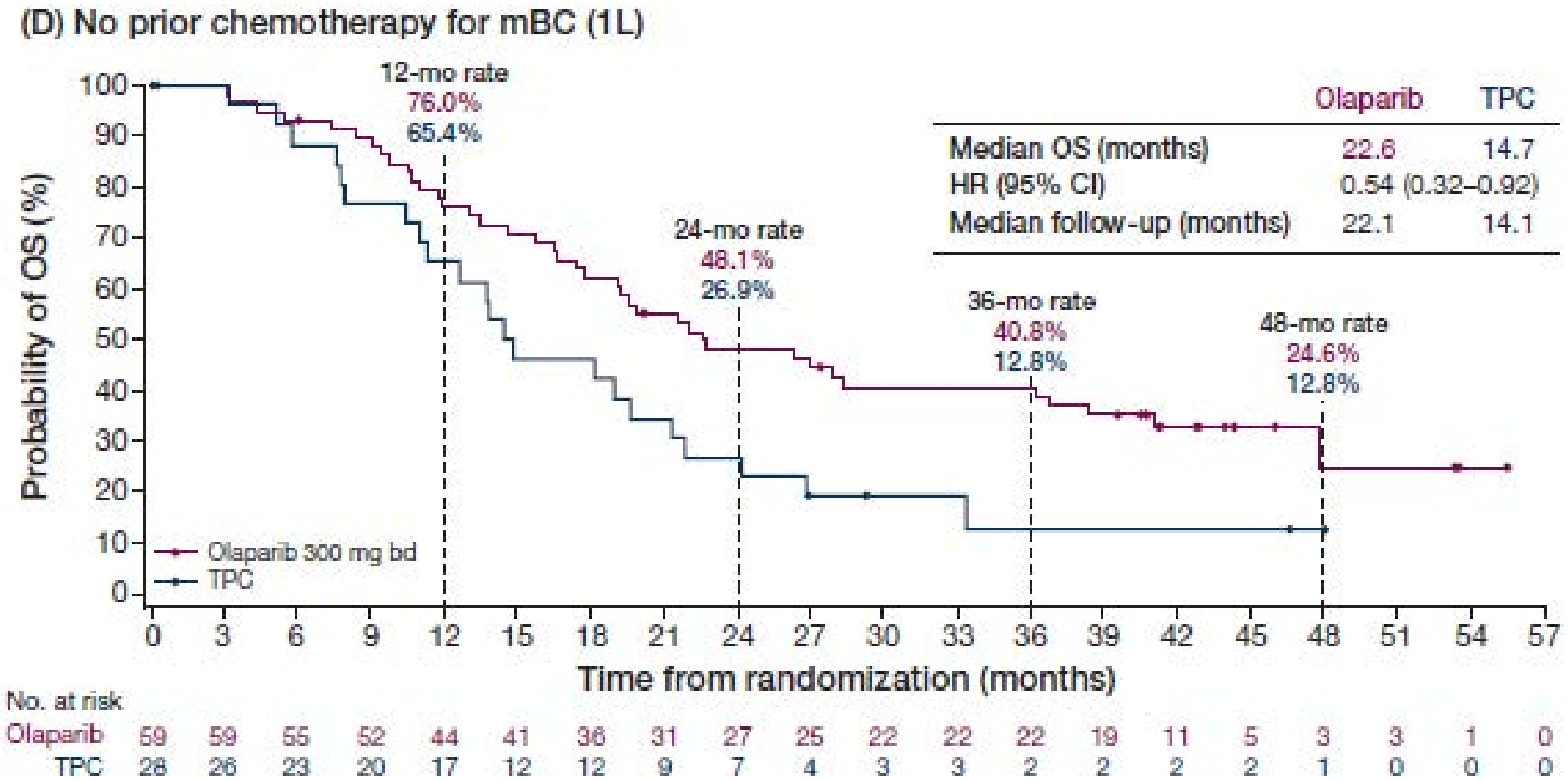
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

Litton JK et al. *N Engl J Med.* 2018;379(8):753-763.
Robson M et al. *N Engl J Med.* 2017;377(6):523-533.

OlympiAD: Extended OS Follow-Up

No statistically significant differences in survival curves in HR+ HER2- or TNBC

No new safety signal –No AML/MDS

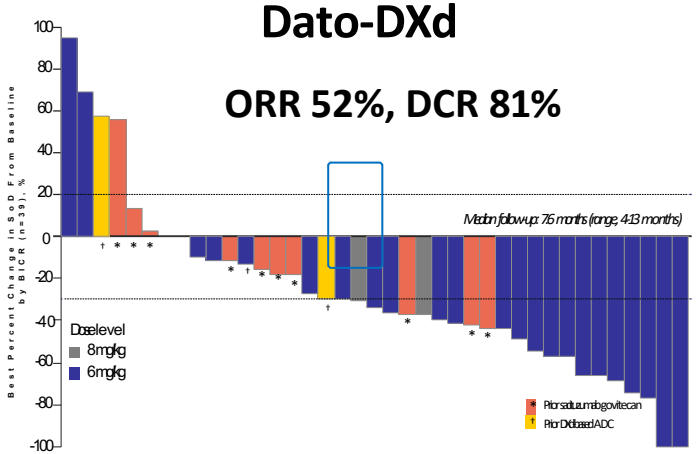


Robson M, et al. SABCS 2019. PD4-03. Robson ME, Im SA, Senkus E, et al. Eur J Cancer. 2023;184:39-47.

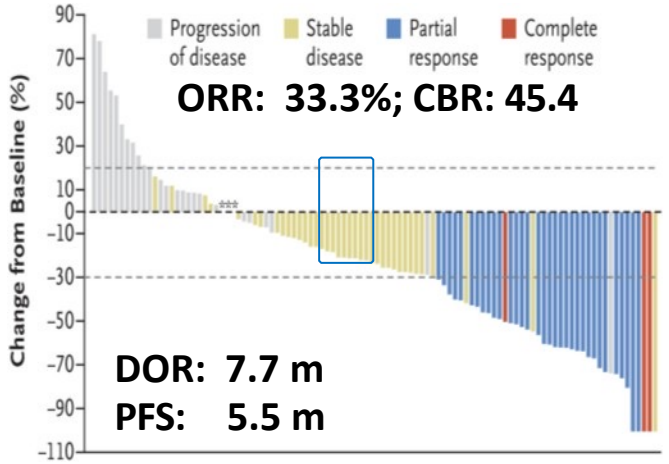
Antibody-Drug Conjugates for TNBC

Dato-DXd

ORR 52%, DCR 81%



Sacituzumab



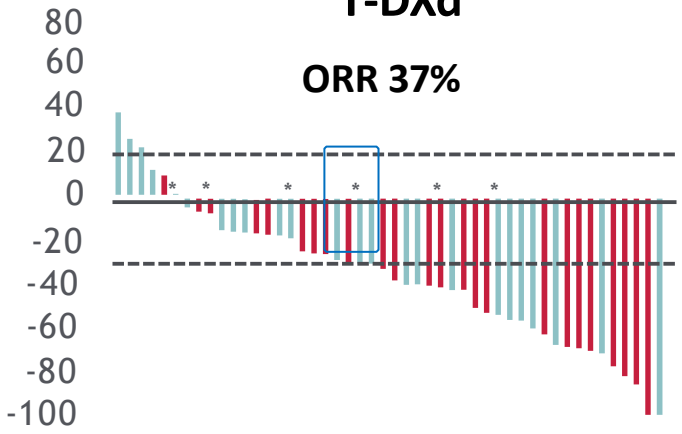
ORR: 33.3%; CBR: 45.4

DOR: 7.7 m

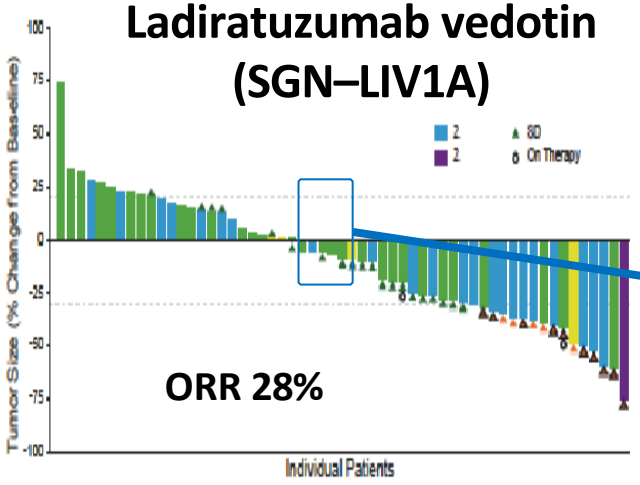
PFS: 5.5 m

T-DXd

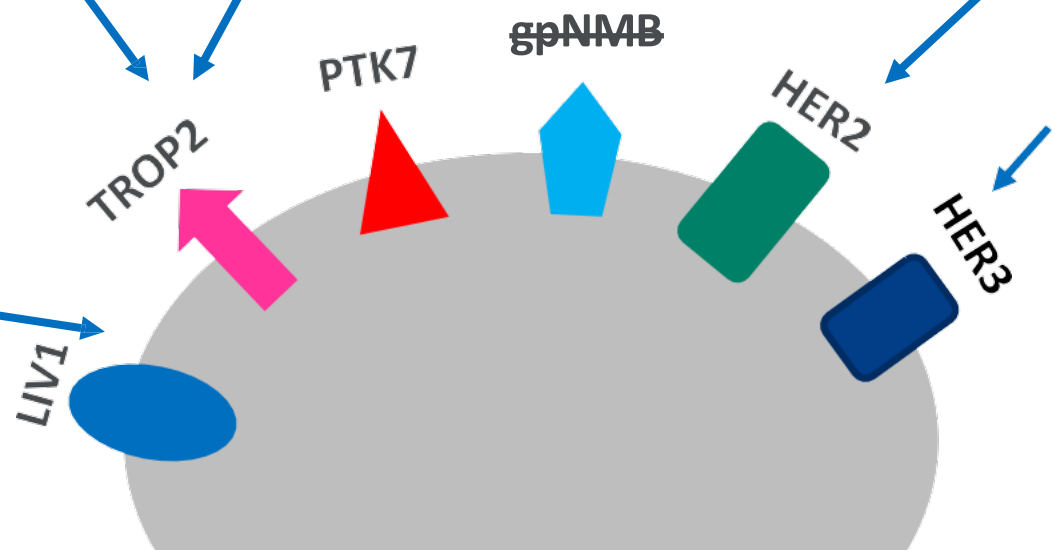
ORR 37%



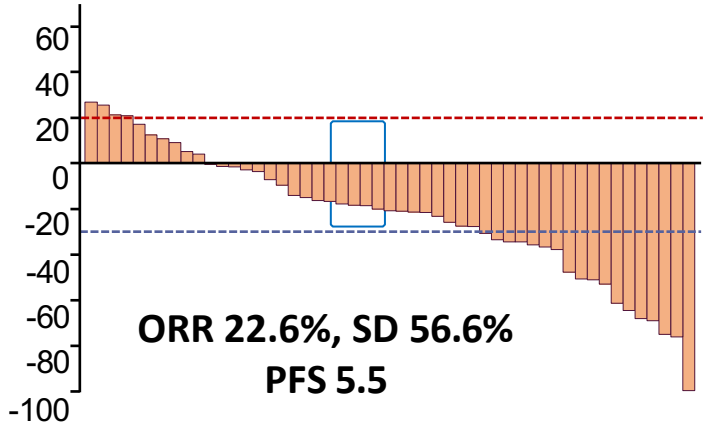
Ladiratuzumab vedotin (SGN–LIV1A)



ORR 28%



HER3-DXd



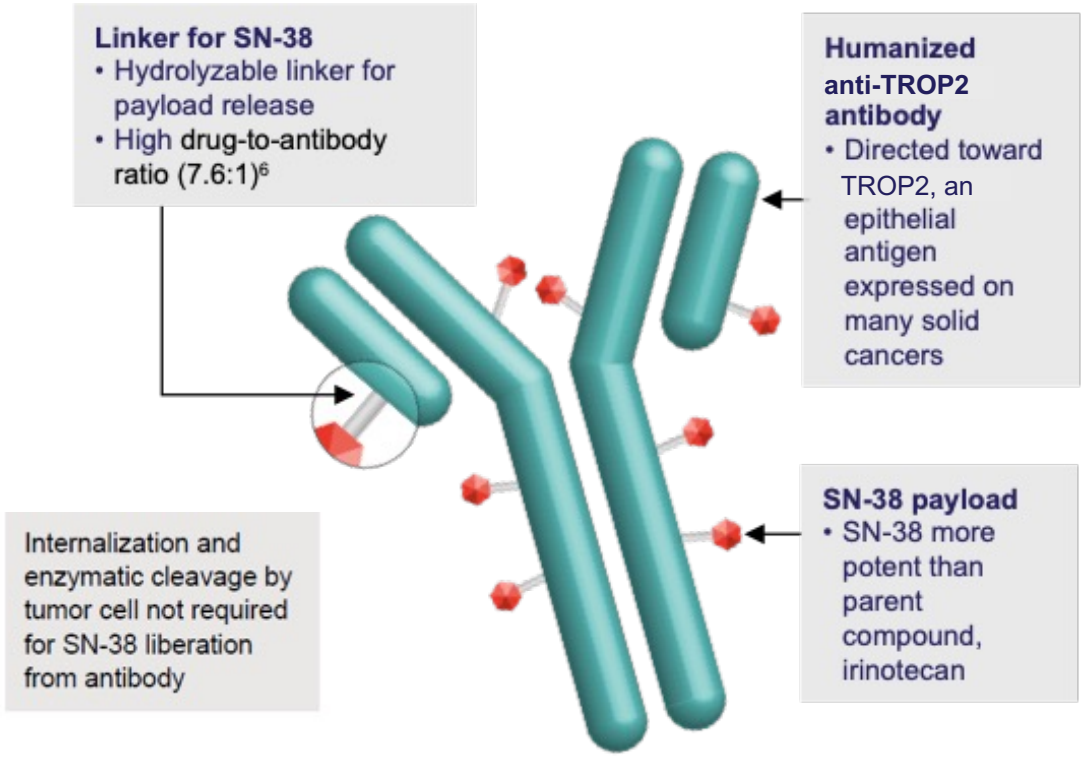
ORR 22.6%, SD 56.6%

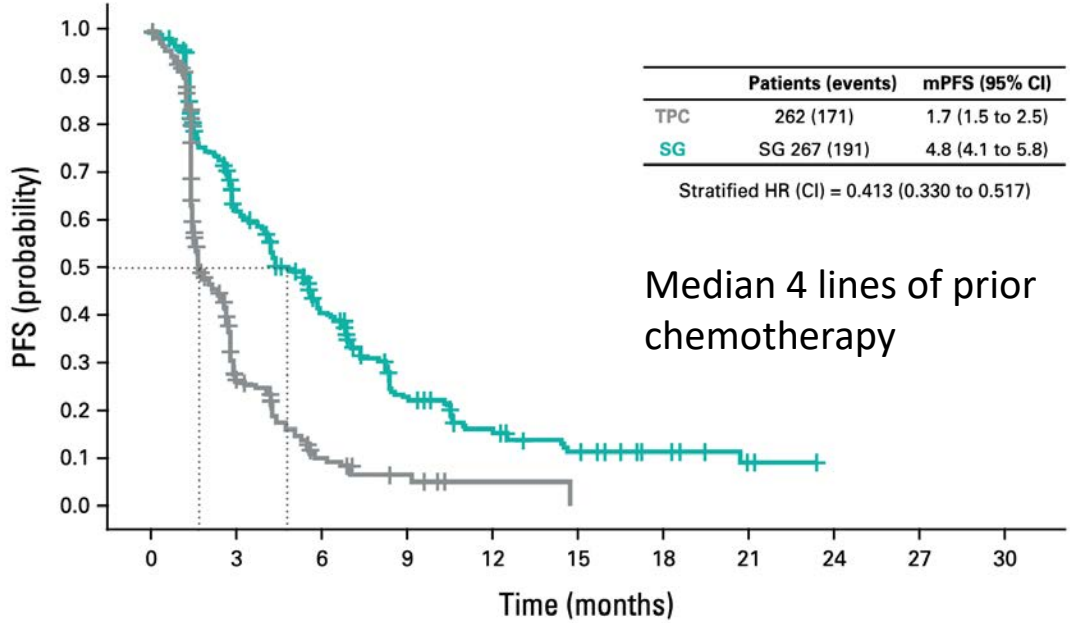
PFS 5.5

Schmid P, Personal Communication

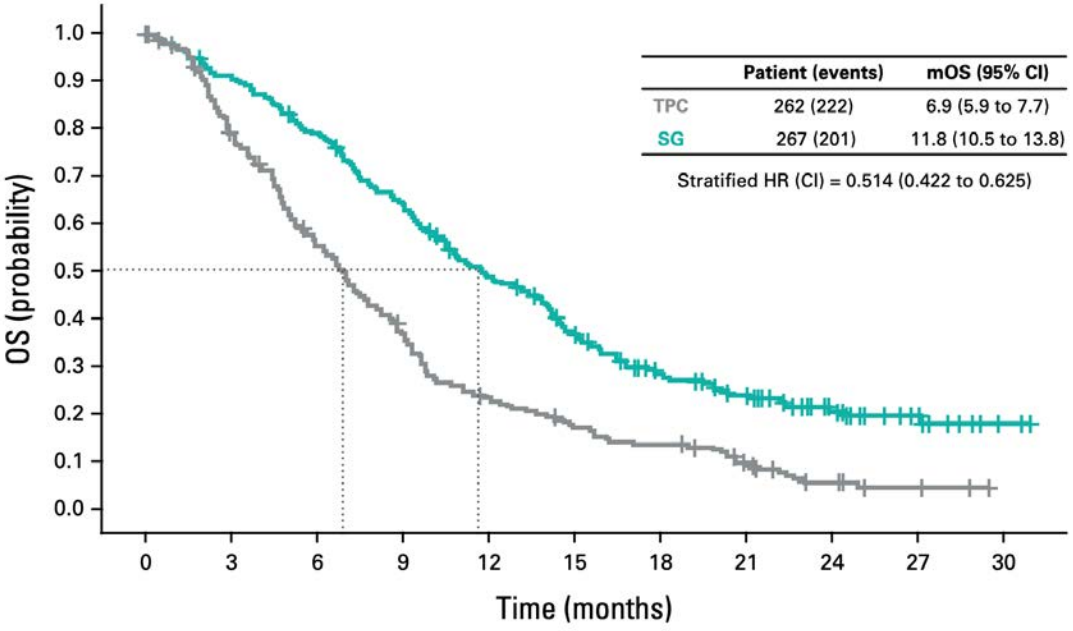
Bardia, NEJM 2021; Krop, SABCS 2021; Krop, ASCO 2022; Modi, JCO 2020; Tsai, ESMO 2021

