Cancer Conference Update: 2025 ESMO Annual Meeting — Breast Cancer Highlights

CME/MOC-Accredited Live Webinar

Thursday, November 13, 2025
5:00 PM – 6:30 PM ET

Faculty

Professor Giuseppe Curigliano, MD, PhD
Priyanka Sharma, MD

Moderator

Neil Love, MD

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Faculty

Professor Giuseppe Curigliano, MD, PhD
Clinical Director
Division of Early Drug Development for
Innovative Therapy
Co-Chair, Cancer Experimental
Therapeutics Program
Department of Oncology and Hemato-Oncology
University of Milano
European Institute of Oncology
Milano, Italy

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Priyanka Sharma, MD
Frank B Tyler Professor in Cancer Research
Division of Medical Oncology
Department of Internal Medicine
Co-Program Leader
Drug Discovery, Delivery and Experimental Therapeutics Program
The University of Kansas Cancer Center
Westwood, Kansas

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Contracted Research	Bristol Myers Squibb, Gilead Sciences Inc, Novartis
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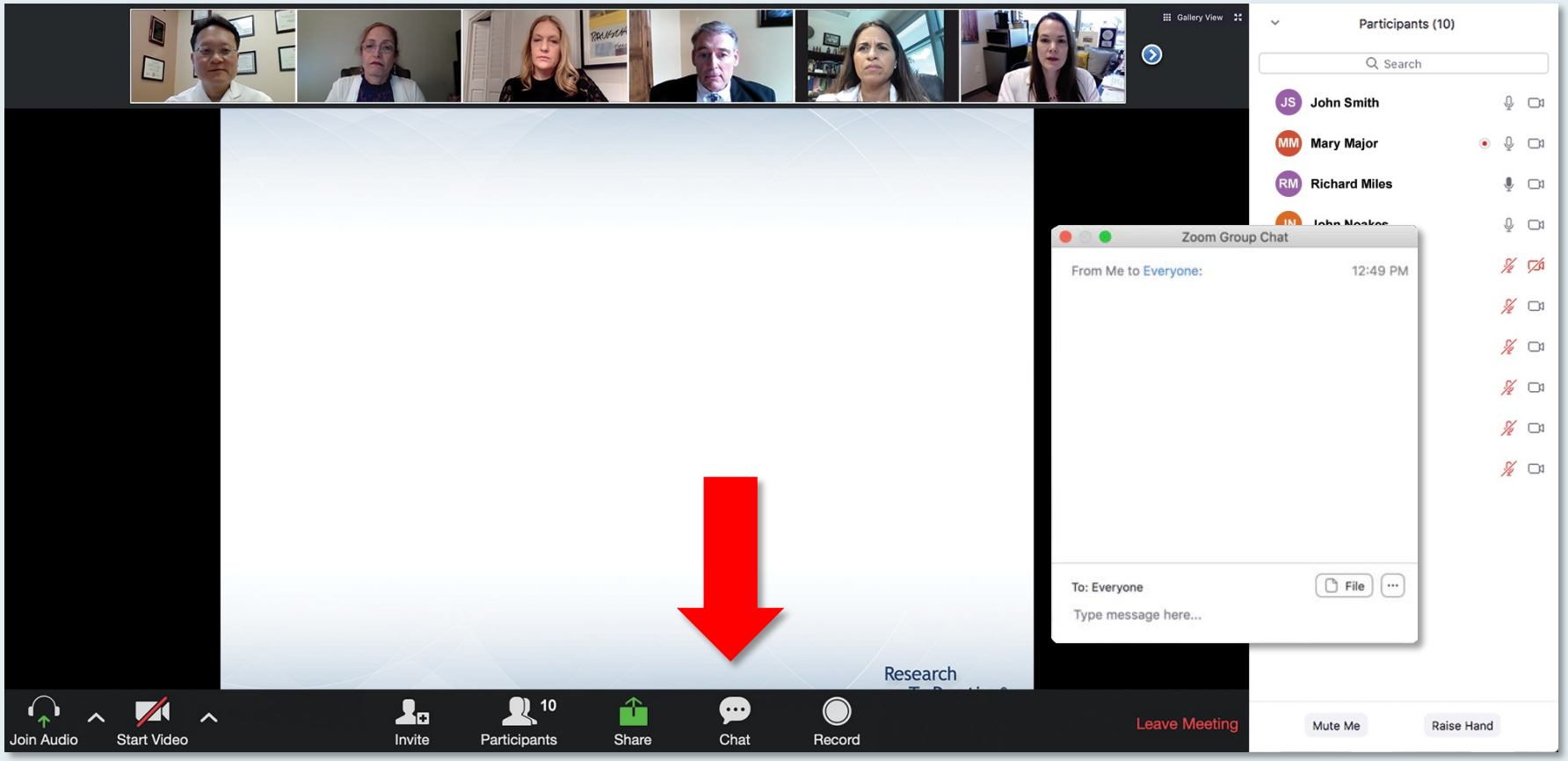

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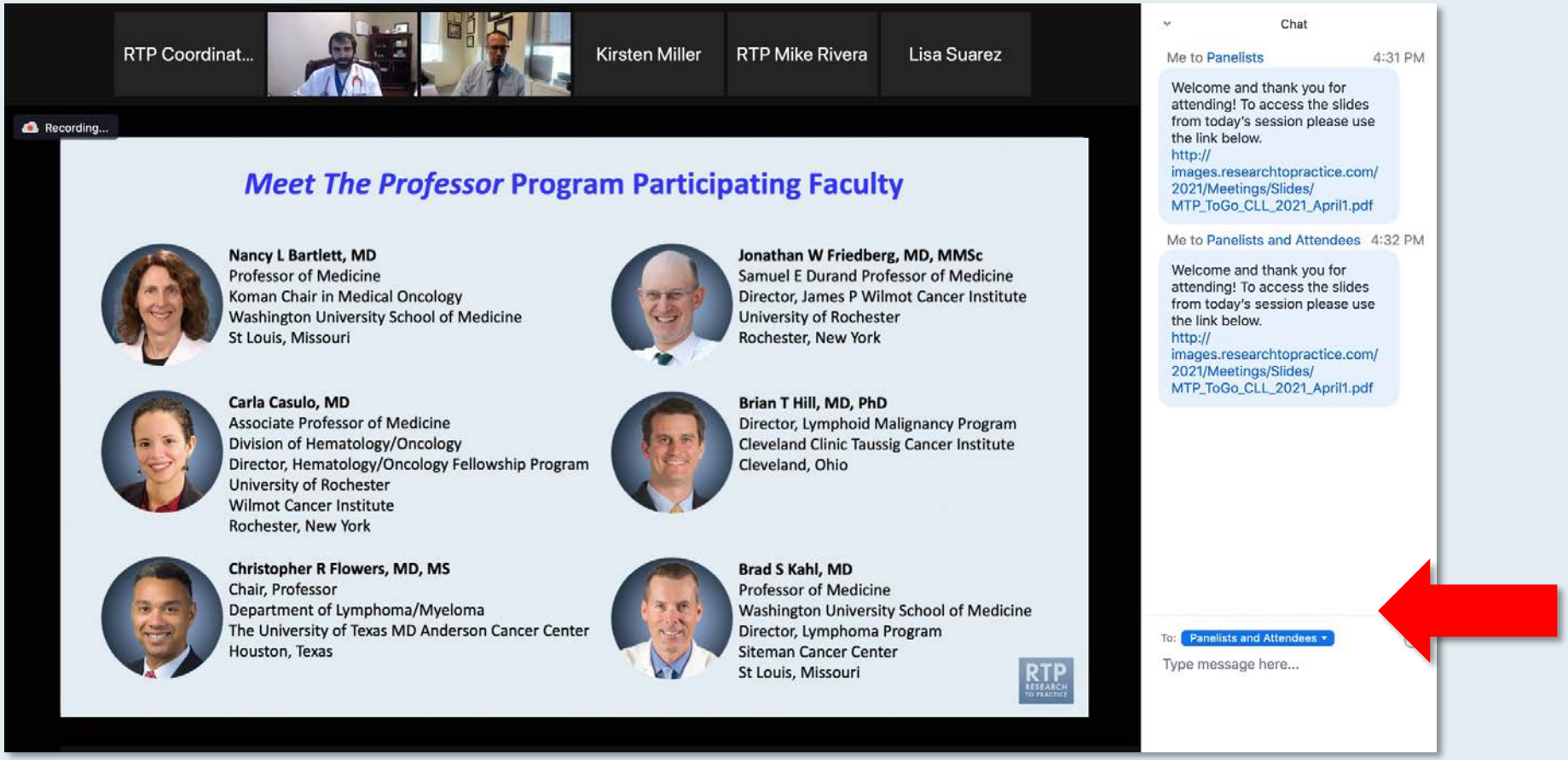