Sacituzumab Govitecan (SG): First-in-Class TROP2–Directed ADC





Median 4 lines of prior chemotherapy



- TROP2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
  - No severe CV toxicity, no grade >2 neuropathy or grade >3 ILD with SG

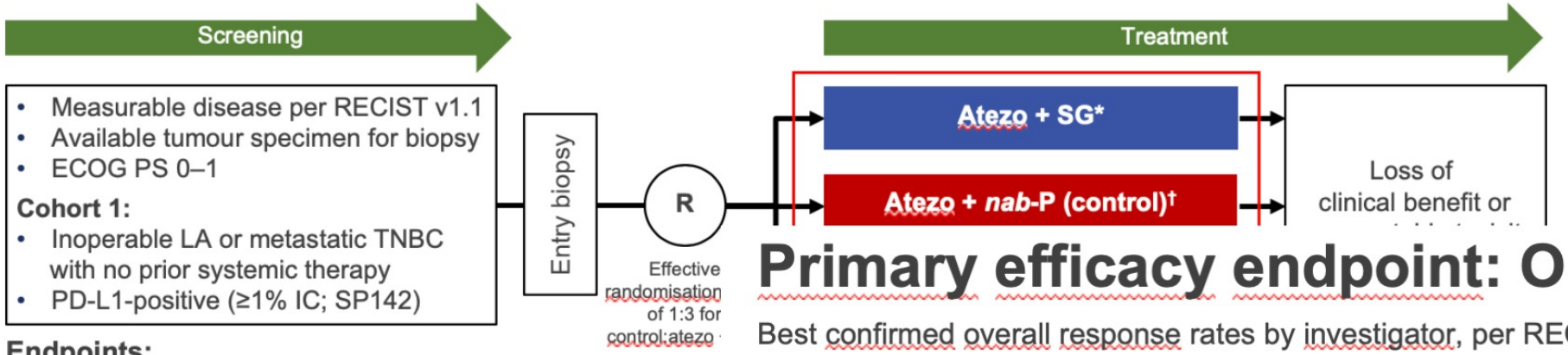
Bardia et al. *JCO*, 2024.

Morpheus-panBC

IA of atezolizumab + sacituzumab govitecan in advanced TNBC

Phase Ib/II, open-label, multicentre, randomised, umbrella study of multiple treatment combinations in LA/mBC (NCT03424005)

N 42p



Endpoints:

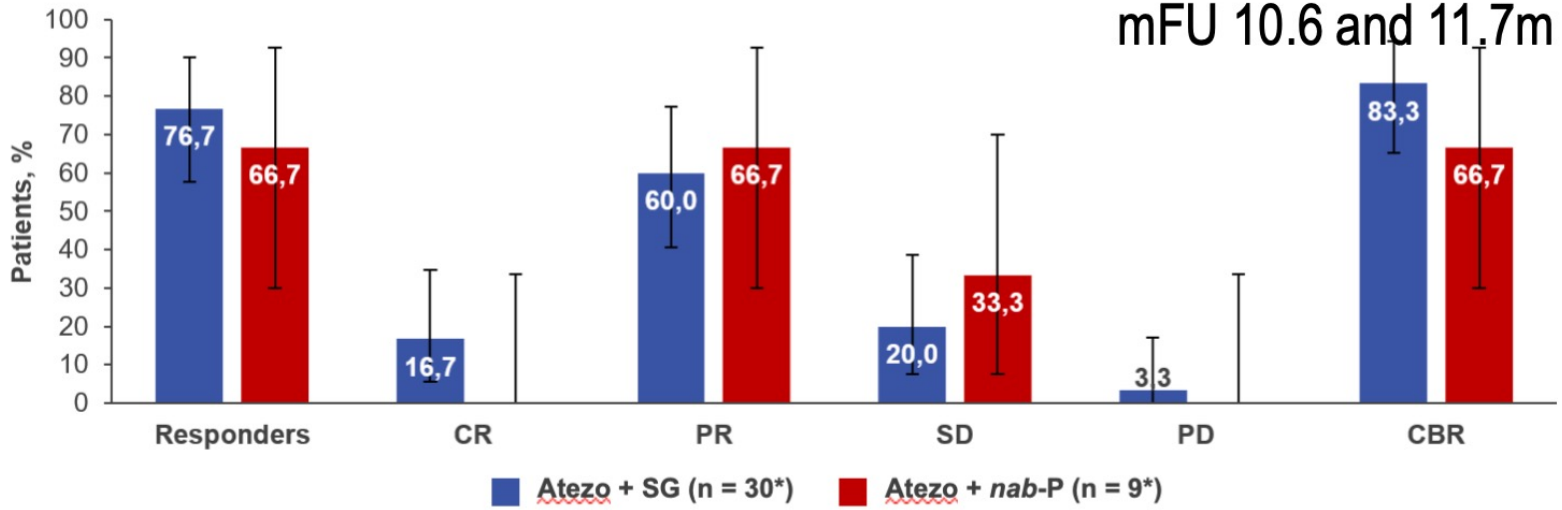
- Primary: ORR, safety
- Secondary: PFS, DCR, OS, DOR

Baseline tumours were evaluated for Trop-2, CD8 immune

Target enrolment: n = 30 in the atezo + SG arm.
* Atezo 1200 mg IV D1 and SG 10 mg/kg IV D1 and 8 (21-D cycles); † Atezo 840 mg IV D1 and 15
Atezo, atezolizumab; BC, breast cancer; D, day; DCR, disease control rate; DOR, duration of respo
LA, locally advanced; *nab*-P, *nab*-paclitaxel; ORR, objective response rate; OS, overall survival; PD
Criteria in Solid Tumors; SG, sacituzumab govitecan; TIL, tumour-infiltrating lymphocyte; TNBC, tri

Primary efficacy endpoint: ORR

Best confirmed overall response rates by investigator, per RECIST v1.1



Atezo + SG: 76.7 ORR
(5 CR)

mFU 10.6 and 11.7m

Higher TROP2 expression,
CD8 and TILs infiltration in responders

2024 ESMO BREAST CANCER

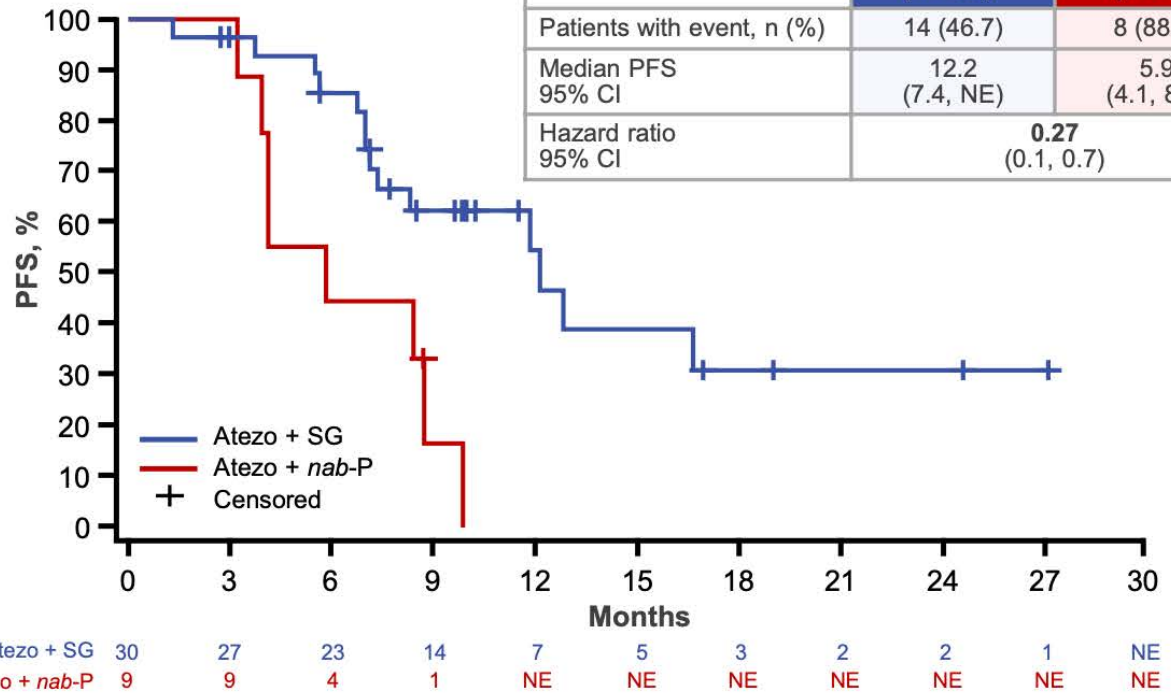
Ciruelos EM

Schmid P, ESMO Breast 2024

Secondary efficacy endpoints: PFS and DOR

PFS

	Atezo + SG (n = 30)*	Atezo + *nab*-P (n = 9)*
Patients with event, n (%)	14 (46.7)	8 (88.9)
Median PFS 95% CI	12.2 (7.4, NE)	5.9 (4.1, 8.7)
Hazard ratio 95% CI	**0.27** (0.1, 0.7)	

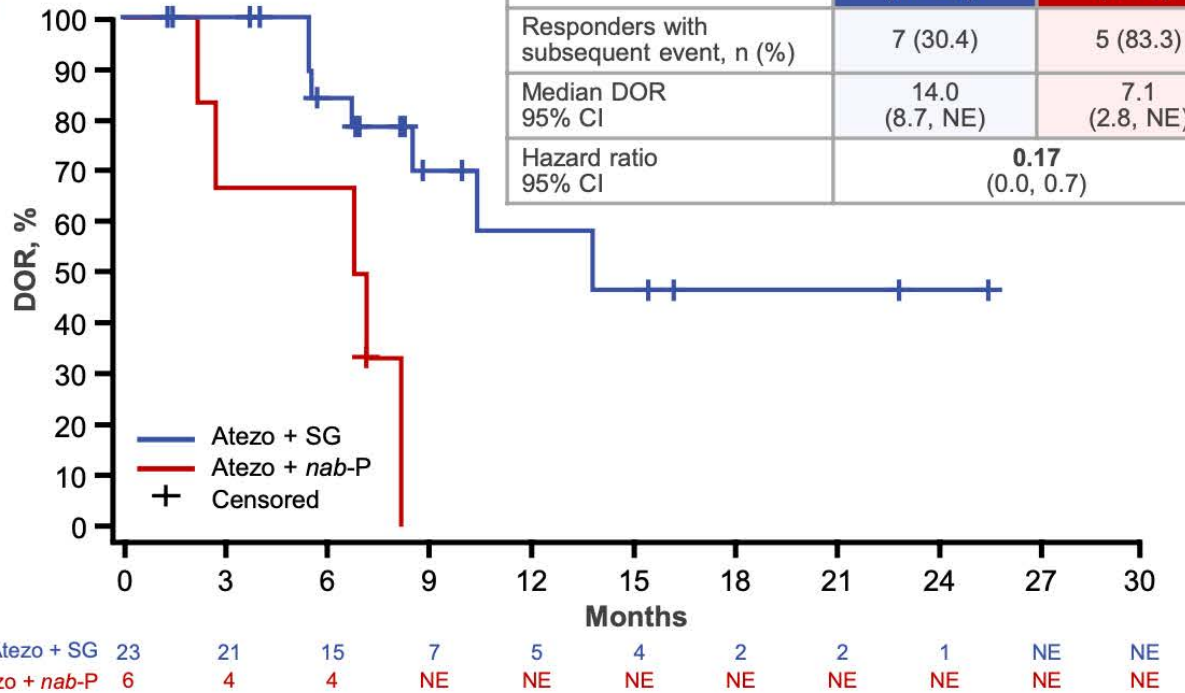


Atezo + SG	30	27	23	14	7	5	3	2	2	1	NE
Atezo + *nab*-P	9	9	4	1	NE	NE	NE	NE	NE	NE	NE

PFS data were immature at this analysis

DOR

	Atezo + SG (n = 23)†	Atezo + *nab*-P (n = 6)†
Responders with subsequent event, n (%)	7 (30.4)	5 (83.3)
Median DOR 95% CI	14.0 (8.7, NE)	7.1 (2.8, NE)
Hazard ratio 95% CI	**0.17** (0.0, 0.7)	



Atezo + SG	23	21	15	7	5	4	2	2	1	NE	NE
Atezo + *nab*-P	6	4	4	NE	NE	NE	NE	NE	NE	NE	NE

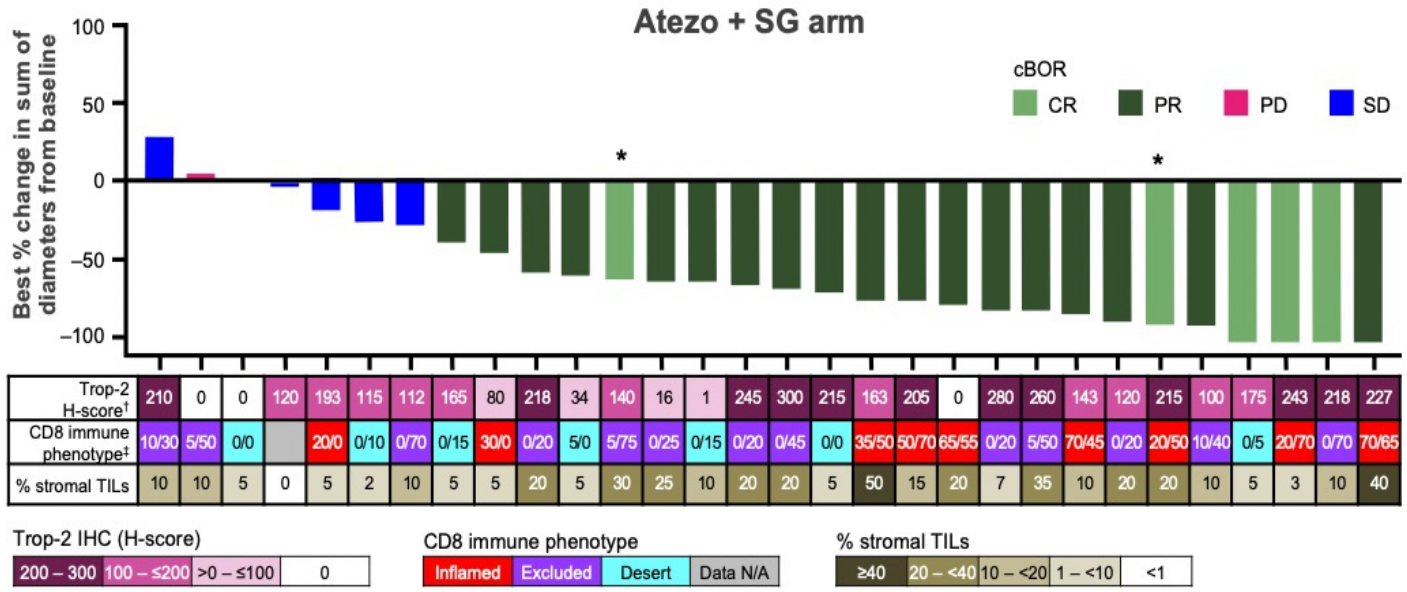
Patients stayed on treatment for longer in the atezo + SG arm

Median duration of follow-up: 10.6 months (atezo + SG) and 11.7 months (atezo + *nab*-P).
* Efficacy- and safety-evaluable population; † 'n' represents number of responders.
Atezo, atezolizumab; CI, confidence interval; DOR, duration of response; *nab*-P, *nab*-paclitaxel; NE, not evaluable; PFS, progression-free survival; SG, sacituzumab govitecan.

Morpheus-panBC

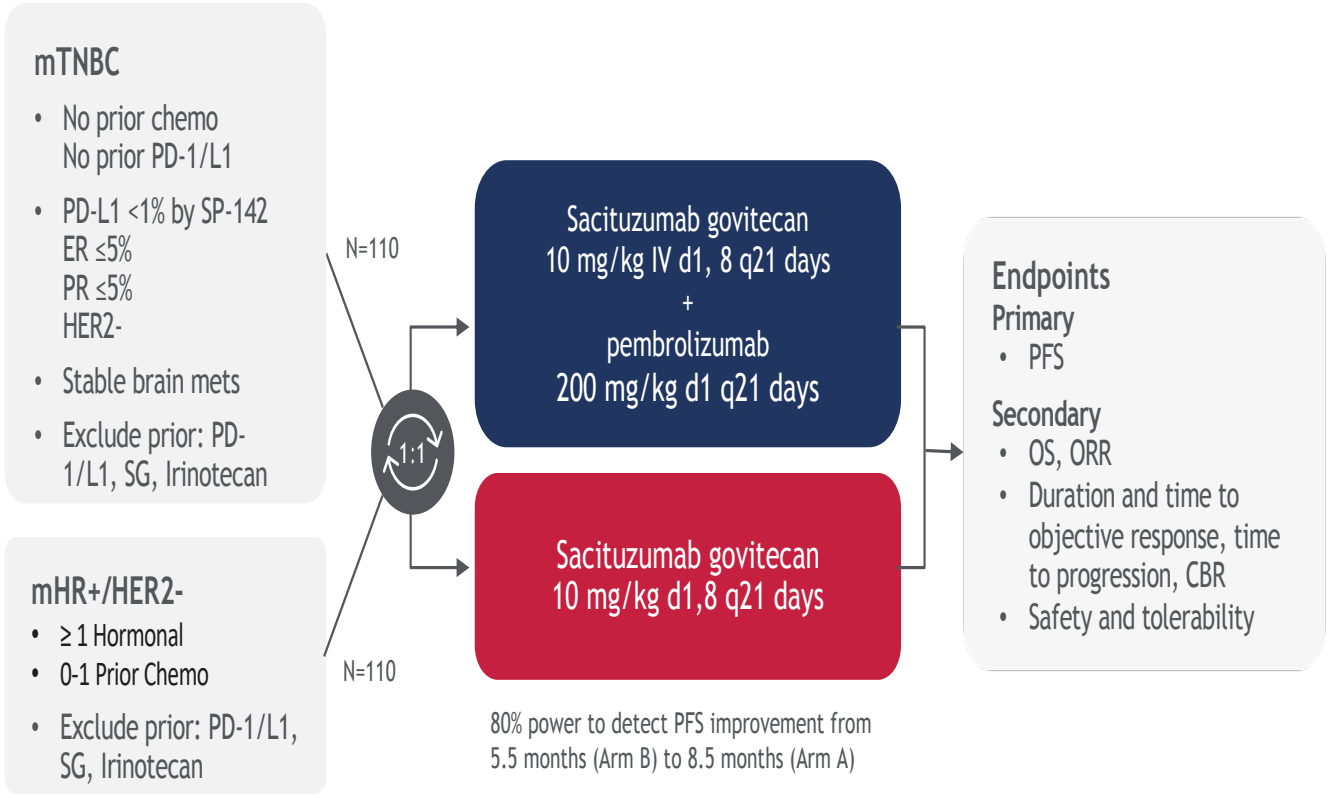
Sacituzumab and Atezolizumab

- 1st line mTNBC
- PD-L1-positive (≥1% IC; SP142)
- N=30; 36% prior taxane use
- Response
  - ORR 76.7%
    - 5 CR
  - Median PFS 12.2 months, DOR 14 months
- AEs
  - As expected with SG
  - Primarily N/V/D and neutropenia



Schmid et al, ESMO BC 2024

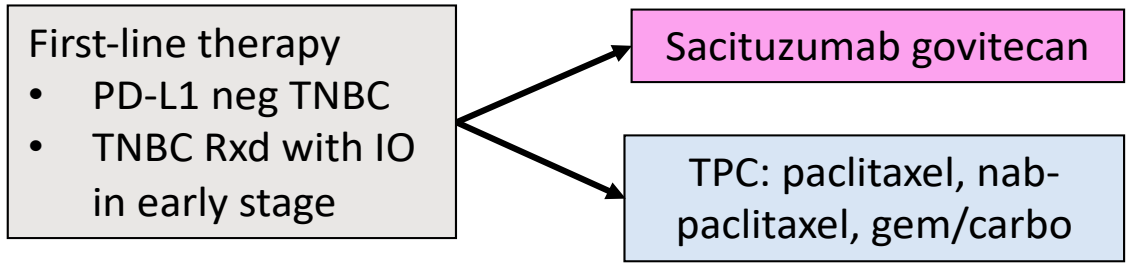
SACI-IO TNBC and HR+: Sacituzumab govitecan +/– pembrolizumab in 1L PD-L1– mTNBC and HR+



Garrido-Castro/Tolaney

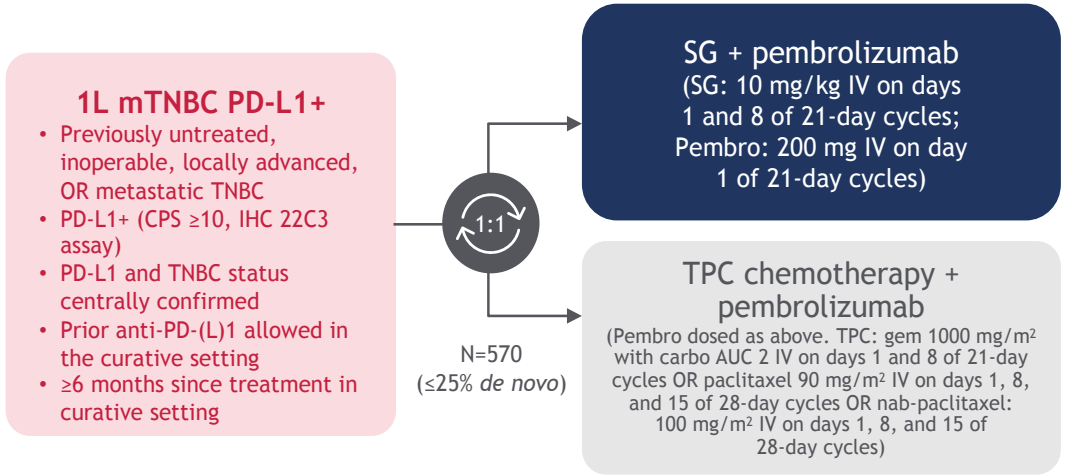
ASCENT-03 (NCT05382299): PD-L1 negative

N=540

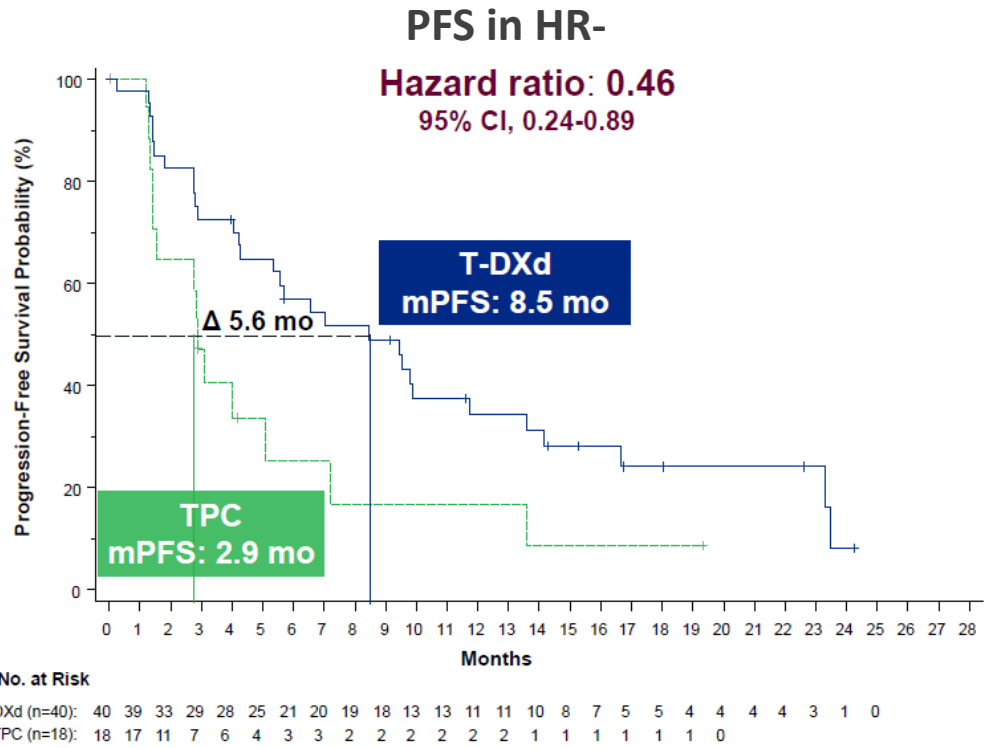


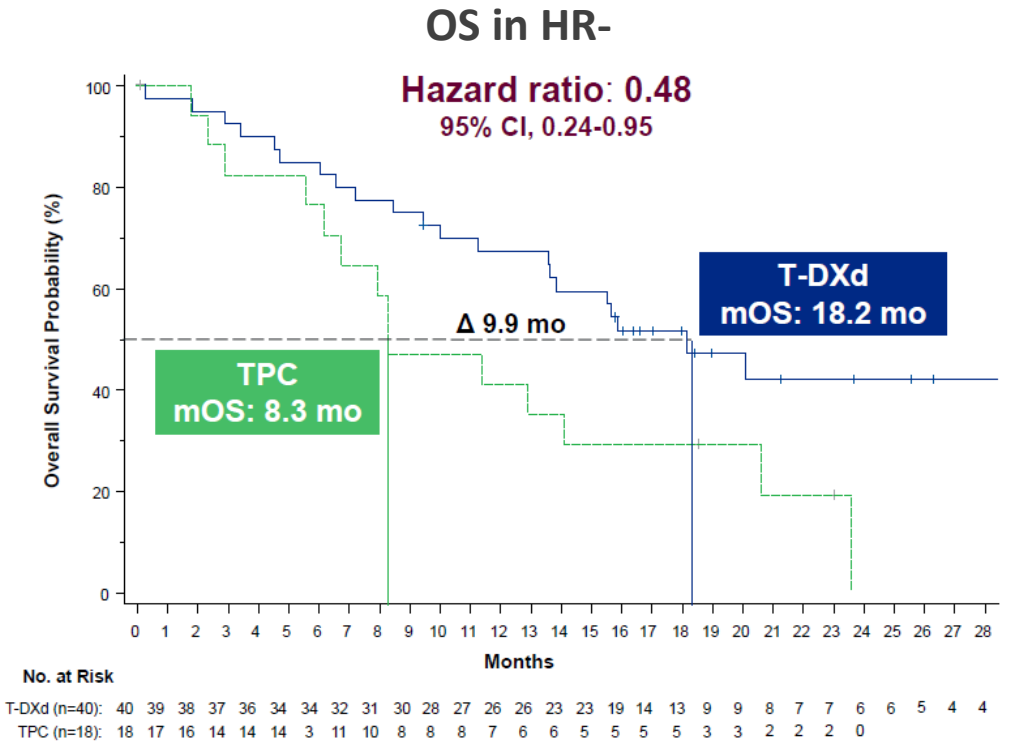
ASCENT-04 (NCT05382286): PD-L1 positive

N=570



DESTINY-Breast04: Exploratory Analysis HR- HER2 low



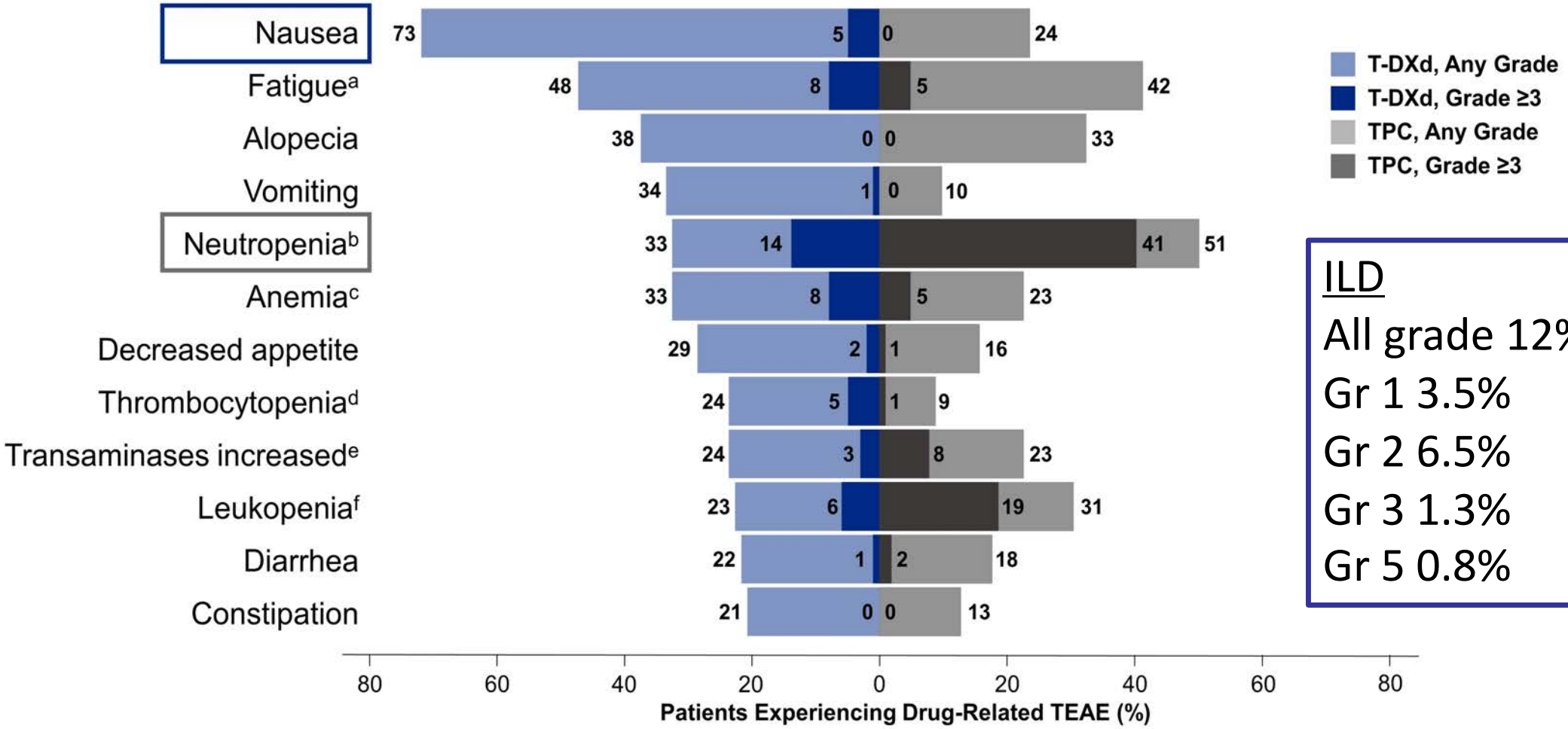


PFS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median PFS, months	8.5	2.9
HR (95% CI)	0.46 (0.24-0.89)	

OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

Modi S, et al. ASCO 2022. Abstract LBA3; Modi S, et al. *New Engl J Med.* 2022 Jun 5. doi: 10.1056/NEJMoa2203690