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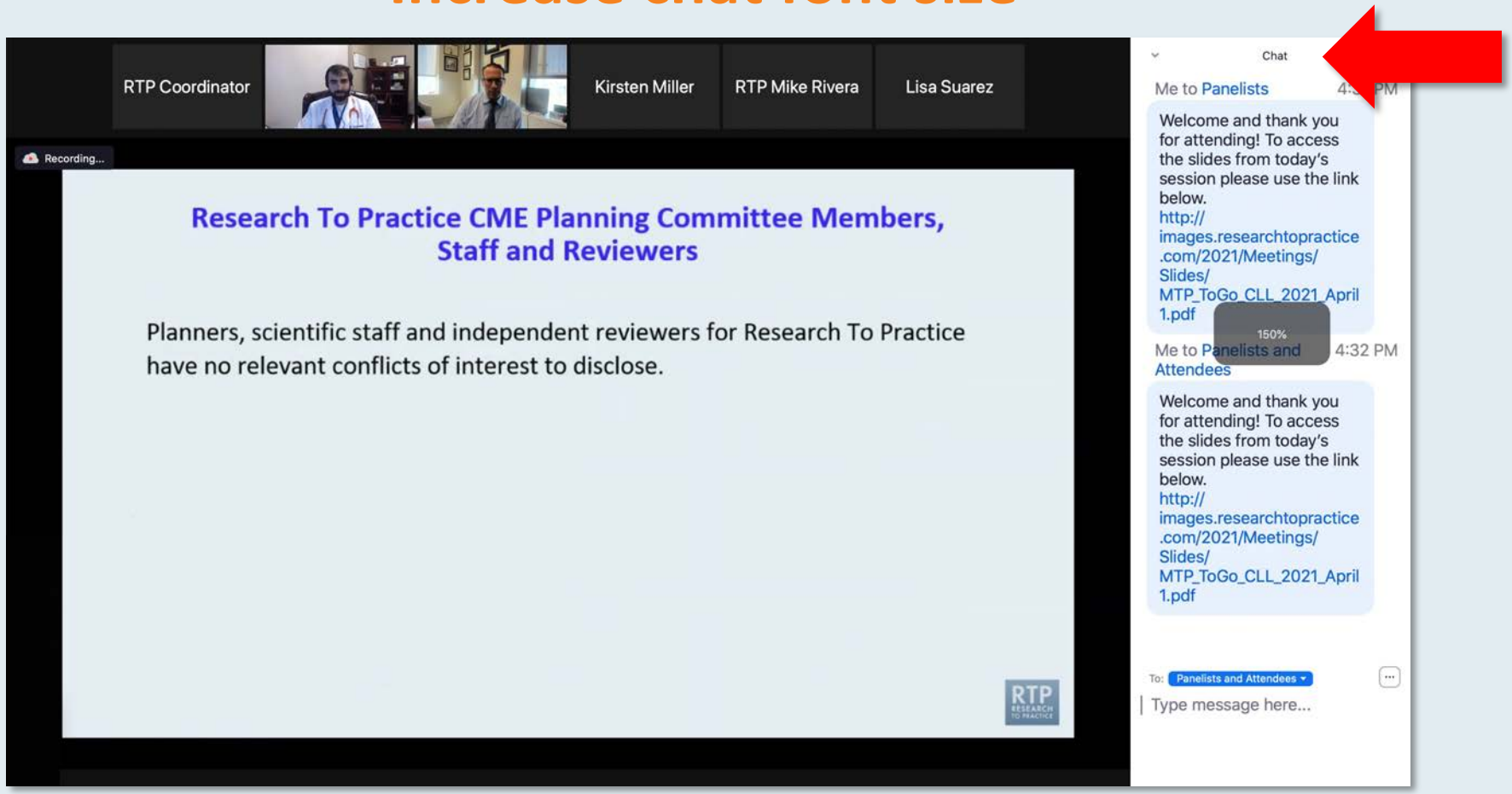

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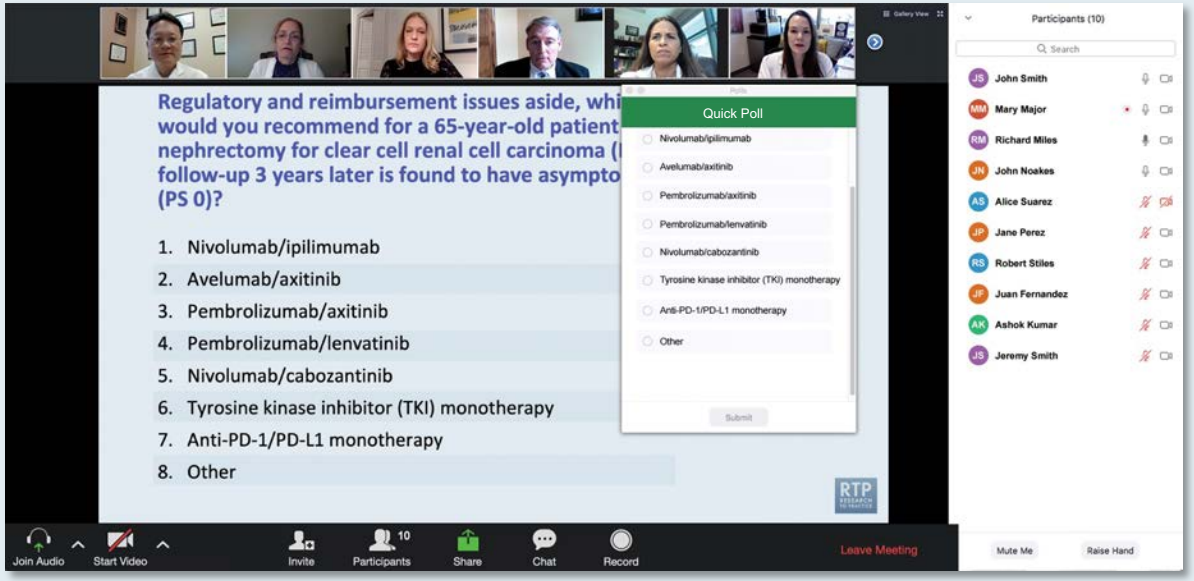

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ER-Positive Metastatic Breast Cancer — An Interview with Prof Patrick Neven on the Role of Oral Selective Estrogen Receptor Degraders

PROF PATRICK NEVEN
UNIVERSITY HOSPITALS LEUVEN

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Practical Perspectives: Clinical Investigators Review Actual Cases of Patients with Advanced Gastroesophageal Cancers

A CME/MOC-Accredited Live Webinar

Tuesday, November 18, 2025
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Moderator

Neil Love, MD

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Preventing and Managing Toxicities Associated with Antibody-Drug Conjugates in the Management of Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, November 19, 2025

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Lisa A Carey, MD, ScM, FASCO

Rita Nanda, MD

Moderator

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Cancer Conference Update: ESMO Congress 2025 — Urothelial Bladder Cancer and Prostate Cancer

A CME/MOC-Accredited Live Webinar

Thursday, November 20, 2025
5:00 PM – 6:00 PM ET

Faculty

Terence Friedlander, MD
Rana R McKay, MD

Moderator

Neil Love, MD

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Exciting CME Events You Do Not Want to Miss

A Friday Satellite Symposium Series Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

Acute Myeloid Leukemia
7:30 AM – 9:30 AM ET

Myelofibrosis and Systemic Mastocytosis
3:15 PM – 5:15 PM ET

Chronic Lymphocytic Leukemia
11:30 AM – 1:30 PM ET

Follicular Lymphoma and Diffuse Large B-Cell Lymphoma
7:00 PM – 9:00 PM ET

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Cases from the Community: Investigators Discuss the Optimal Management of Breast Cancer

A 3-Part CME Satellite Symposium Series

Antibody-Drug Conjugates for Metastatic Breast Cancer

Tuesday, December 9, 2025

7:00 PM – 8:30 PM CT

HER2-Positive Breast Cancer

Wednesday, December 10, 2025

7:00 PM – 9:00 PM CT

Endocrine-Based Therapy

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT

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Grand Rounds

CME/MOC-Accredited Interactive Series

November 2025 to April 2026

Two Series

Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Optimizing the Use of Novel Therapies for Patients with Diffuse Large B-Cell Lymphoma

Host a 1-hour session at your institution:
Email Meetings@ResearchToPractice.com
or call (800) 233-6153