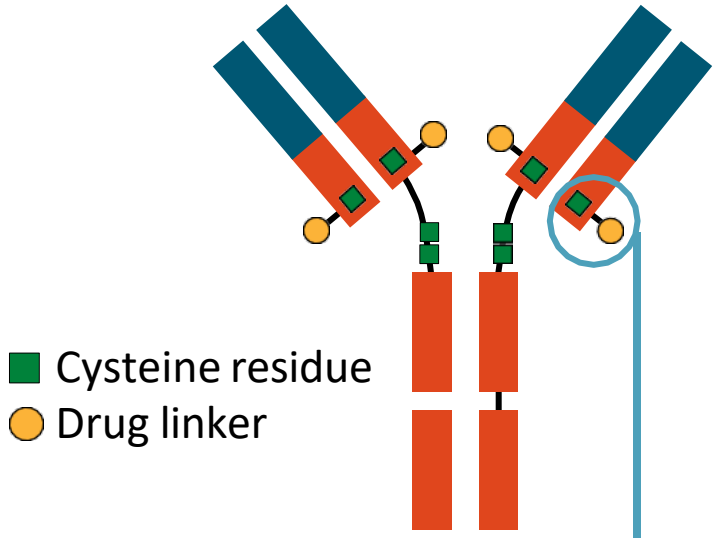
Drug-Related TEAEs in ≥20% of Patients



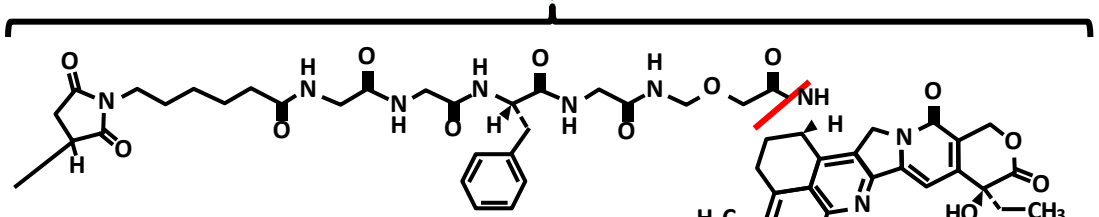
ILD
All grade 12%
Gr 1 3.5%
Gr 2 6.5%
Gr 3 1.3%
Gr 5 0.8%

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Datopotamab Deruxtecan (DS-1062; Dato-DXd): TROP2 Antibody–Drug Conjugate



- **Dato-DXd ADC:**
  - A humanized anti-TROP2 IgG1 mAb
  - Attached to topoisomerase I inhibitor payload (exatecan derivative)
  - Tetrapeptide-based cleavable linker



Cleavable tetrapeptide-based linker

Payload (DXd)
Exatecan derivative

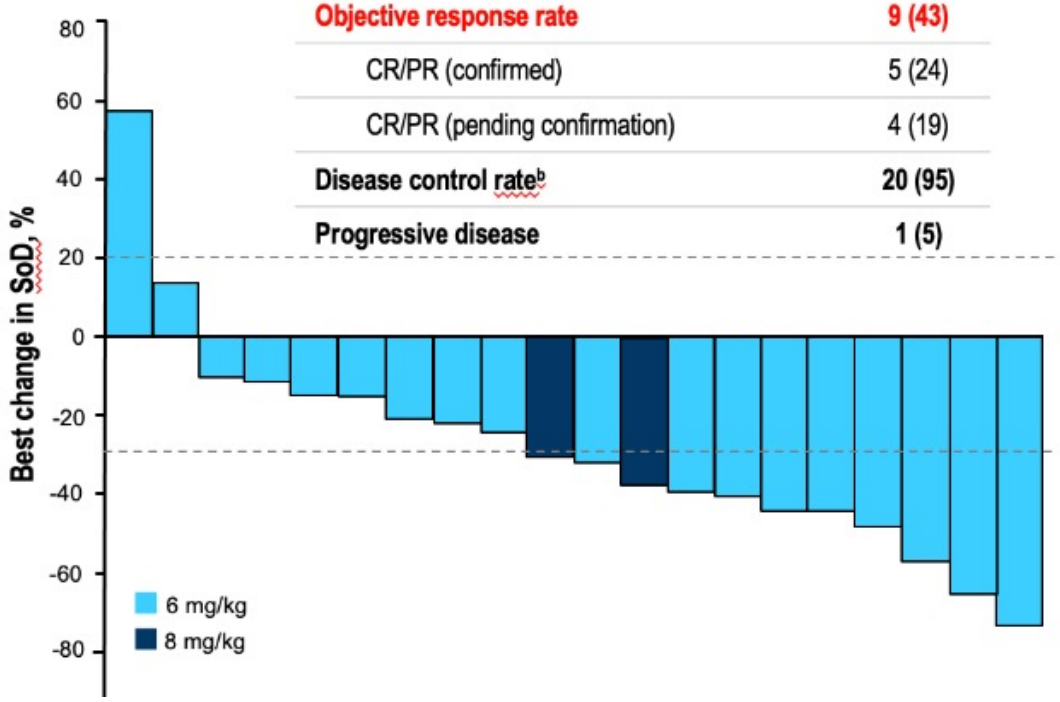
Heist. WCLC 2019. Abstract 3854. Krop. SABCS 2019 Abstr GS1-03.

TROPION-PanTumor01
Dato-DXd Efficacy Signal

71% had ≥3 prior lines
8% had prior sacituzumab

Antitumor Activity (by BICR)

Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)



Preferred Term, n (%)[a]	N=24	
	Any grade	**Grade ≥3**
TEAEs	**24 (100)**	**8 (33)**
Stomatitis	15 (63)	3 (13)
Nausea	15 (63)	0
Fatigue	10 (42)	1 (4)
Vomiting	10 (42)	0
Alopecia	6 (25)	–
Cough	5 (21)	0
Pruritus	5 (21)	0
Anemia	4 (17)	1 (4)
Headache	4 (17)	0
Constipation	4 (17)	0

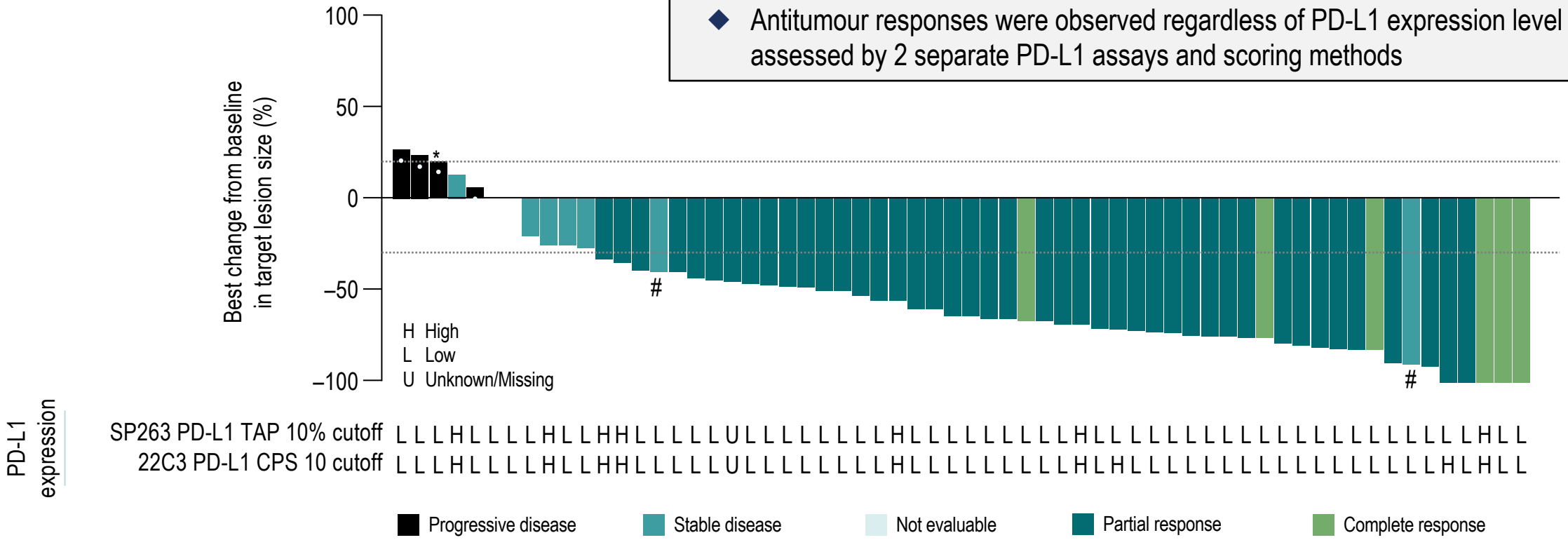
Bardia A, et al. ESMO 2021. *Ann Oncol.* 2021;32 (suppl_2):S60-S78.

BEGONIA Arm 7: Dato-DXd + Durvalumab

- Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Schmid et al. ESMO 2023

TROPION-Breast02 (n=625)

NCT05374512

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI ≤12 months vs DFI >12 months)

Dual primary endpoints:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

- Dato-DxD
- Investigator's choice of chemotherapy

- 1st line therapy for TNBC
- PD-L1 negative

TROPION-Breast05 (n=625)

NCT06103864

Key Eligibility Criteria

- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors

- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625

1:1:1[c]

Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Primary endpoint:
PFS (BICR)

Key secondary endpoint:
OS

Secondary endpoints including:
PFS (inv), ORR, DoR, CBR, TTD, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints including:
TROP2

[a] DFI 6 to 12 months capped at 20%.
[b] Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
[c] Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
[d] In selected countries only.

TROPION-Breast03 (n=1075)

NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

R
1:1:1

- Datopotamab deruxtecan x 8 cycles Durvalumab x 9 cycles
- Datopotamab deruxtecan x 8 cycles
- Capecitabine x 8 cycles OR Pembrolizumab x 9 cycles OR Cape + Pembro

TROPION-Breast04 (n=1728)

NCT06112379

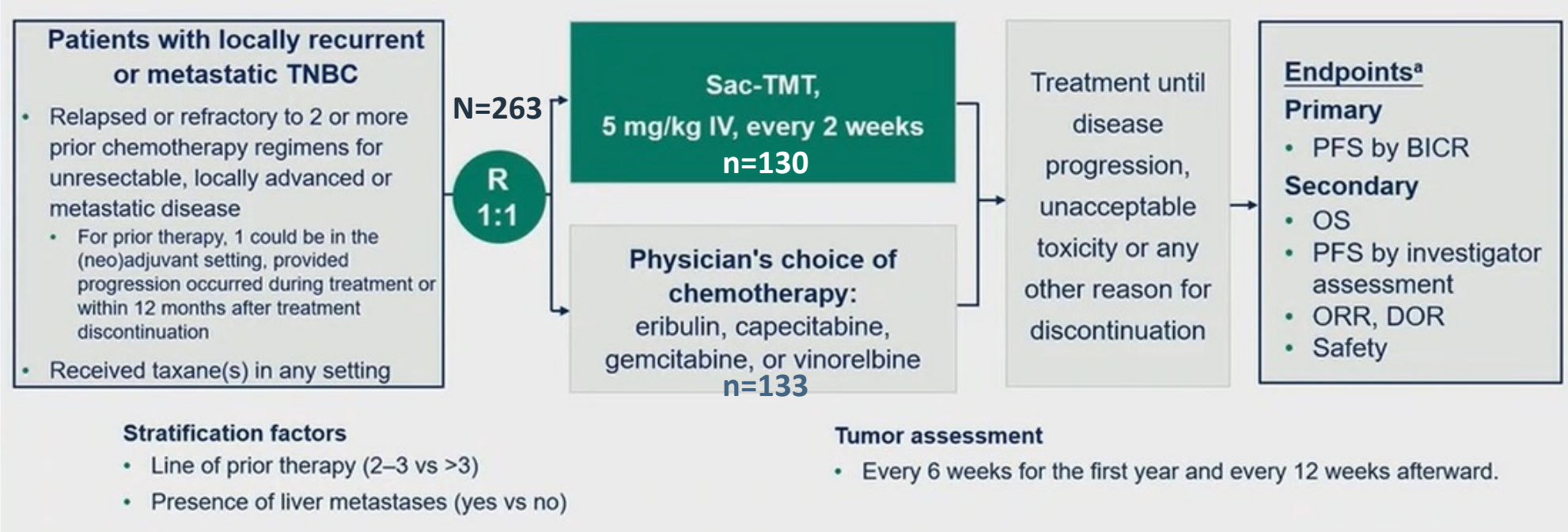
Neoadjuvant therapy for TNBC

- Durvalumab + Dato-DXd x 8 cycles followed by surgery; durva x 9 cycles postop vs KN522

OptiTROP-Breast01 (Phase 3): Sacituzumab tirumotecan for previously treated locally recurrent or metastatic TNBC

- Sacituzumab tirumotecan (sac-TMT) is a TROP2-directed ADC (>80% of TNBCs overexpress TROP2) with a Kthiol (pyrimidine-thiol) linker and a novel topoisomerase I inhibitor (DAR 7.4)

OptiTROP-Breast01: randomized, controlled, open-label study



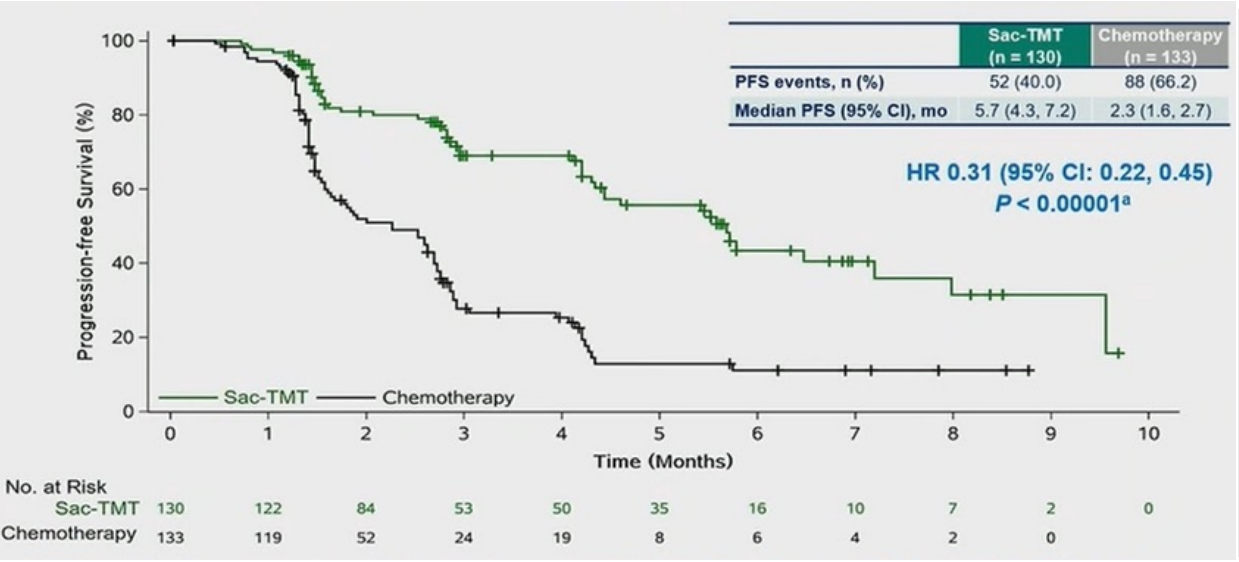
- 67 patients randomized to sac-TMT and 109 patients to PCC discontinued treatment, mostly due to disease progression

Data cutoff: Jun 2023.

Xu B, et al. ASCO 2024. Abstract 104

OptiTROP-Breast01 (Phase 3): Efficacy, PFS

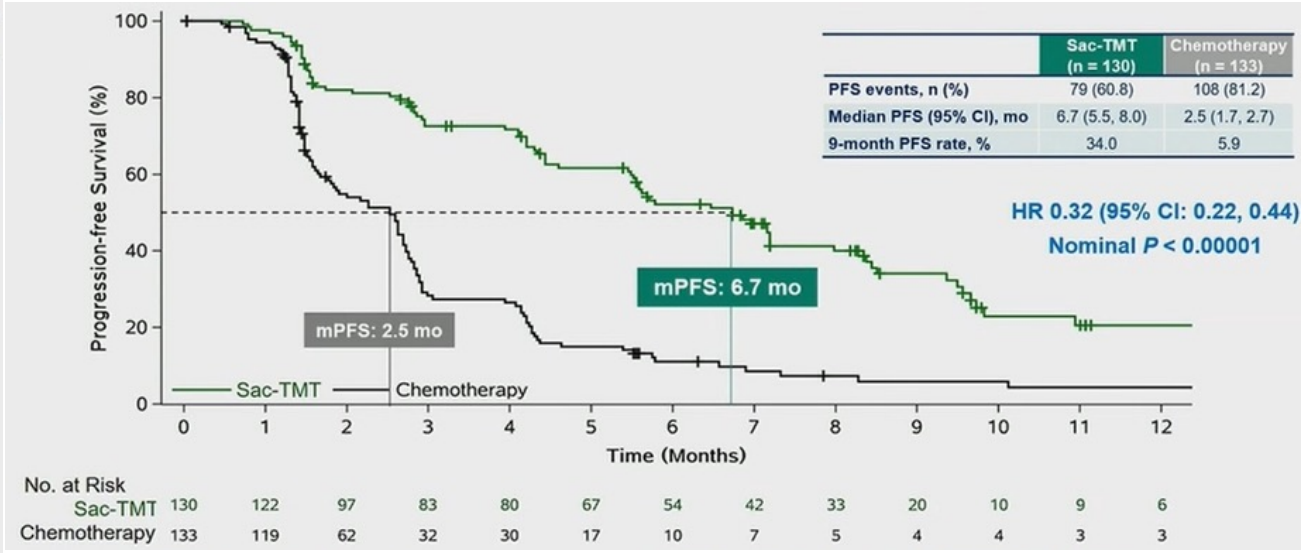
PFS by BICR (interim analysis)



	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	52 (40.0)	88 (66.2)
Median PFS (95% CI), mo	5.7 (4.3, 7.2)	2.3 (1.6, 2.7)

- PFS by investigator assessment: Median 5.7 vs 2.4 months; HR 0.31 (95% CI: 0.21, 0.45)
- Data cutoff: June 21, 2023
- Median follow-up: 5.1 months

PFS by BICR (final analysis)



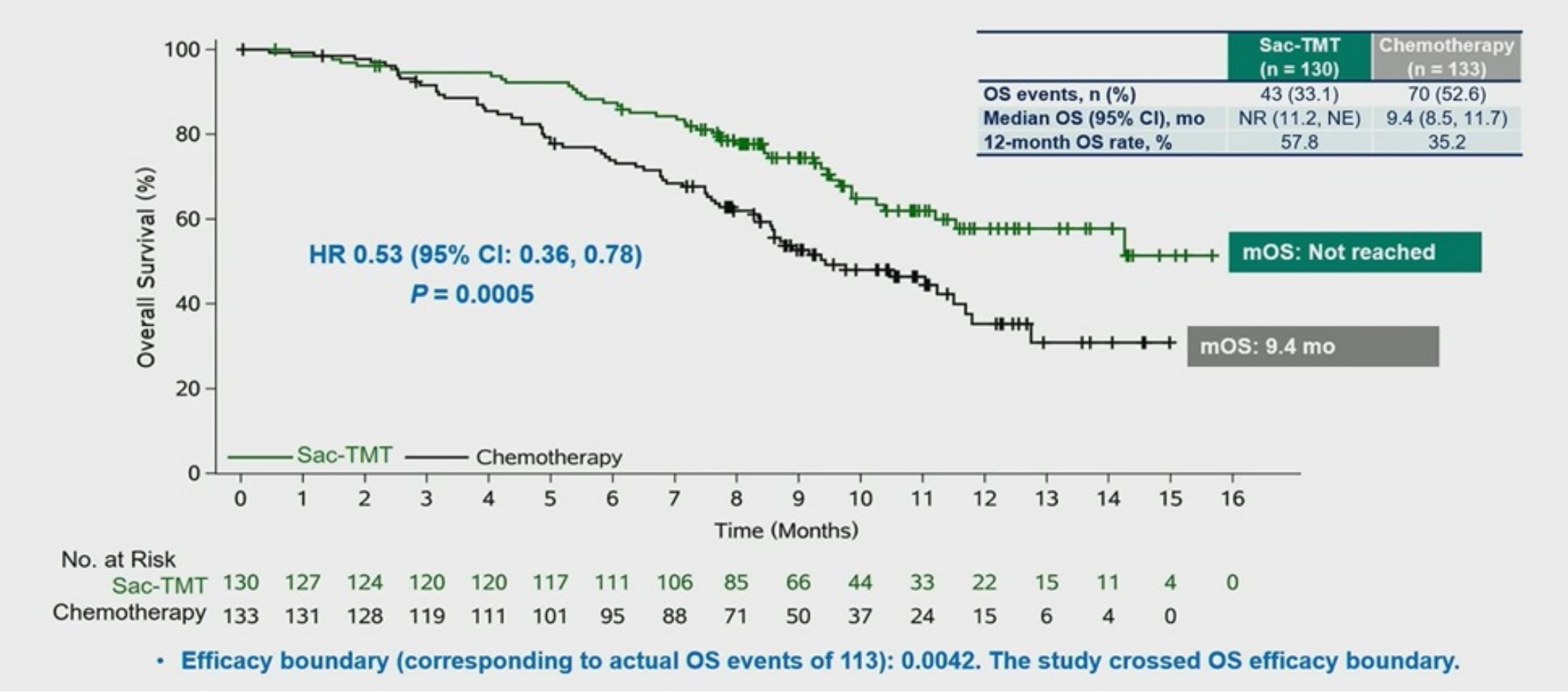
	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	79 (60.8)	108 (81.2)
Median PFS (95% CI), mo	6.7 (5.5, 8.0)	2.5 (1.7, 2.7)
9-month PFS rate, %	34.0	5.9

- PFS by investigator assessment: Median 6.5 vs 2.6 months; HR 0.32 (95% CI: 0.24, 0.44)
- Data cutoff: Nov 30, 2023
- Median follow-up: 10.4 months
- Benefit with sac-TMT observed in all subgroups, HR ≤0.36

TNBC, triple negative breast cancer.

Xu B, et al. ASCO 2024. Abstract 104

OptiTROP-Breast01 (Phase 3): OS (interim analysis)



- Efficacy boundary (corresponding to actual OS events of 113): 0.0042. The study crossed OS efficacy boundary.

Data cutoff: Nov 30, 2023

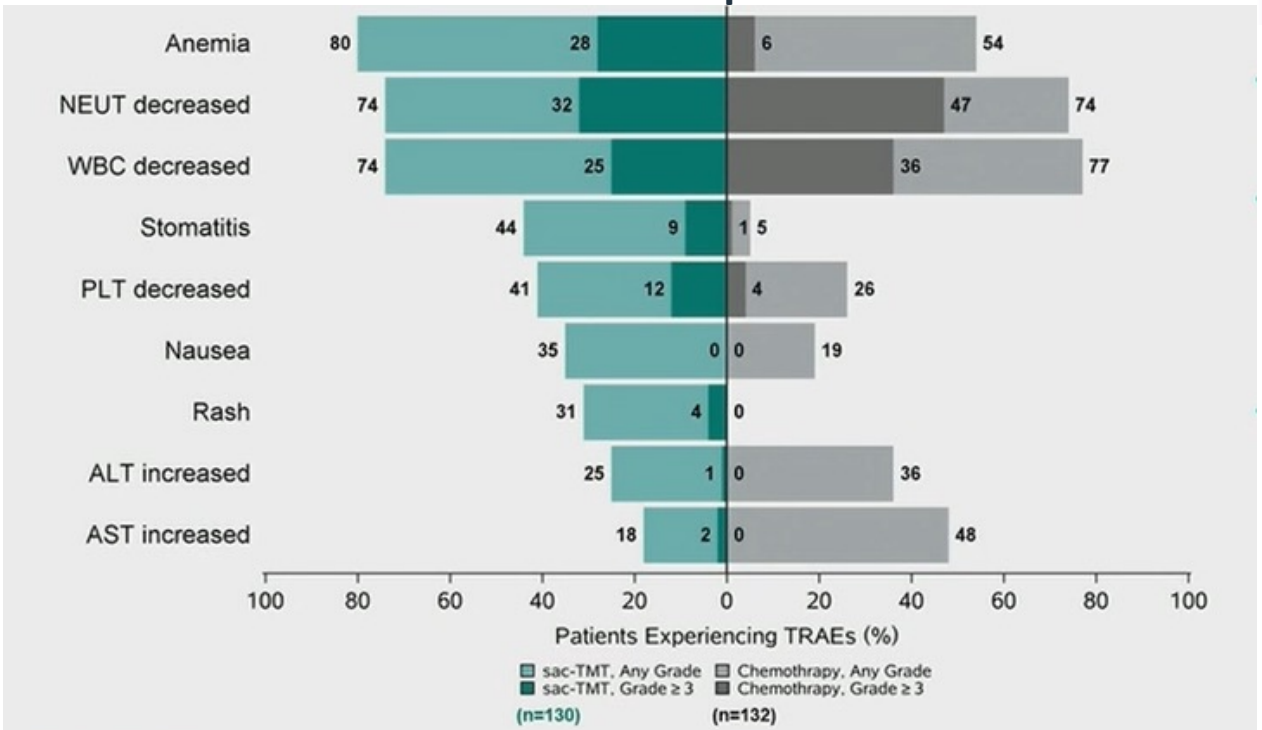
Xu B, et al. ASCO 2024. Abstract 104

OptiTROP-Breast01 (Phase 3): Safety

	Sac-TMT (n=130) n (%)	Chemotherapy (n=132) n (%)
TRAEs	130 (100.0)	127 (96.2)
Grade ≥ 3 TRAEs	75 (57.7)	75 (56.8)
Serious TRAEs	27 (20.8)	17 (12.9)
TRAEs associated with treatment discontinuation	2 (1.5)	2 (1.5)
TRAEs associated with dose reduction	33 (25.4)	21 (15.9)
TRAEs associated with dose interruption	67 (51.5)	53 (40.2)
TRAEs associated with an outcome of death	1 (0.8)	0

- **Median duration of treatment**
  - **Sac-TMT: 15.4 weeks (range, 2.0–44.0)**
  - **Chemotherapy: 8.6 weeks (range, 1.0–40.7)**
- Most common TRAEs associated with dose reduction
  - Sac-TMT: anemia (13.8%) and stomatitis (5.4%)
  - Chemotherapy: NEUT decreased (11.4%) and WBC decreased (6.8%)
- Most common TRAEs associated with dose interruption
  - Sac-TMT *vs* chemotherapy: NEUT decreased (19.2% *vs* 28.0%) and WBC decreased (18.5% *vs* 25.0%)
- One death with sac-TMT was attributed to multiple causes, including COVID-19 infection as well as disease progression.

TRAEs in ≥30% of patients



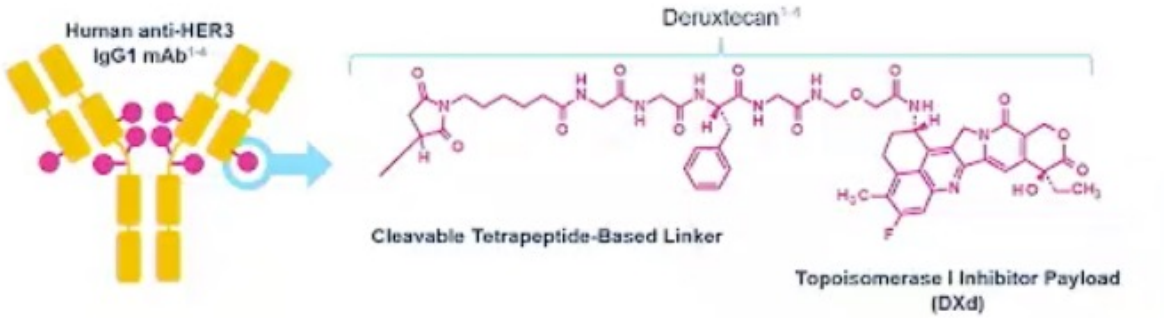
Data cutoff: Jun 21, 2023

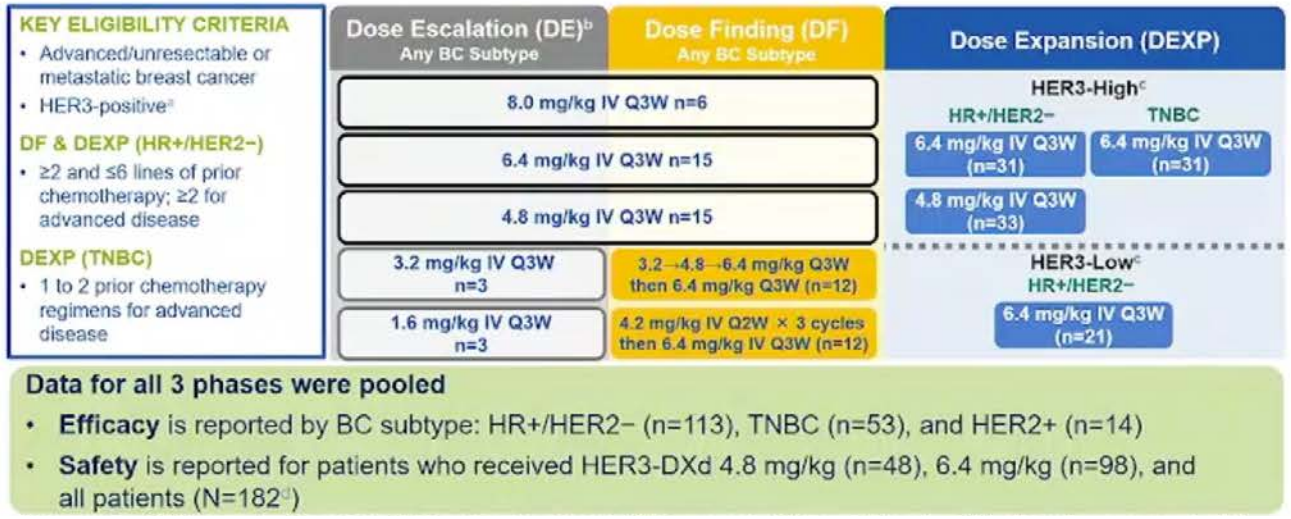
Xu B, et al. ASCO 2024. Abstract 104

RD

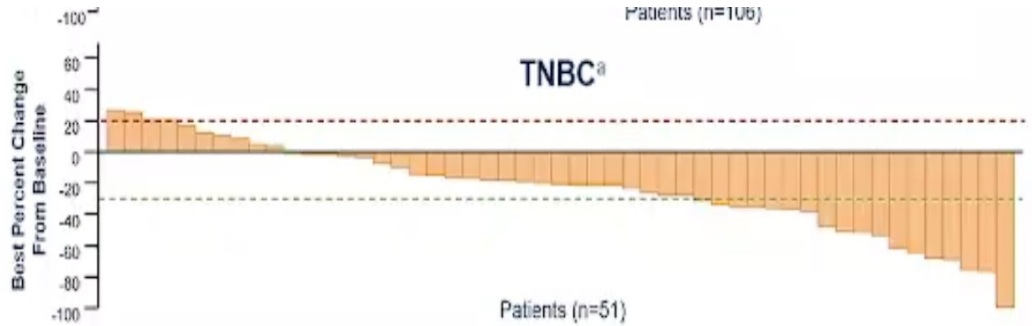
GC

HER3-DXd (Patritumab deruxtecan) in HER3“+” BC





TNBC (n=53)
(HER2 0 36%; HER2 “low” 55%)
Brain metastases 9%
Liver/Lung metastases 64%
Med # prior regimens 2 (1-13)



TNBC	
ORR	22.6%
mDOR	5.9m
mPFS	5.5m
mOS	14.6m

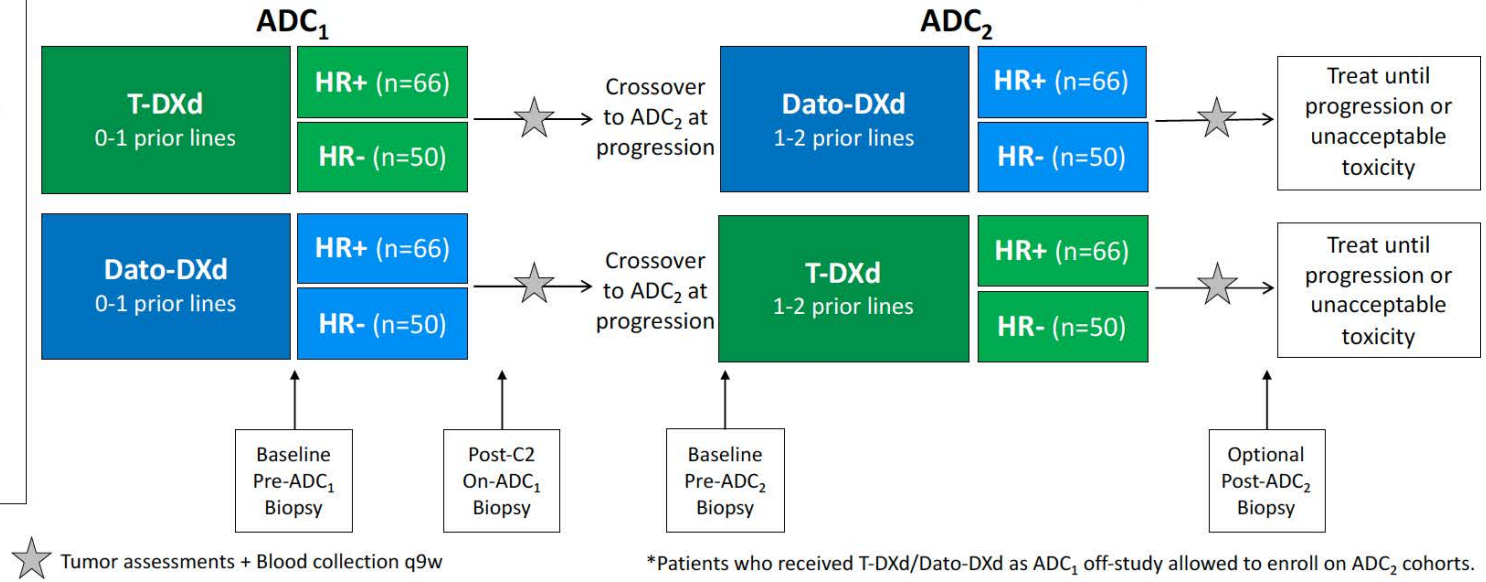
Krop et al, ASCO 2022; Krop et al, *JCO* 2023.

TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd).
PI: Ana Garrido-Castro

Eligibility:
- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

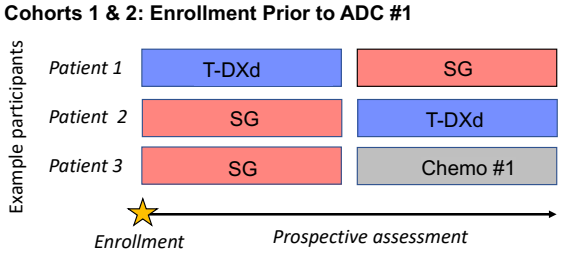
*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



Registry Sequencing Study:
Laura Huppert UCSF

Trials evaluating sequencing of SG, Dato-DXd and T-DXd

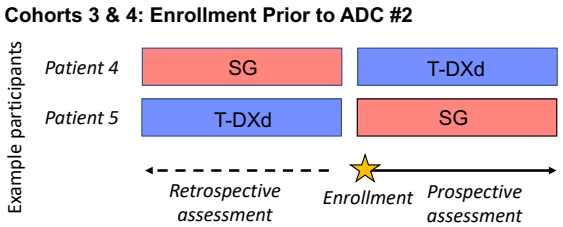


Cohort 1: HR+/HER2- HER2 low
~35 patients

Cohort 2: TNBC, HER2 low
~25 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:
- Allows for prospective assessment of ADC #1 and ADC #2 efficacy, including PRO data and collection of blood for translational endpoints
- Potential barrier: Patient not guaranteed to get ADC #2 (e.g., example patient #3 shown here)



Cohort 3: HR+/HER2-
~25 patients

Cohort 4: TNBC
~15 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:
- Allows for prospective assessment of ADC #2 safety and efficacy, including PRO data and translational endpoints
- Allows for retrospective safety and efficacy of ADC #1

Agenda

Module 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Hurvitz

Module 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Burstein

Module 3: Selection and Sequencing of Treatment for Patients with HR-Positive, HER2-Negative Disease Who Experience Progression on CDK4/6 Inhibition — Dr Rugo

Module 4: Current and Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Prof Curigliano

Module 5: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 6: Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC — Dr Bardia

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Utility of ctDNA testing for patients with ER-positive breast cancer

Dr Gigi Chen (Pleasant Hill, California)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

In what situations, if any, will you use tumor-informed ctDNA monitoring in patients with localized or metastatic breast cancer?

QUESTIONS FOR THE FACULTY

Would you like to have access to Dato-DXd at the current time?

If this agent were to become available, how do you envision selecting between it and sacituzumab govitecan?

QUESTIONS FOR THE FACULTY

Do you have any concerns about using Dato-DXd for a patient who has experienced disease progression on T-DXd given that they both rely on a deruxtecan backbone?

Would you consider using this agent for a patient whose disease has progressed on sacituzumab govitecan?

Current and Future Strategies for the Care of Individuals with Endocrine-Refractory HR-Positive mBC

Aditya Bardia, MD, MPH

Program Director, Breast Medical Oncology, UCLA,
Assistant Chief, Hem Onc (Translational Research),
Director of Translational Research Integration,
Jonsson Comprehensive Cancer Center, Los Angeles

UCLA Health
Jonsson Comprehensive Cancer Center

David Geffen School of Medicine

Objectives

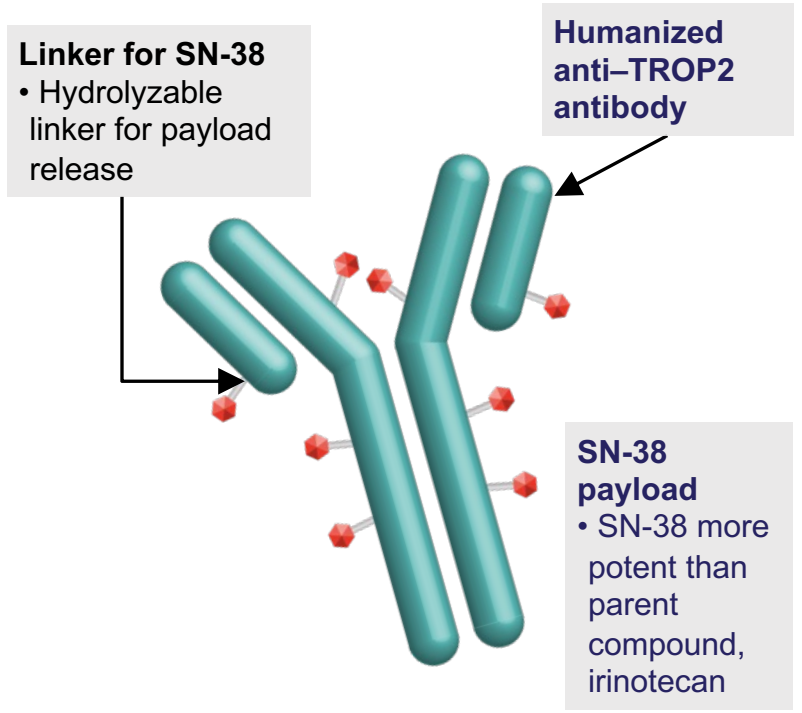
Spotlight on TROP2 ADCs:

- Current status
- Where the field is going
- Potential challenges and opportunities

Sacituzumab Govitecan: First-in-class TROP2 ADC

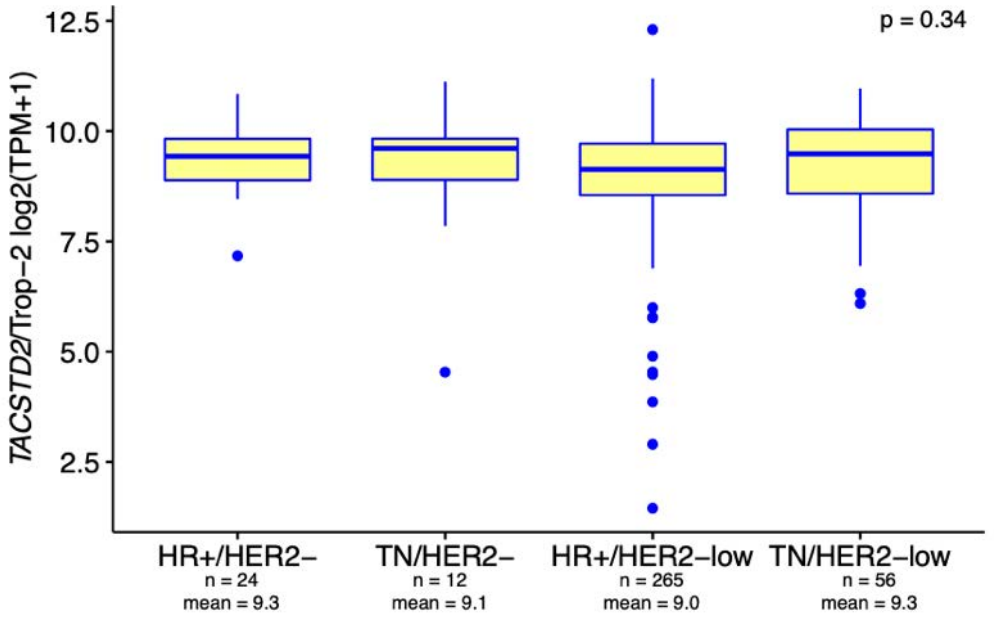
SG is distinct from other ADCs

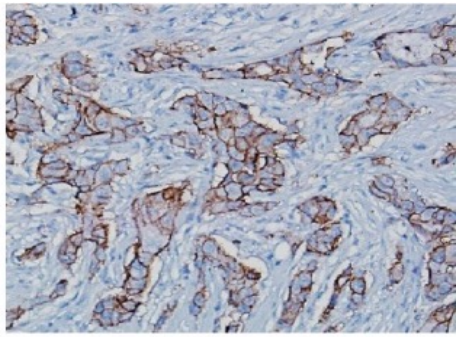
- Antibody highly specific for TROP2
- High drug-to-antibody ratio (7.6:1)
- Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
- Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Nagayama A et al. *Ther Adv Med Oncol*. 2020; Cardillo TM et al. *Bioconjugate Chem.* 2015.

Rationale for TROP2 ADC: HR+ MBC



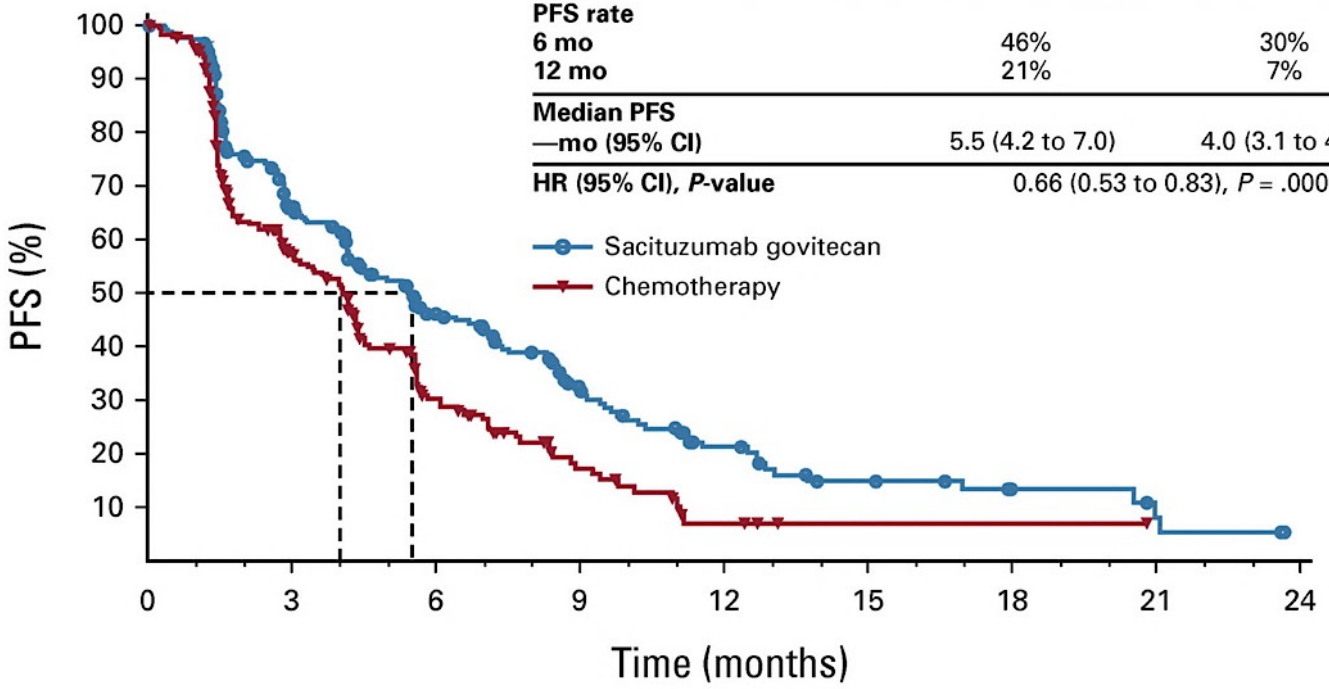


HR+ Breast Cancer

Medford A et al.

Sacituzumab Govitecan vs TPC: PFS in HR+ MBC (TROPiCS-02)

	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	

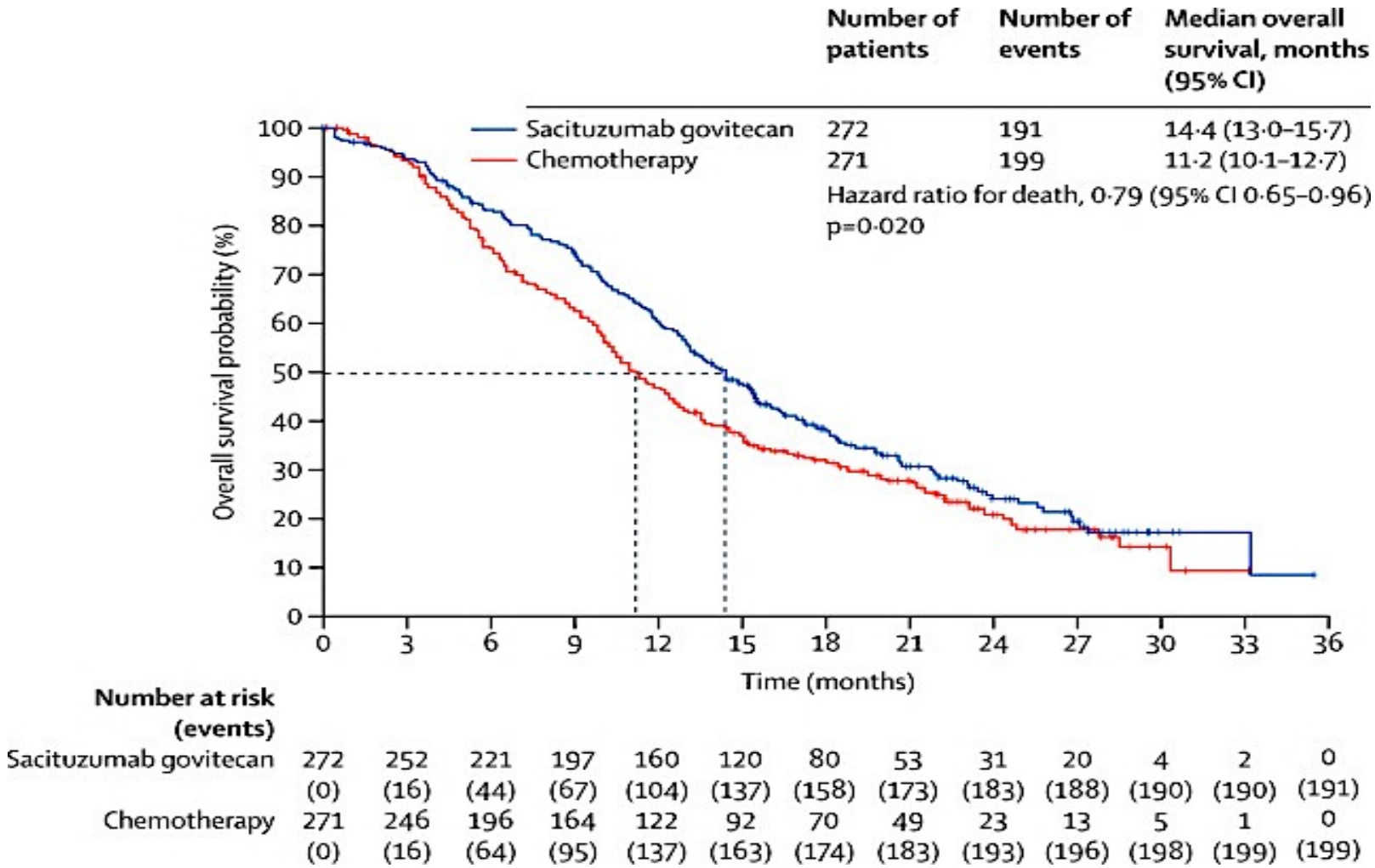


No. at risk:									
Sacituzumab govitecan	272	148	82	44	22	12	6	3	0
Chemotherapy	271	105	41	17	4	1	1	0	