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

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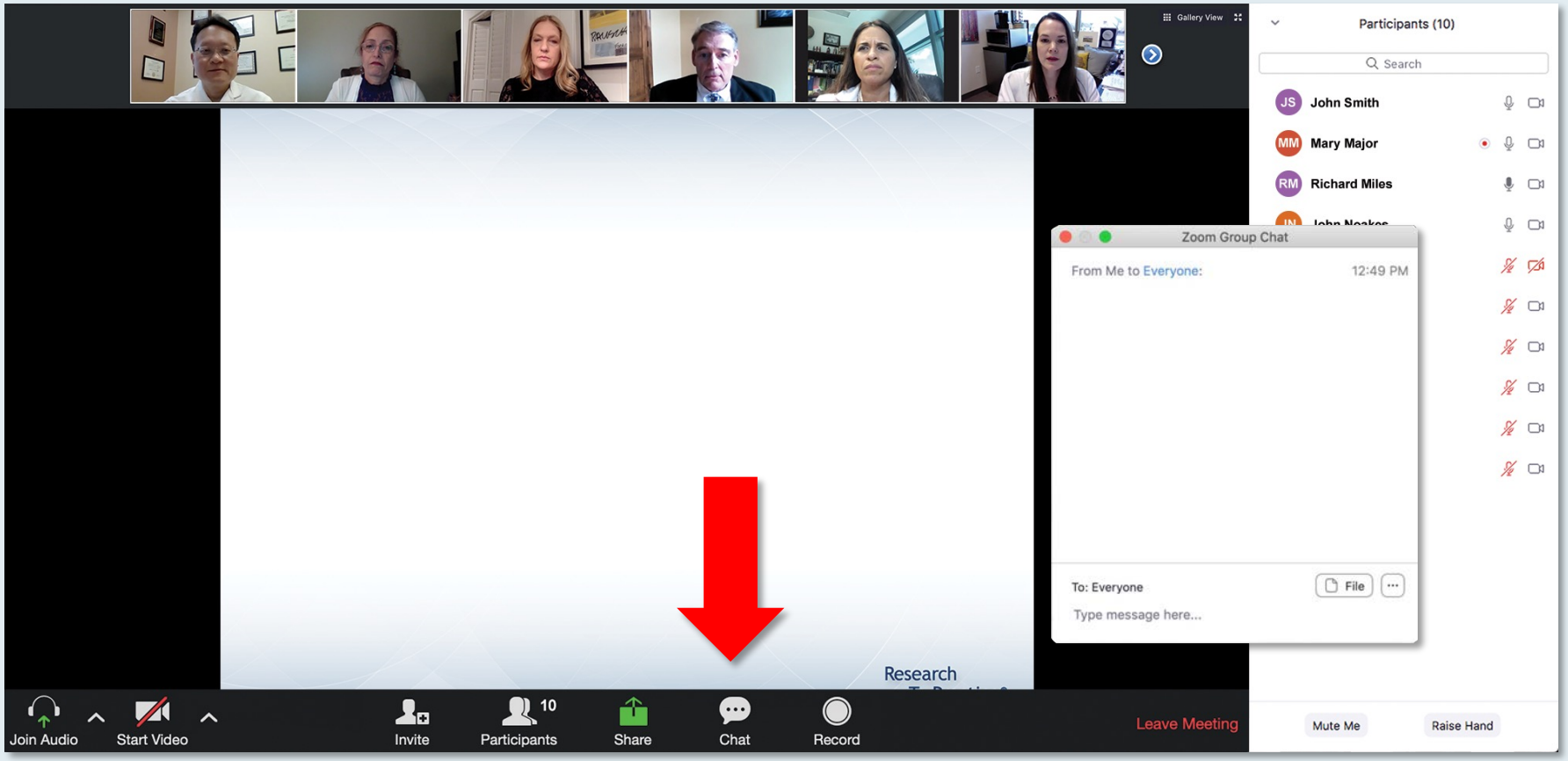

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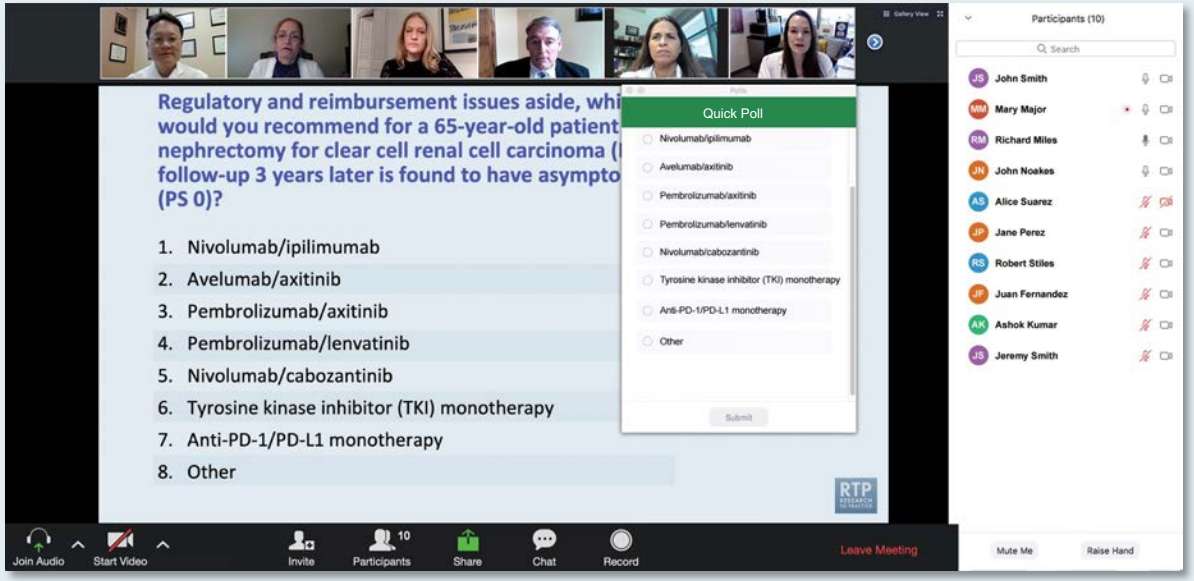

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The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

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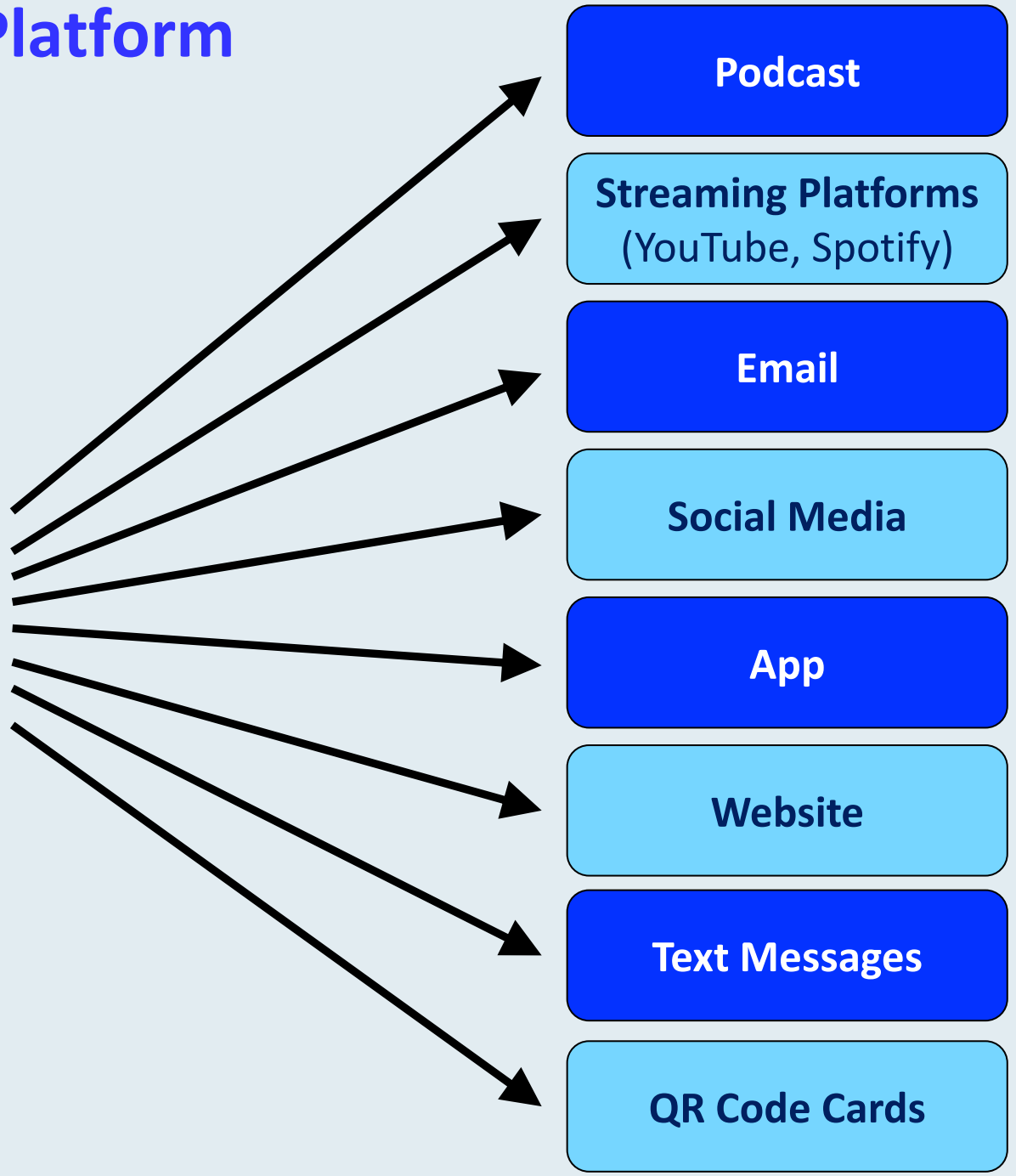
	Year	Month
Total (hours)	280	24
Recordings	93	7
Webinars	41	4
Cases	62	5
Meetings	84	7
Final	218	18



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Agenda

Module 1: HER2-Positive Breast Cancer

Module 2: HR-Positive Breast Cancer

Module 3: Triple-Negative Breast Cancer

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Agenda

Module 1: HER2-Positive Breast Cancer

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DESTINY-Breast09

- Loibl S et al. **Trastuzumab deruxtecan (T-DXd)** + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for patients (pts) with **HER2+ advanced/metastatic breast cancer (a/mBC): Additional analyses of DESTINY-Breast09** in key subgroups of interest. ESMO 2025;Abstract LBA18.

Abstract LBA18

BERLIN 2025 ESMO congress

DESTINY Breast09

Trastuzumab deruxtecan (T-DXd) + pertuzumab vs taxane + trastuzumab + pertuzumab (THP) for patients with HER2+ advanced/metastatic breast cancer: additional analyses of DESTINY-Breast09 in key subgroups of interest

Sibylle Loibl, MD, PhD

University Hospital Goethe, University Frankfurt/M, GBG Neu-Isenburg, Germany

Co-authors: Zefei Jiang, Romualdo Barroso-Sousa, Yeon Hee Park, Cristina Saura, Mothaffar F Rimawi, Andreas Schneeweiss, Masakazu Toi, Seock-Ah Im, Zhongsheng Tong, Umut Demirci, Cynthia Villarreal-Garza, Chiun-Sheng Huang, Toshimi Takano, Valentina Guarneri, Shoubhik Mondal, Doudou Huang, Angela Zeng, Sara M Tolaney

On behalf of the DESTINY-Breast09 investigators

Sunday, October 19, 2025
Presentation LBA18

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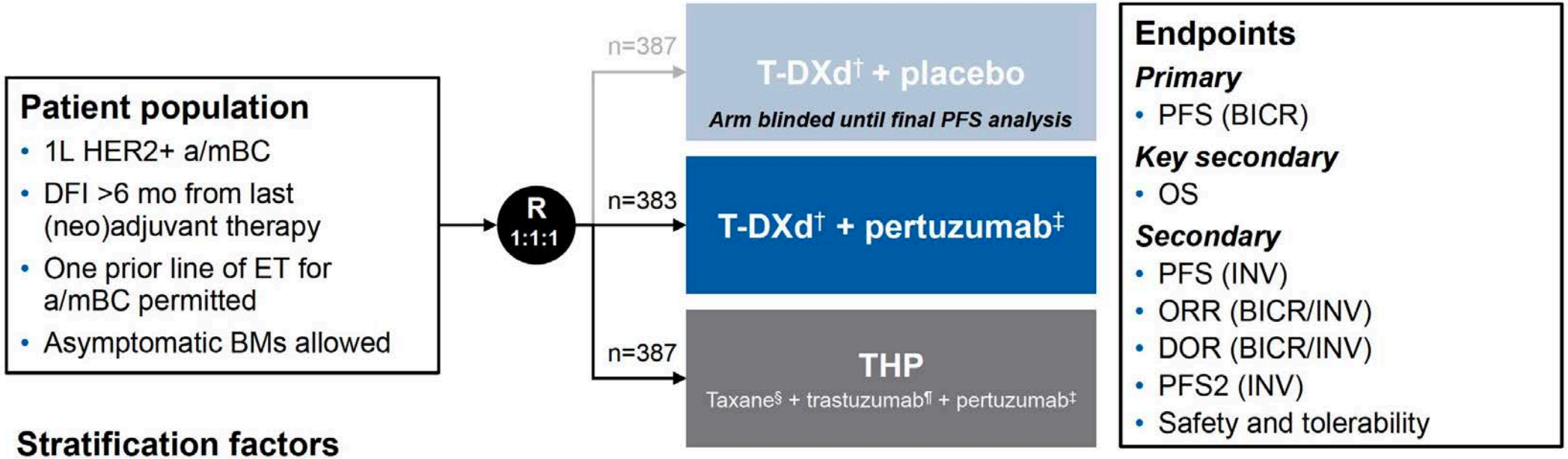
Phase III DESTINY-Breast09 Study Design



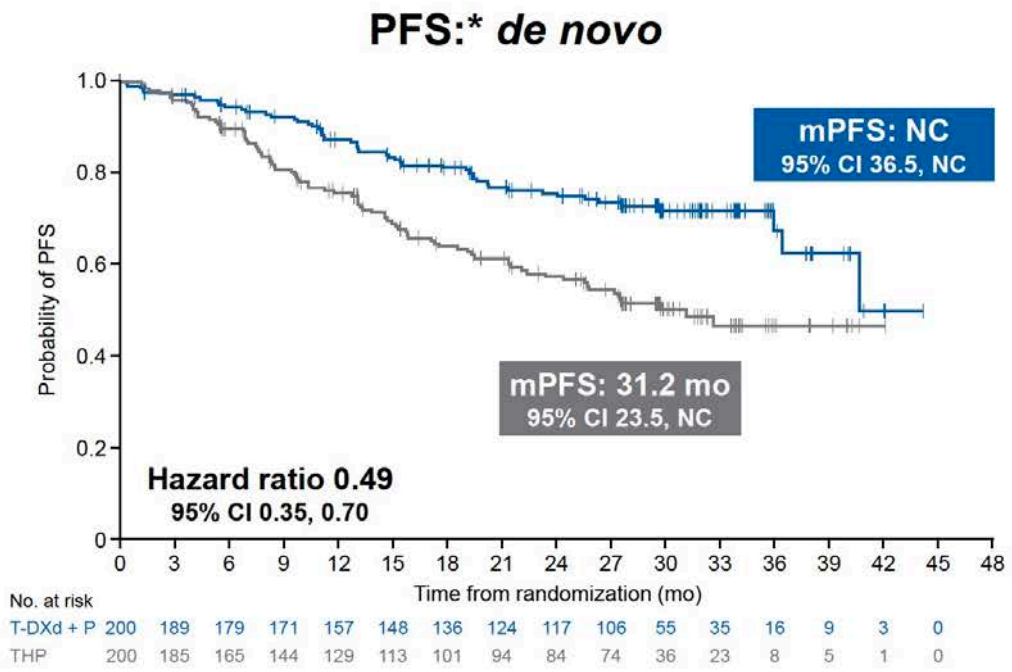
*Open label for THP arm, double blinded for pertuzumab in experimental arms; †5.4 mg/kg Q3W; ‡840 mg loading dose, then 420 mg Q3W; §paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for a minimum of six cycles or until intolerable toxicity; ¶8 mg/kg loading dose, then 6 mg/kg Q3W; ‖without loading dose

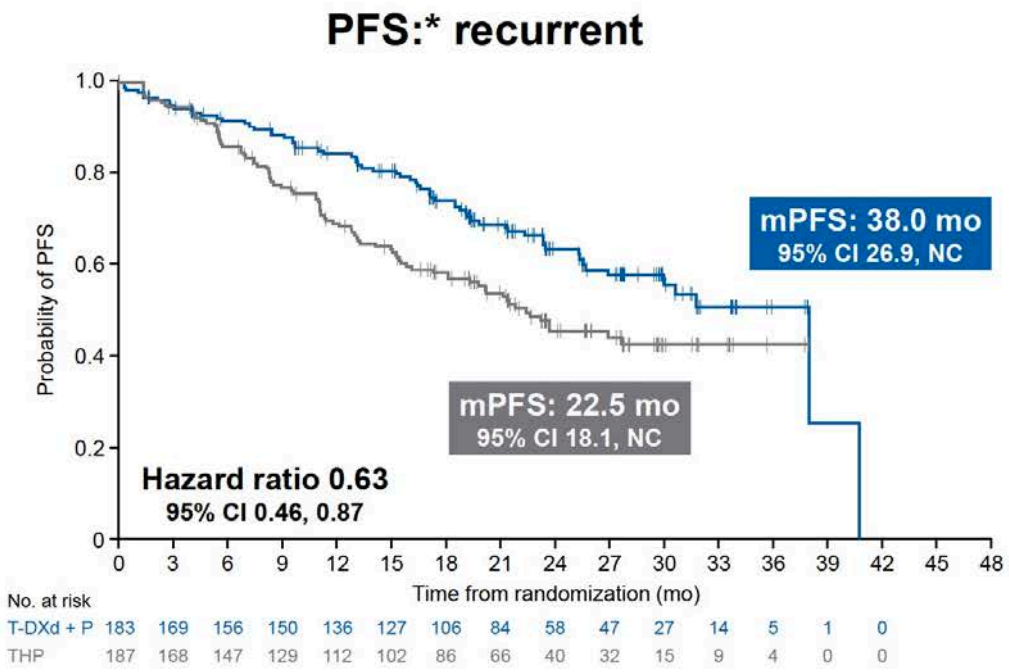
1L, first-line; AE, adverse event; a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; BM, brain metastasis; DFI, disease-free interval; DOR, duration of response; ET, endocrine therapy; HER2+, human epidermal growth factor receptor 2–positive; HR+/−, hormone receptor–positive/–negative; ILD, interstitial lung disease; INV, investigator; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, *PIK3CA* mutation; Q3W, every 3 weeks; QW, once weekly; R, randomization; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

1. Tolaney SM, et al. Oral presentation at ASCO 2025 (Abstract LBA1008); 2. NCT04784715. Updated. August 1, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed October 15, 2025)

Loibl S et al. ESMO 2025;Abstract LBA18.