Included in NCCN guidelines

Rugo H and Bardia A et al. JCO 2022

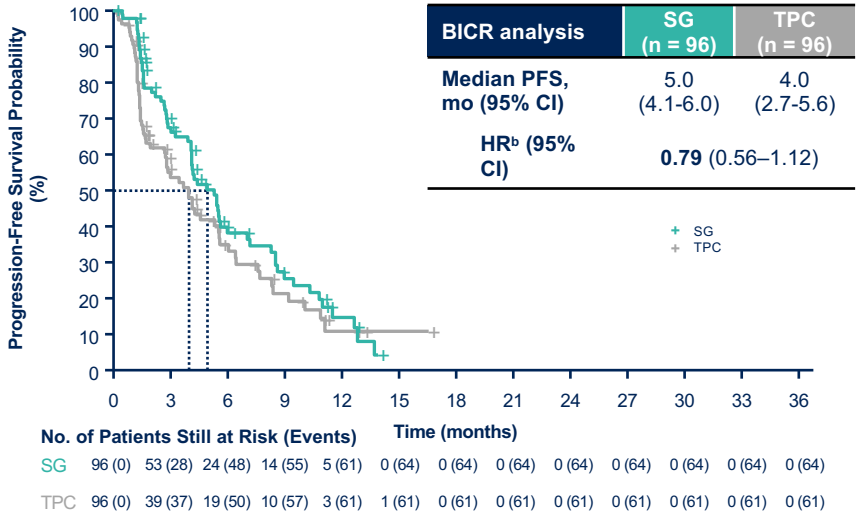
Sacituzumab Govitecan vs TPC: Overall Survival (TROPiCS-02)



Rugo H and Bardia A et al. Lancet 2023

Sacituzumab Govitecan vs TPC: Efficacy by TROP2 status (TROPiCS-02)

H-score < 100[a]

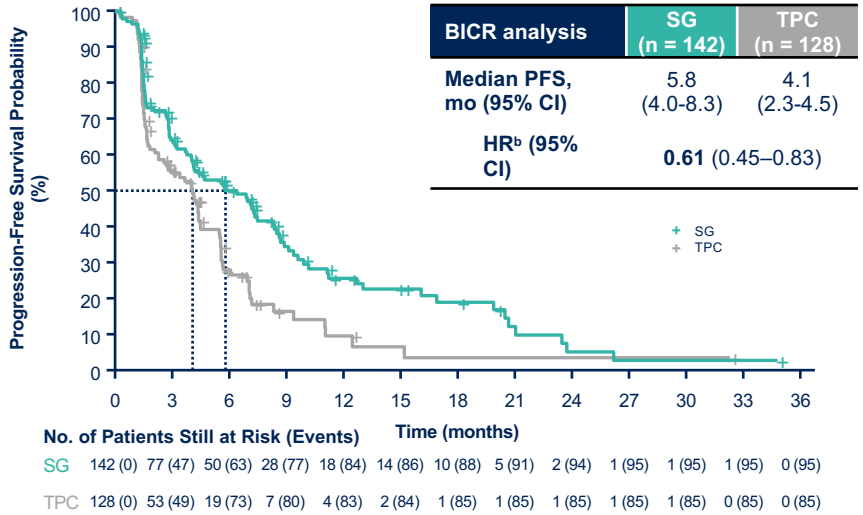


BICR analysis	SG (n = 96)	TPC (n = 96)
Median PFS, mo (95% CI)	5.0 (4.1-6.0)	4.0 (2.7-5.6)
HR[b] (95% CI)	**0.79** (0.56–1.12)	

No. of Patients Still at Risk (Events)

SG	96 (0)	53 (28)	24 (48)	14 (55)	5 (61)	0 (64)	0 (64)	0 (64)	0 (64)	0 (64)	0 (64)	0 (64)	0 (64)
TPC	96 (0)	39 (37)	19 (50)	10 (57)	3 (61)	1 (61)	0 (61)	0 (61)	0 (61)	0 (61)	0 (61)	0 (61)	0 (61)

H-score ≥ 100[a]



BICR analysis	SG (n = 142)	TPC (n = 128)
Median PFS, mo (95% CI)	5.8 (4.0-8.3)	4.1 (2.3-4.5)
HR[b] (95% CI)	**0.61** (0.45–0.83)	

No. of Patients Still at Risk (Events)

SG	142 (0)	77 (47)	50 (63)	28 (77)	18 (84)	14 (86)	10 (88)	5 (91)	2 (94)	1 (95)	1 (95)	1 (95)	0 (95)
TPC	128 (0)	53 (49)	19 (73)	7 (80)	4 (83)	2 (84)	1 (85)	1 (85)	1 (85)	1 (85)	1 (85)	0 (85)	0 (85)

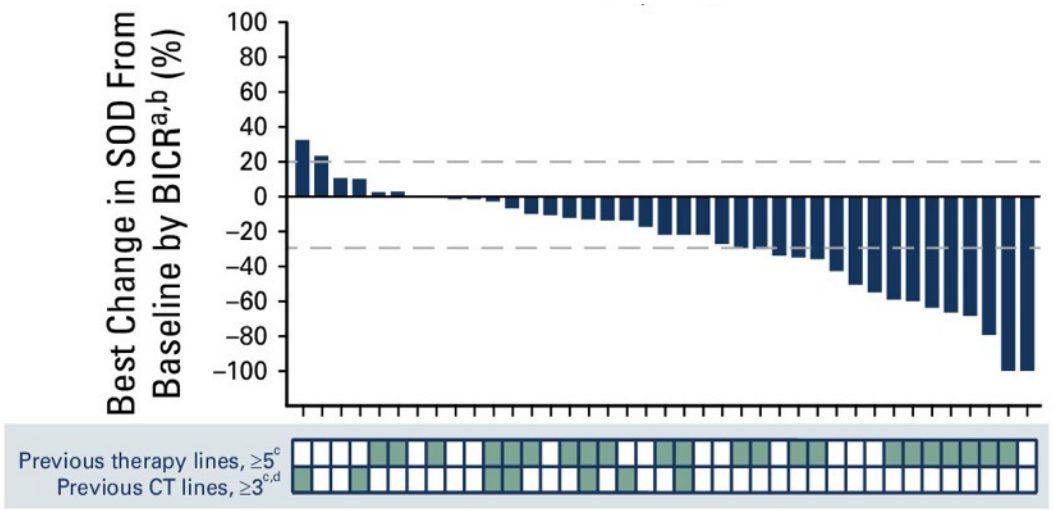
PFS outcome favored SG over TPC in the H-score < 100 and the H-score ≥ 100 groups with longer follow-up, consistent with a previous analysis[1]

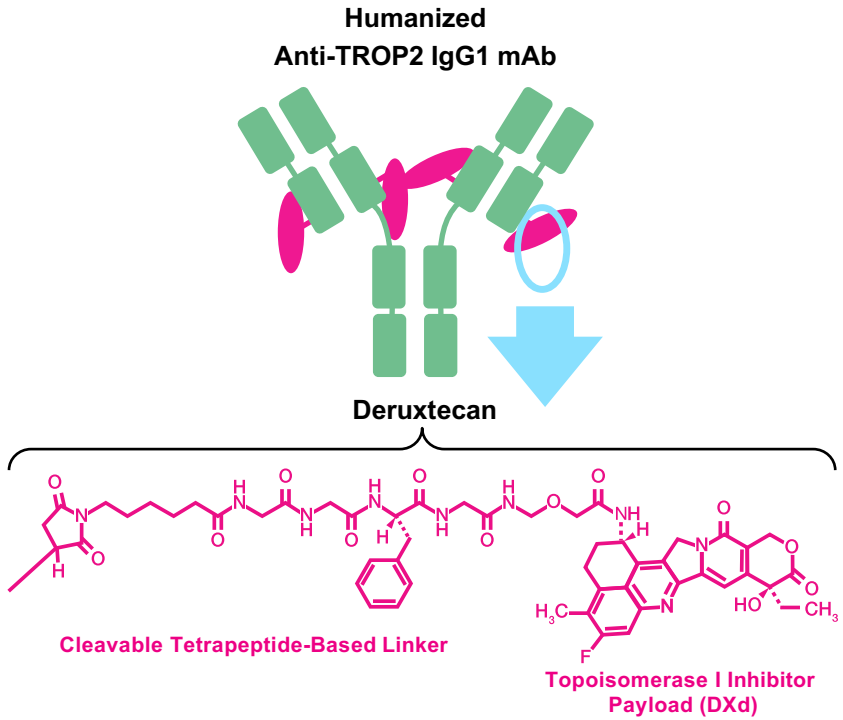
BICR, blinded independent central review; CI, confidence interval; H-score, histochemical score; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TROP2, trophoblast cell surface antigen 2.
[a]42% of patients had H-score < 100 and 58% had H-score ≥ 100. [b]HR is from an unstratified Cox Regression analysis.
1. Rugo HS, et al. Oral presentation at San Antonio Breast Cancer Symposium (SABCS); December 6-10, 2022; San Antonio, TX, USA. Abstract GS1-11.

Tolaney S et al. ASCO 2023

How about other drugs?

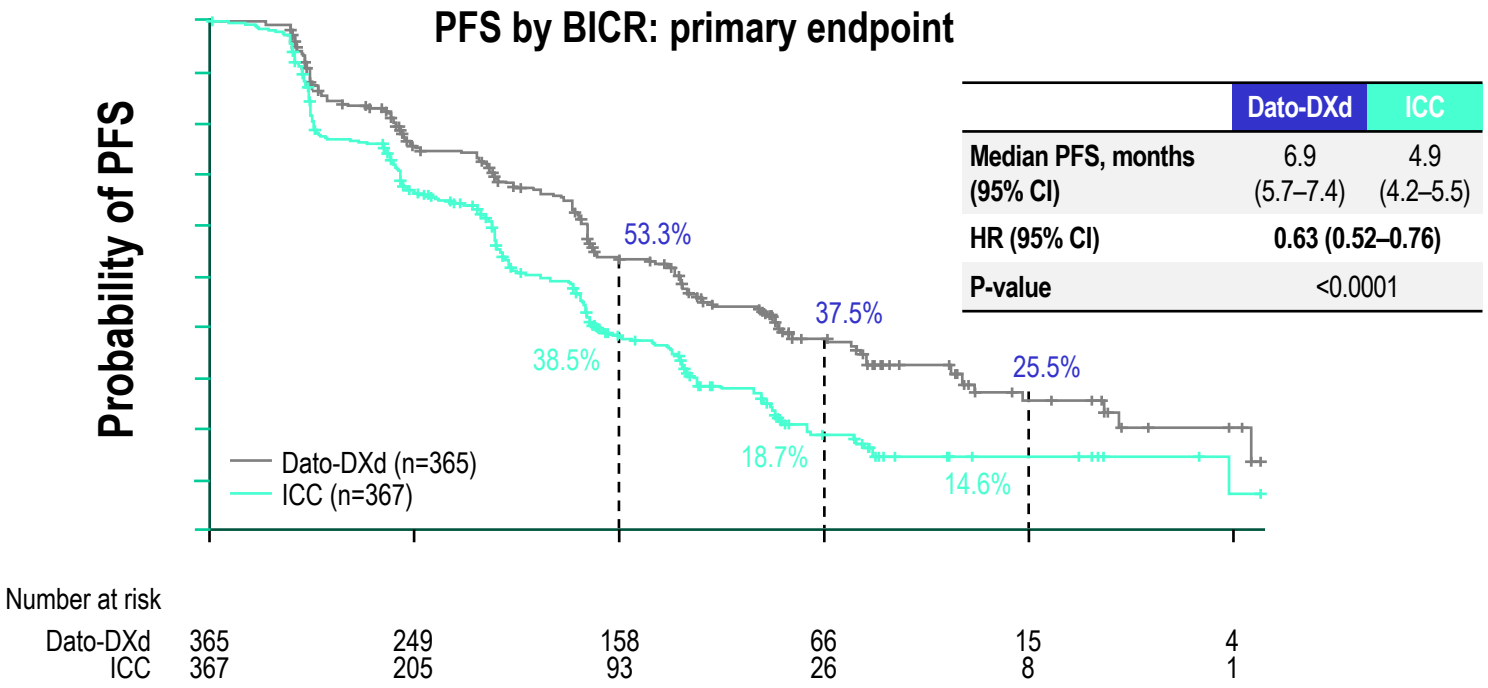
- Dato-DXd is a differentiated TROP2-directed ADC designed with 3 components different from SG:
  - Different humanized anti-TROP2 IgG1 mAb
  - Different topoisomerase I inhibitor payload (exatecan derivative, DXd)
  - Different tetrapeptide-based cleavable linker
- Given IV every 3 weeks (different from SG)
- Dato-DXd has demonstrated highly encouraging antitumor activity in breast cancer, including HR+ MBC and TNBC





Bardia A et al. JCO 2024

Dato-DXd: Progression-Free Survival (TROPION-Breast01)



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

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

Bardia A, et al ESMO 2023.

Dato-DXd in HR+ MBC (TROPION-Breast01)

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

- Most TRAEs were grade 1–2 and manageable

AESIs

- Oral mucositis/stomatitis:† led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events:‡ most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD:§ rate was low; mainly grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)¶	0

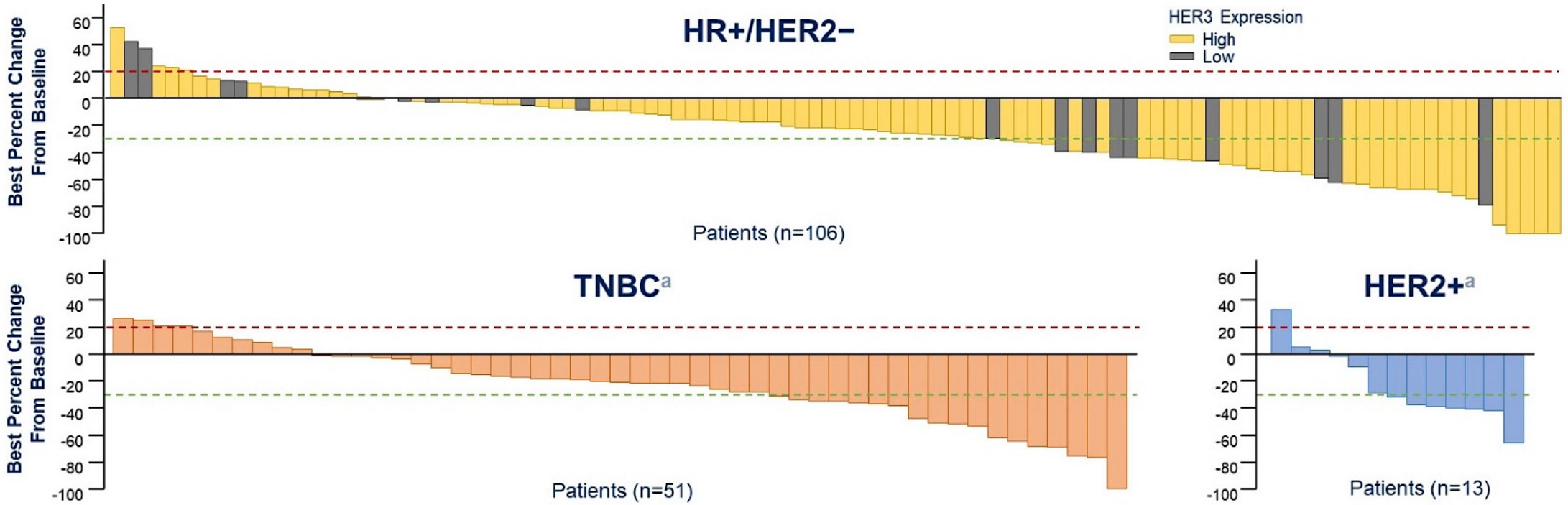
MADRID 2023 ESMO congress

Bardia A, et al ESMO 2023.