Phase III DESTINY-Breast09: PFS by Treatment Status



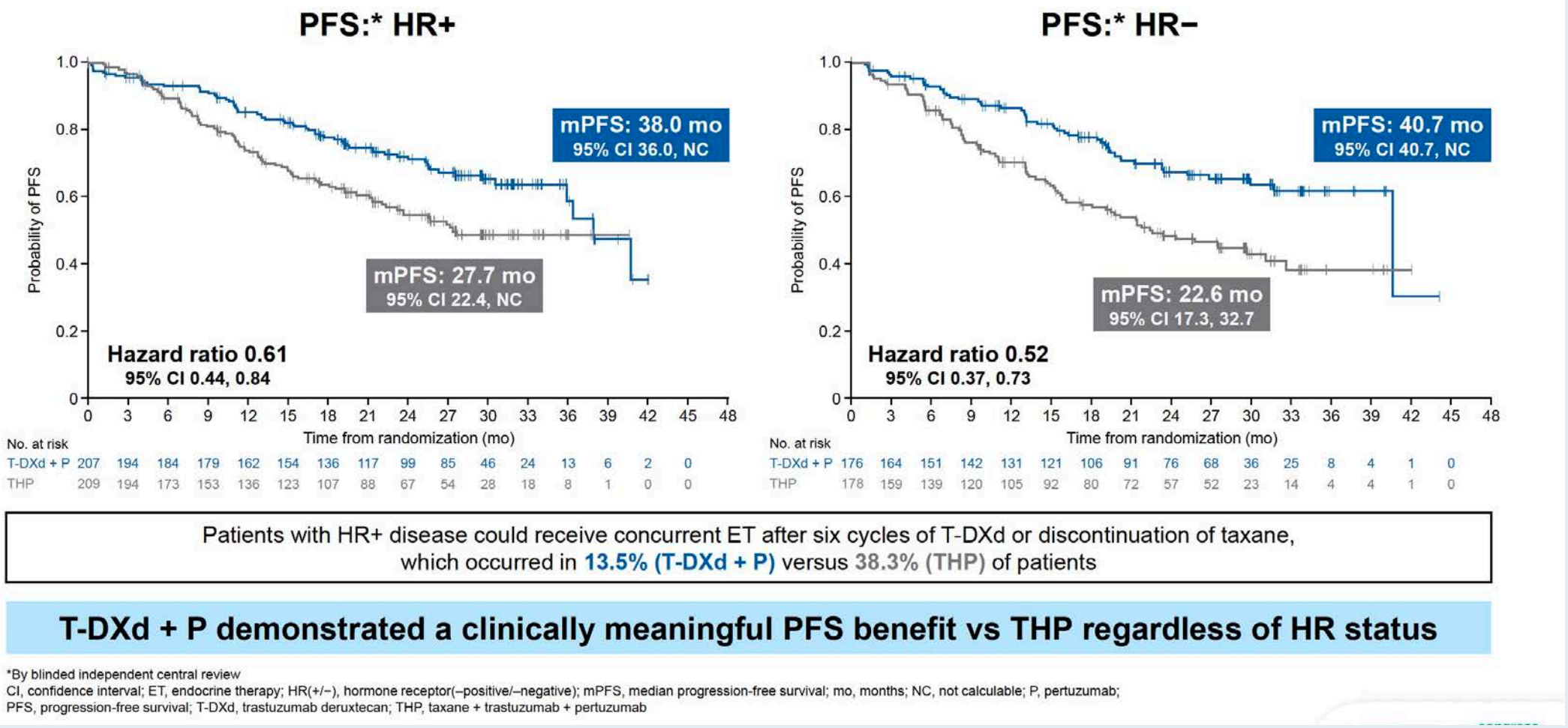


T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of de-novo or recurrent status

*By blinded independent central review
CI, confidence interval; mPFS, median progression-free survival; mo, months; NC, not calculable; P, pertuzumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Loibl S et al. ESMO 2025;Abstract LBA18.

Phase III DESTINY-Breast09: PFS by HR Status



Patients with HR+ disease could receive concurrent ET after six cycles of T-DXd or discontinuation of taxane, which occurred in **13.5% (T-DXd + P)** versus **38.3% (THP)** of patients

T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of HR status

*By blinded independent central review
CI, confidence interval; ET, endocrine therapy; HR(+/−), hormone receptor(–positive/–negative); mPFS, median progression-free survival; mo, months; NC, not calculable; P, pertuzumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Loibl S et al. ESMO 2025;Abstract LBA18.

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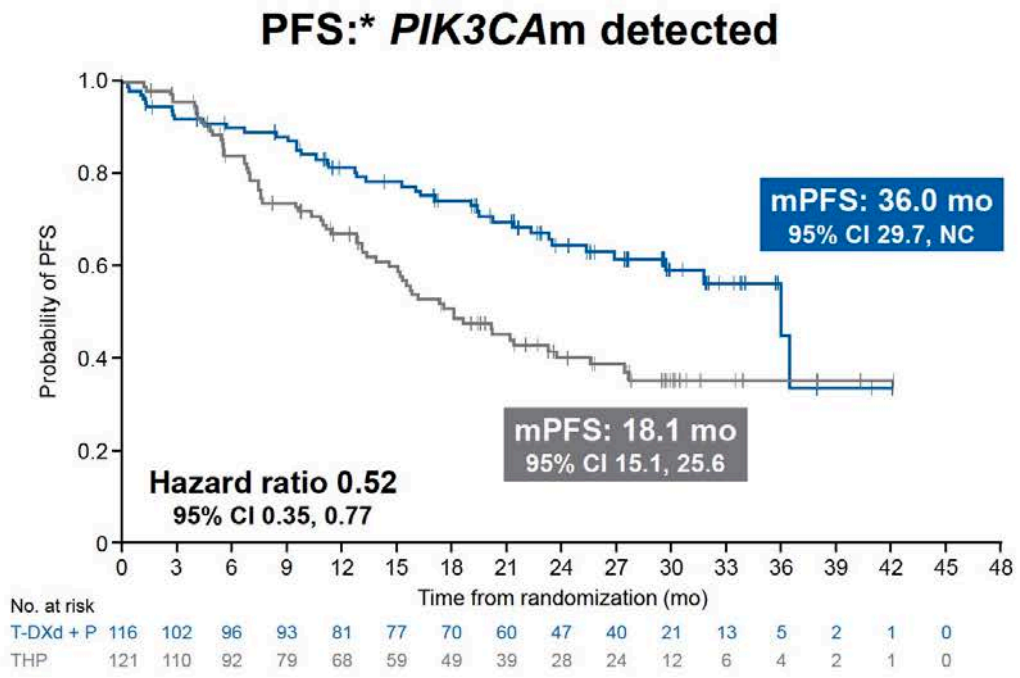
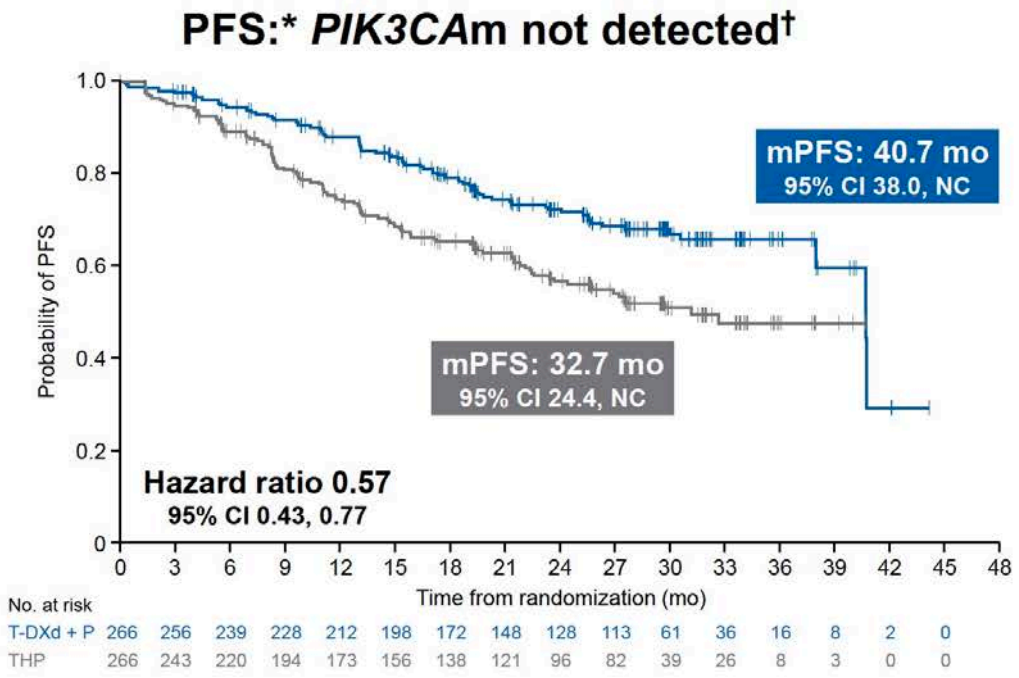
Phase III DESTINY-Breast09: PFS by PIK3CAm Status





T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of *PIK3CA*m status

*By blinded independent central review; †one patient in the T-DXd + P arm had missing *PIK3CA*m status
CI, confidence interval; mo, months; mPFS, median progression-free survival; NC, not calculable; P, pertuzumab; PFS, progression-free survival; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Loibl S et al. ESMO 2025;Abstract LBA18.