Ongoing Clinical Trials with SG and Dato-DXd in Breast Cancer

Clinical Trial	Setting	Intervention
ASCENT-03/04	1st line Metastatic TNBC	SG vs TPC (+/- IO)
ASCENT-05	Residual disease after NACT for localized TNBC	SG+Pembro vs Pembro +/- Cape
ASCENT-07	1st line Metastatic HR+ MBC (endocrine-resistant setting)	SG vs TPC
TROPION-Breast02	1st line Metastatic TNBC (PD-L1 neg)	Dato-DXd vs TPC
TROPION-Breast03	Residual disease after NACT for localized TNBC	Dato-DXd ± durvalumab vs ICT
TROPION-Breast04	Neoadjuvant therapy for TNBC	Dato-DXd+Durva vs TPC + IO
TROPION-Breast05	1st line Metastatic TNBC (PD-L1 pos)	Dato-DXd +/- Durva vs TPC + IO

Patritumab Deruxtecan (U3-1402): ADC Targeting HER3



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

Krop IE et al. J Clin Oncol 2023

ADCs to target MBC: Multiple Agents in Development

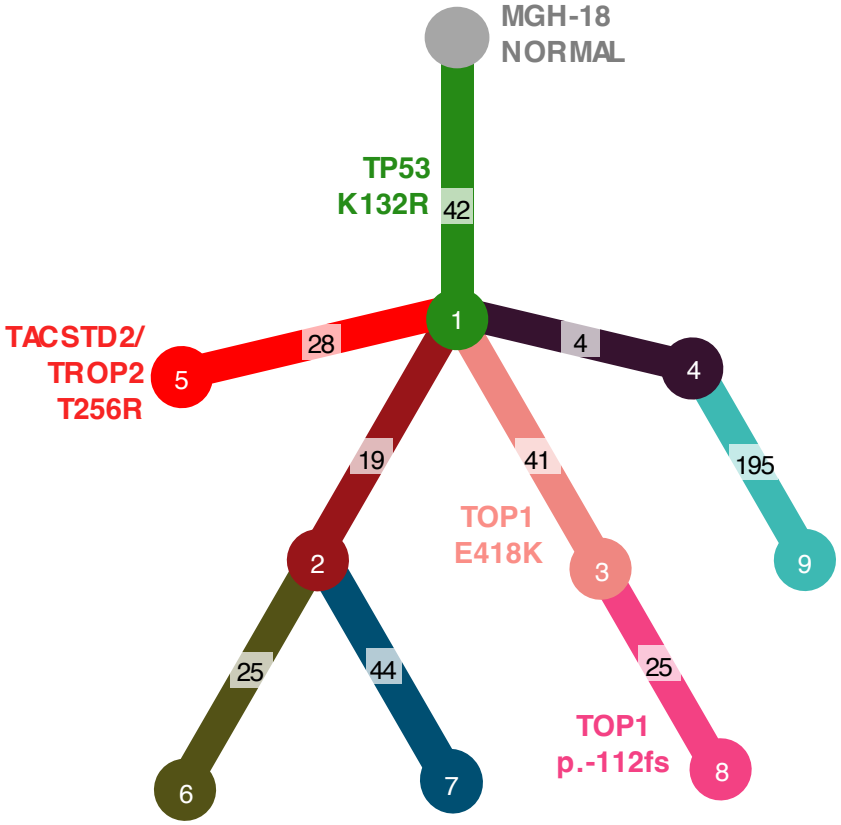
Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	TROP2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	TROP2	Topo-1 inhibitor
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
NBE-002	ROR1	Topo-2 inhibitor
Praluzatamab ravtansine	CD166	Microtubule inhibitor

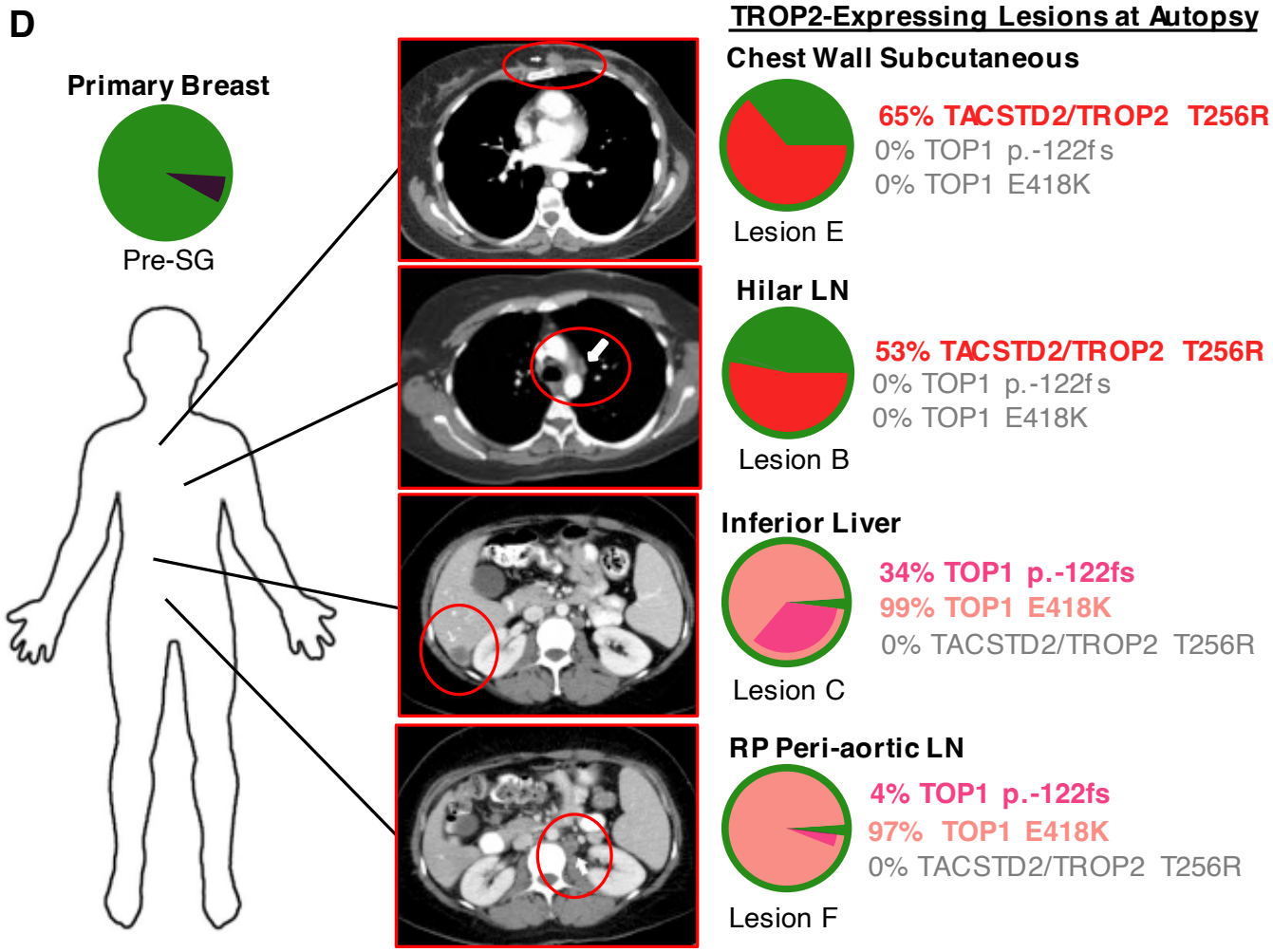
Challenge

How to sequence ADC after ADC?

Understand mechanism governing resistance to ADC

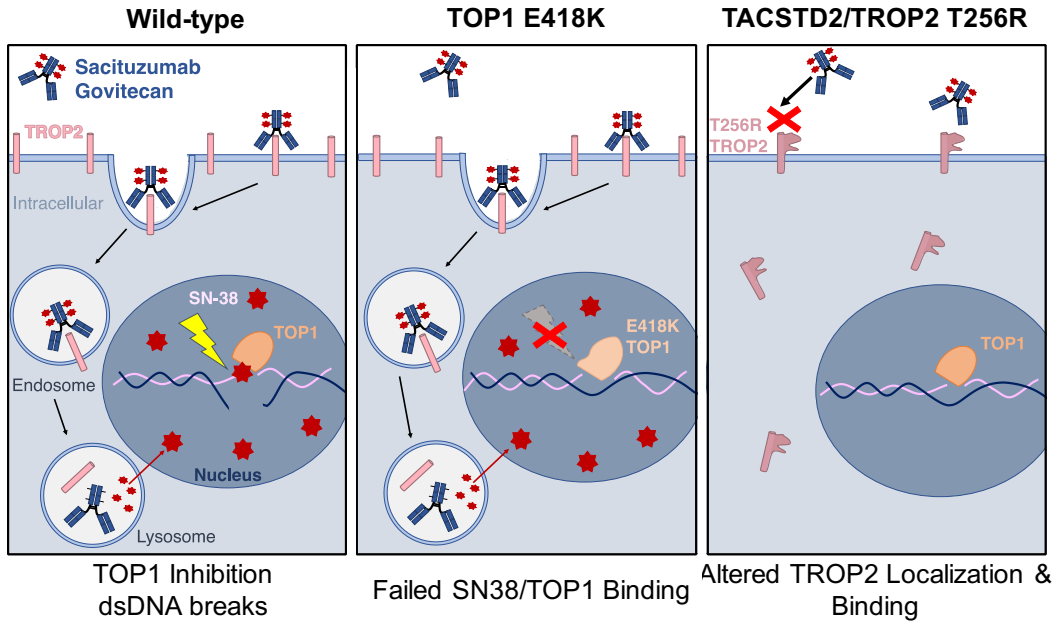
Mechanism Governing Resistance: Antibody vs Payload

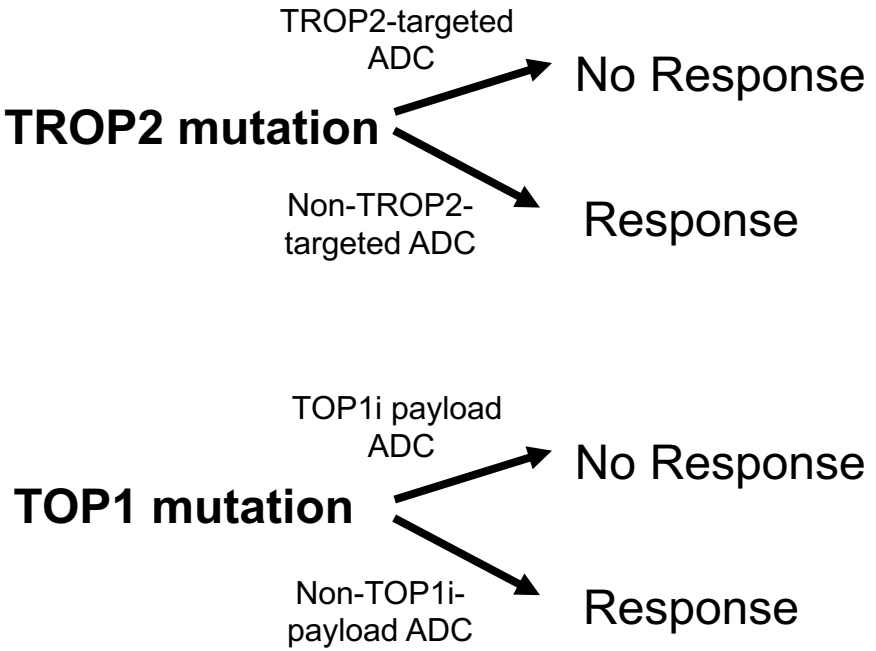




Coates, Sun et al Cancer Discovery 2021.

Implications of resistance mechanisms for ADC sequencing

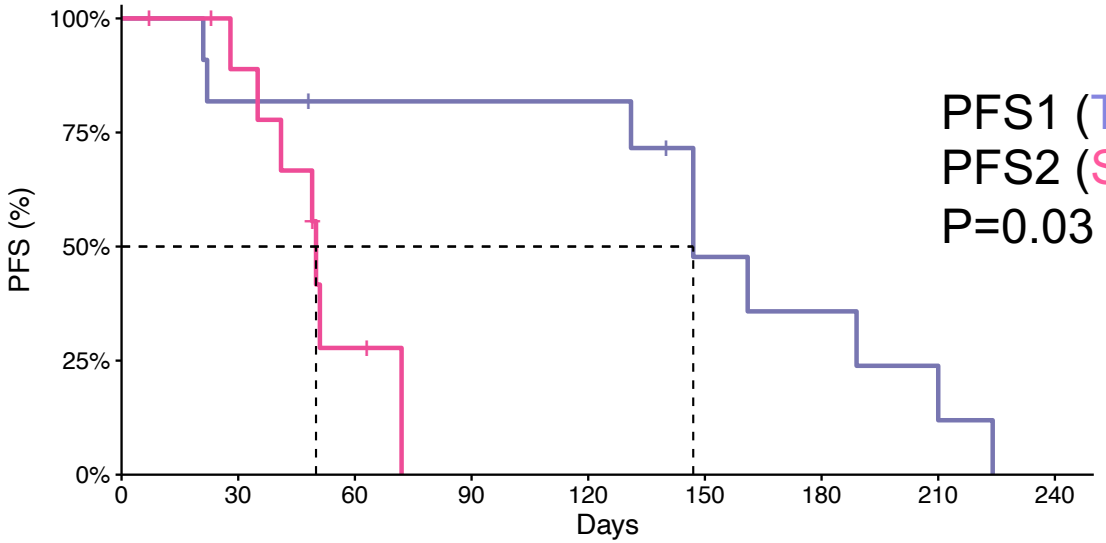




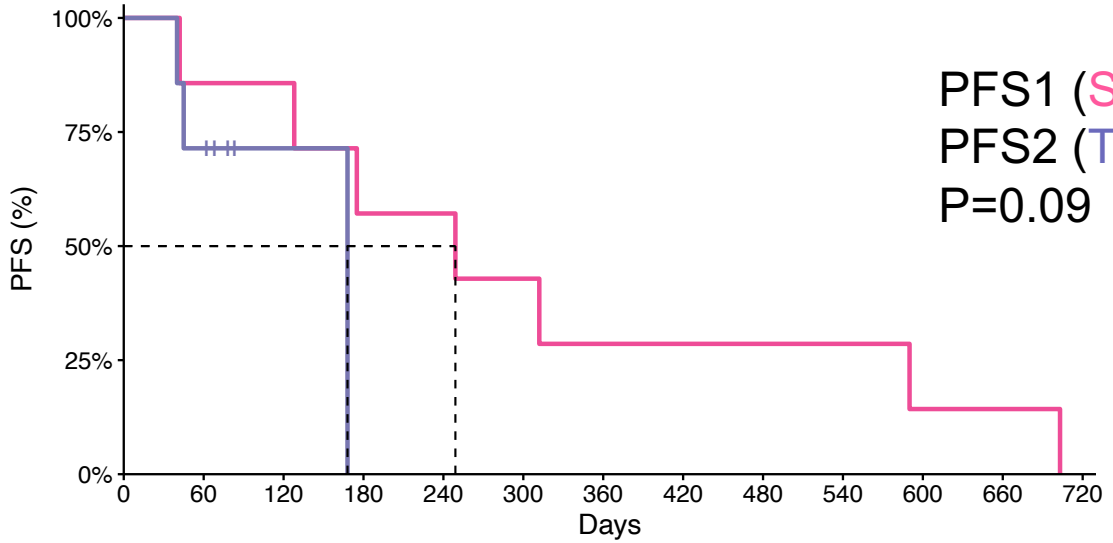
How frequent do these mutations occur?
Does TOP1 mutation mediate cross-resistance to ADCs with TOP1 payloads? → Abelman R et al. AACR 2024

Coates, Sun et al Cancer Discovery 2021.

ADC after ADC in MBC: Cross Resistance in subset of patients



PFS1 (T-DXd): 147 days (131-210)
PFS2 (SG): 50 days (41-72)
P=0.03



PFS1 (SG): 249 days (128-590)
PFS2 (T-DXd): 168 days (45-168)
P=0.09

Abelman R et al. SABCS 2023
Huppert L et al. SABCS 2023

How to select therapy?

- Efficacy
- Toxicity

ADCs targeting similar antigen can have different toxicity profiles

Most common adverse events observed with Datopotamab Deruxtecan:
-- stomatitis

- Different from Sacituzumab Govitecan and Trastuzumab Deruxetcan!

Most common adverse events observed with Trastuzumab Duocarmazine: - keratitis

- Different from T-DM1 and Trastuzumab Deruxtecan
- Resulted in CRL despite positive phase 3 results

Most common adverse events observed with Farletuzumab Ecteribulin:
- pneumonitis

- Different from BB1701 (HER2 ADC with Eribulin payload)

Besides efficacy, specific features of ADC composition could impact toxicity profile, which requires multidisciplinary management

Summary

- The composition of the ADC – antigen selectivity, stability of linker, and type of toxic payload, all important considerations that could impact efficacy/toxicity ratio of ADC and therapeutic sequencing.

- Sacituzumab govitecan approved for metastatic HR+ breast cancer after 2 prior lines of systemic therapy.
- Similarly, trastuzumab deruxtecan: approved for HER2 low MBC (both HR+ and TNBC) after 1 prior line of chemotherapy.
- There are multiple other ADCs in development to target antigens overexpressed in MBC.

- Additional studies evaluating efficacy of ADCs alone and in combination as well as other indications in breast cancer could redefine the receptor classification of breast cancer.

RTP Live from Chicago: Investigator Perspectives on the Role of Bispecific Antibodies in the Management of Lymphoma

A CME-Accredited Virtual Event Held in Conjunction with the 2024 ASCO® Annual Meeting

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Joshua Brody, MD

Ian W Flinn, MD, PhD

Tycel Phillips, MD

Moderator

Neil Love, MD

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