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Phase III DESTINY-Breast09: Authors' Conclusions

- In this subgroup analysis of DESTINY-Breast09, 1L treatment with T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of prior treatment, HR, or *PIK3CA*m status, reflecting results in the overall population
- DOR consistently favored T-DXd + P (**median of ~3 years**), and CR rates were higher with T-DXd + P (**13.7–16.5%**) than THP (**4.1–10.7%**) in all subgroups
- No new safety signals were identified for T-DXd + P; safety outcomes for each arm were broadly similar across subgroups and in line with the overall population

T-DXd + P represents an effective 1L treatment for patients with HER2+ a/mBC, regardless of prior treatment, HR, or *PIK3CA*m status

1L, first-line; a/mBC, advanced/metastatic breast cancer; CR, complete response; DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; P, pertuzumab; PFS, progression-free survival; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

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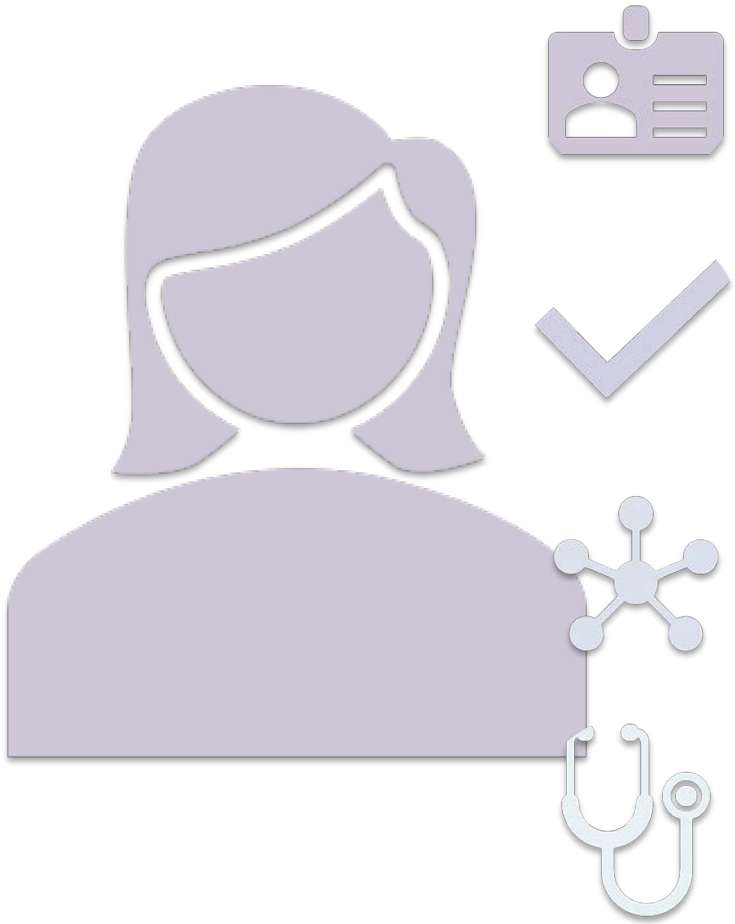
Prof Curigliano: Case Presentation #1

The patient



24-year-old (pre-menopausal)

PS ECOG 0, 43 kg, 155 cm

Family history: aunt (mother-side), aunt (father-side) with breast cancer

Former smoker, no comorbidities; previous fibroadenoma of left breast

Prof Curigliano: Case Presentation #1 (Continued)

Diagnosis

March 2024
Self examination of left breast: lump detected

01.03.24
Mammography + ultrasonography: lump of 13 mm

21.03.24
Core biopsy of left breast: ductal infiltrating carcinoma, multifocal, ER: 70%; PgR: 40%; Ki67:30%; HER2+: 3+

26.03.24: CT scan: bilateral lung lesions; nodes in the left axilla (30 mm); multiple hepatic lesions (max 20 mm)

29.03.24 breast MRI:
Left breast: 20 and 15 mm with many foci;
left axilla: multiple nodes of 33 mm and 25 mm

31.03.24 PET FDG: uptake in left breast, left axilla, internal mammary nodes, liver lesions

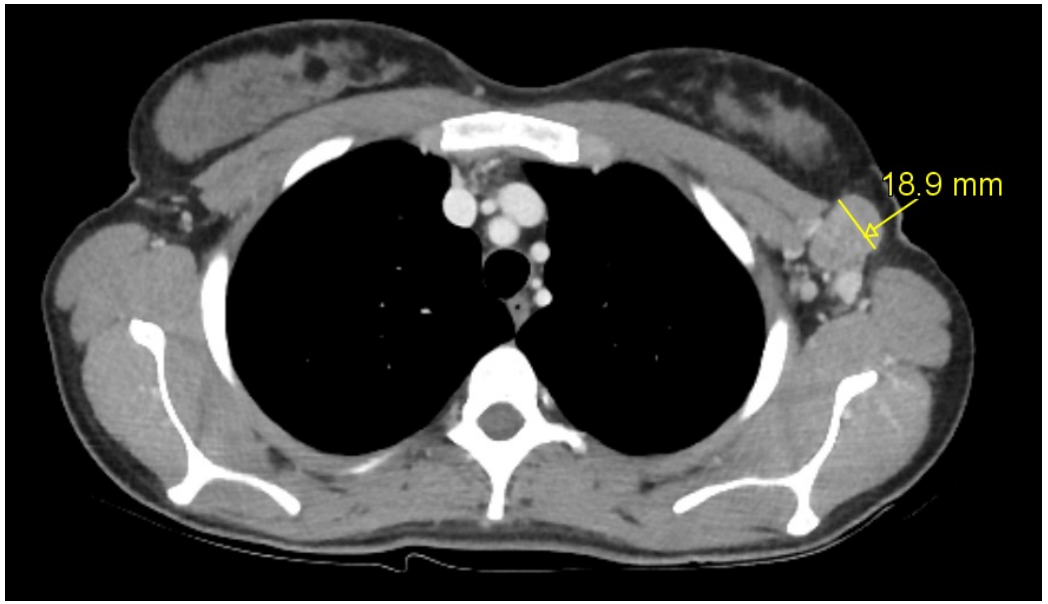
Genetic counselling:
BRCA1-2 WT,
TP53 WT,
PALB2 WT

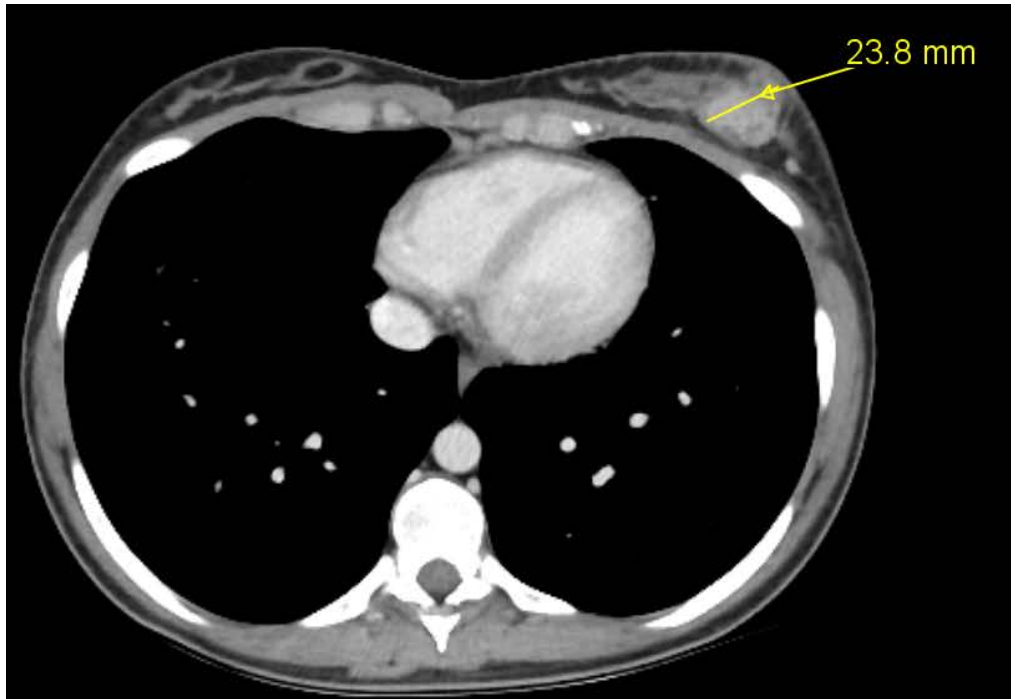
Prof Curigliano: Case Presentation #1 (Continued)

First line

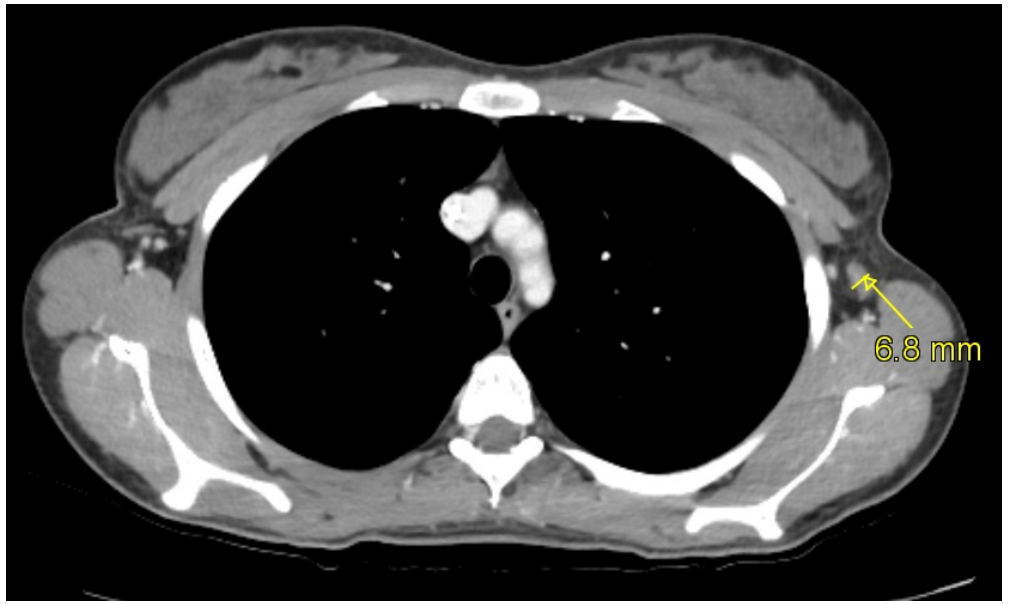
- 22.04.24 Core biopsy left breast: ductal infiltrating carcinoma,
  ER: 90%; PgR: 0%; HER2: 3+
- 11.05.24 start triptorelin 3.75 mg q4w
- 10.05.24 start trastuzumab deruxtecan and pertuzumab

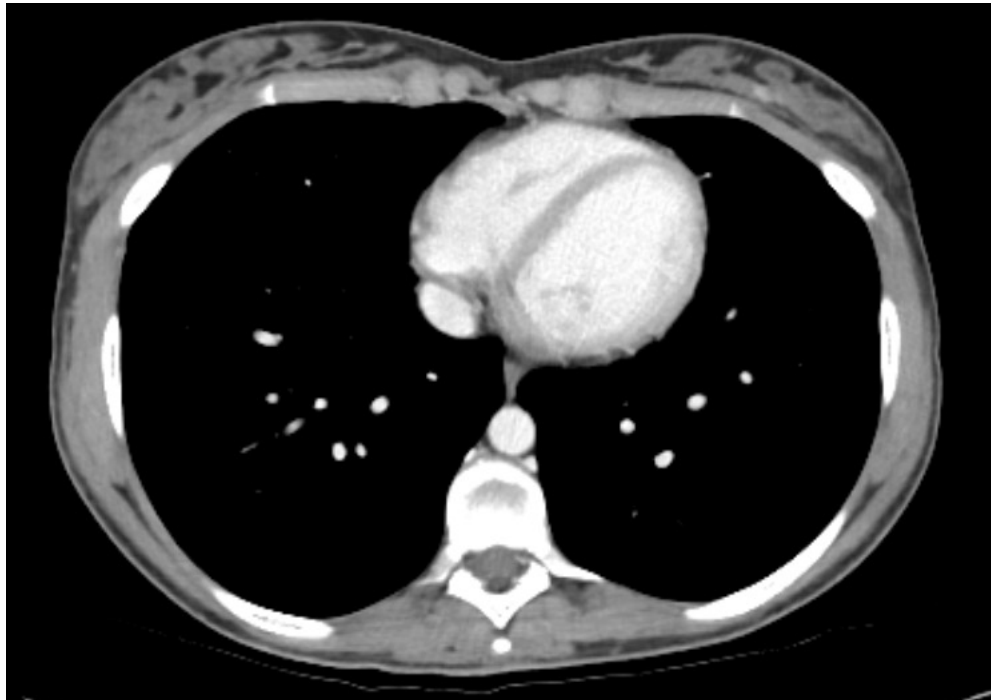
20.04.24





27.07.24





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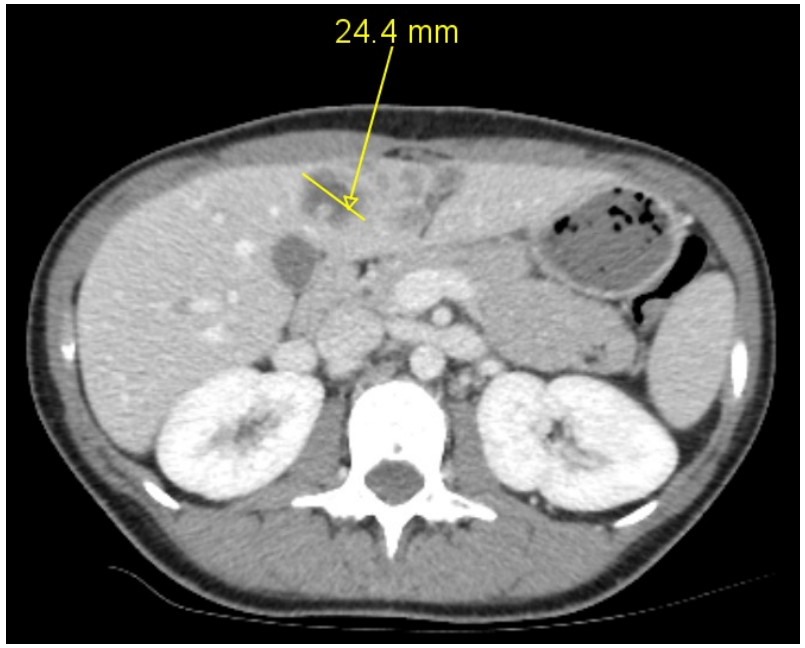

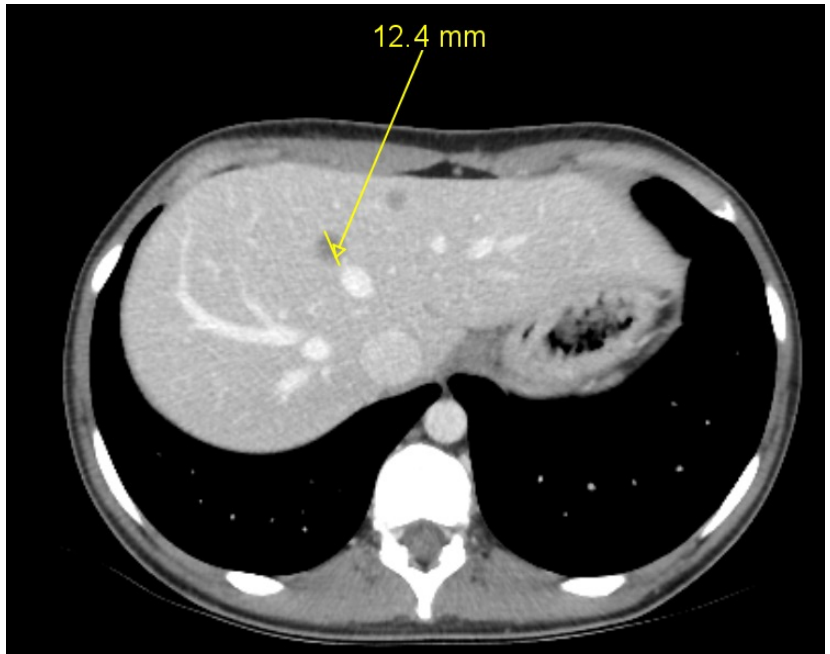

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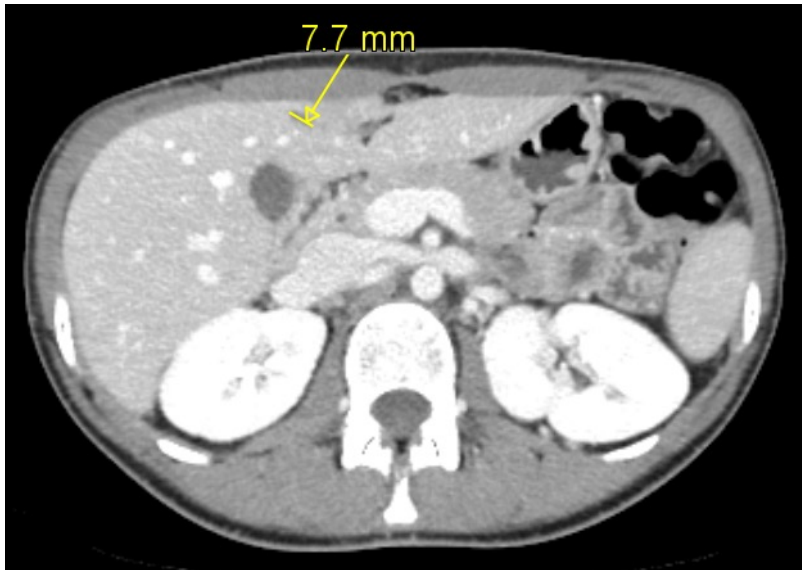
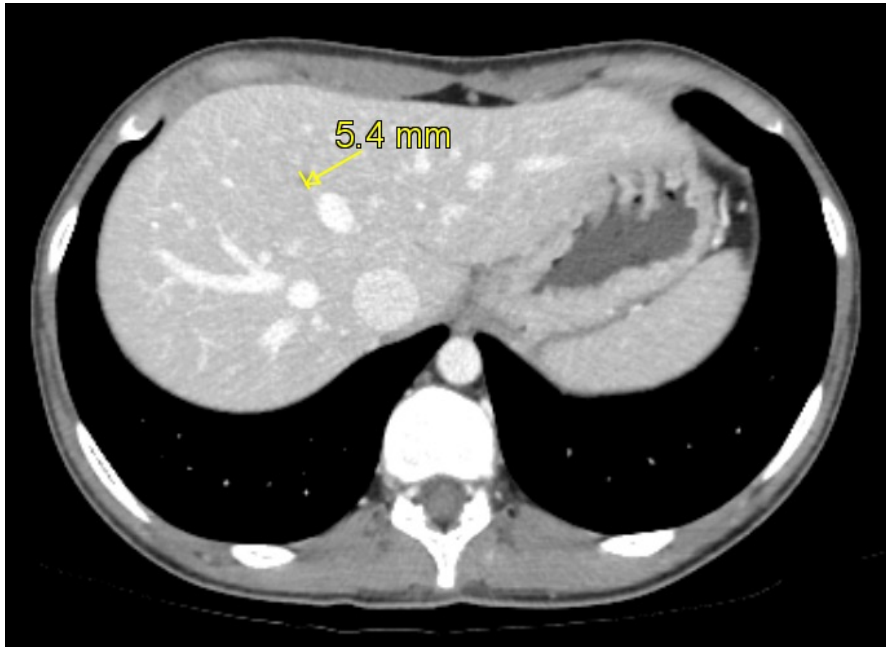




Prof Curigliano: Case Presentation #1 (Continued)

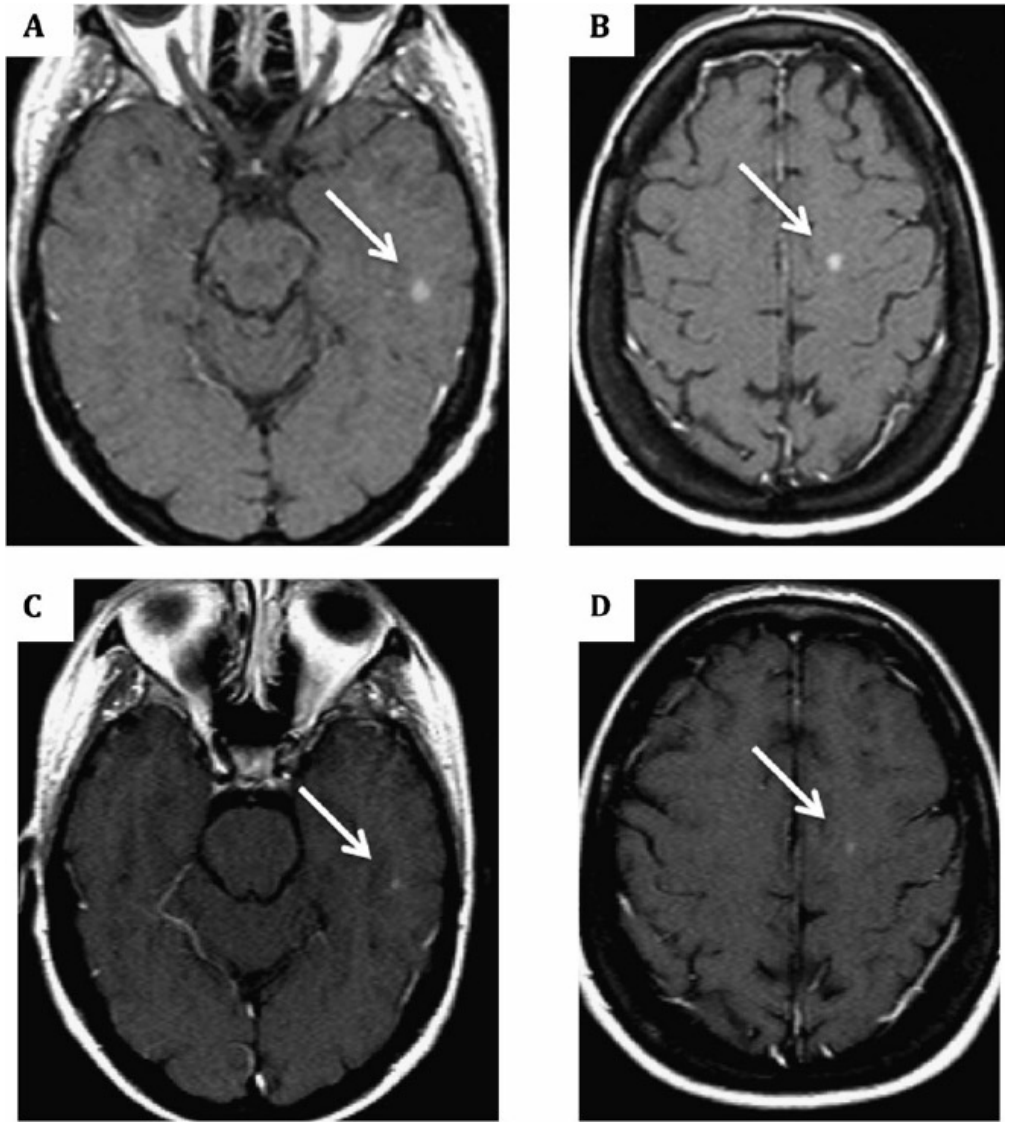
Evaluation of response

The patient is currently on treatment, with partial response by RECIST 1.1 criteria

T-DXd and pertuzumab was well tolerated with only G1 AEs (anemia, leukopenia, neutropenia, alopecia)

July 2025: Asymptomatic brain metastases, appearance of a new liver lesion

Stable and asymptomatic brain metastases



Prof Curigliano: Case Presentation #1 (Continued)

What's next?

T-DXd + pertuzumab is well tolerated with only G1 AEs (anemia, leukopenia, neutropenia, alopecia)

July 2025: Asymptomatic brain metastases, appearance of a new liver lesion

Proceed same therapy after RT

Tucatinib, trastuzumab and capecitabine?

DESTINY-Breast11

- Harbeck N et al. **DESTINY-Breast11: Neoadjuvant trastuzumab deruxtecan** alone (T-DXd) or followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs SOC for **high-risk HER2+ early breast cancer (eBC)**. ESMO 2025;Abstract 291O.

Abstract 291O

BERLIN 2025 ESMO congress

DESTINY Breast11

DESTINY-Breast11: neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel + trastuzumab + pertuzumab vs ddAC-THP for high-risk HER2+ early breast cancer

Nadia Harbeck

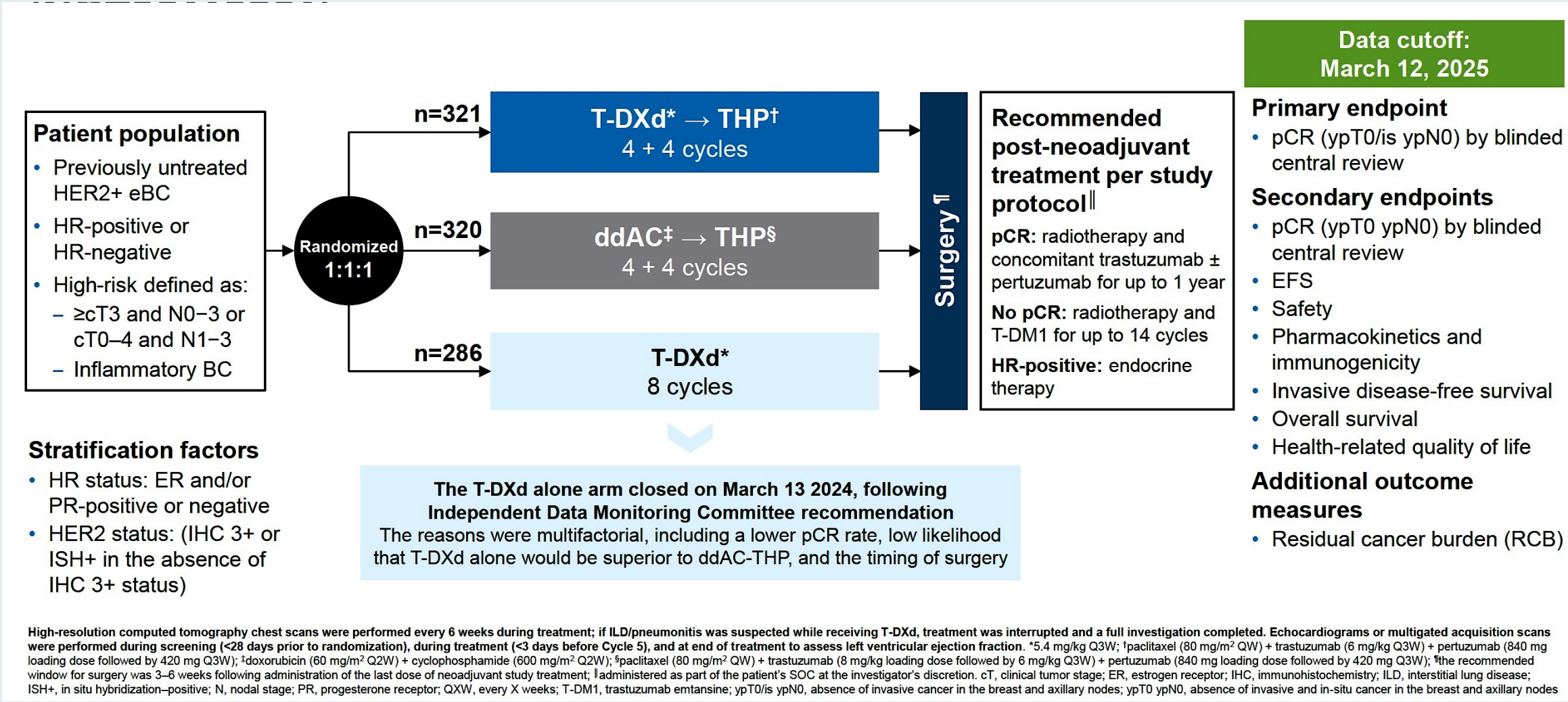
Breast Center, Department of OB&GYN and CCC Munich,
LMU University Hospital, Munich, Germany

Co-authors: Shanu Modi, Lajos Pusztai, Shinji Ohno, Jiong Wu, Sung-Bae Kim, Alessandra Fabi, Xuchen Cao, Rona Joseph, Rubi Li, Bogdan Żurawski, Santiago Escrivá-de-Romaní, Shin-Cheh Chen, Catherine Kelly, Giuseppe Curigliano, William Fraser Symmans, Shoubhik Mondal, Shahana Safdar, Pia Herbolsheimer, Jean-François Boileau
On behalf of the DESTINY-Breast11 investigators

Saturday October 18, 2025

Presentation 291O

Phase III DESTINY-Breast11 Study Design

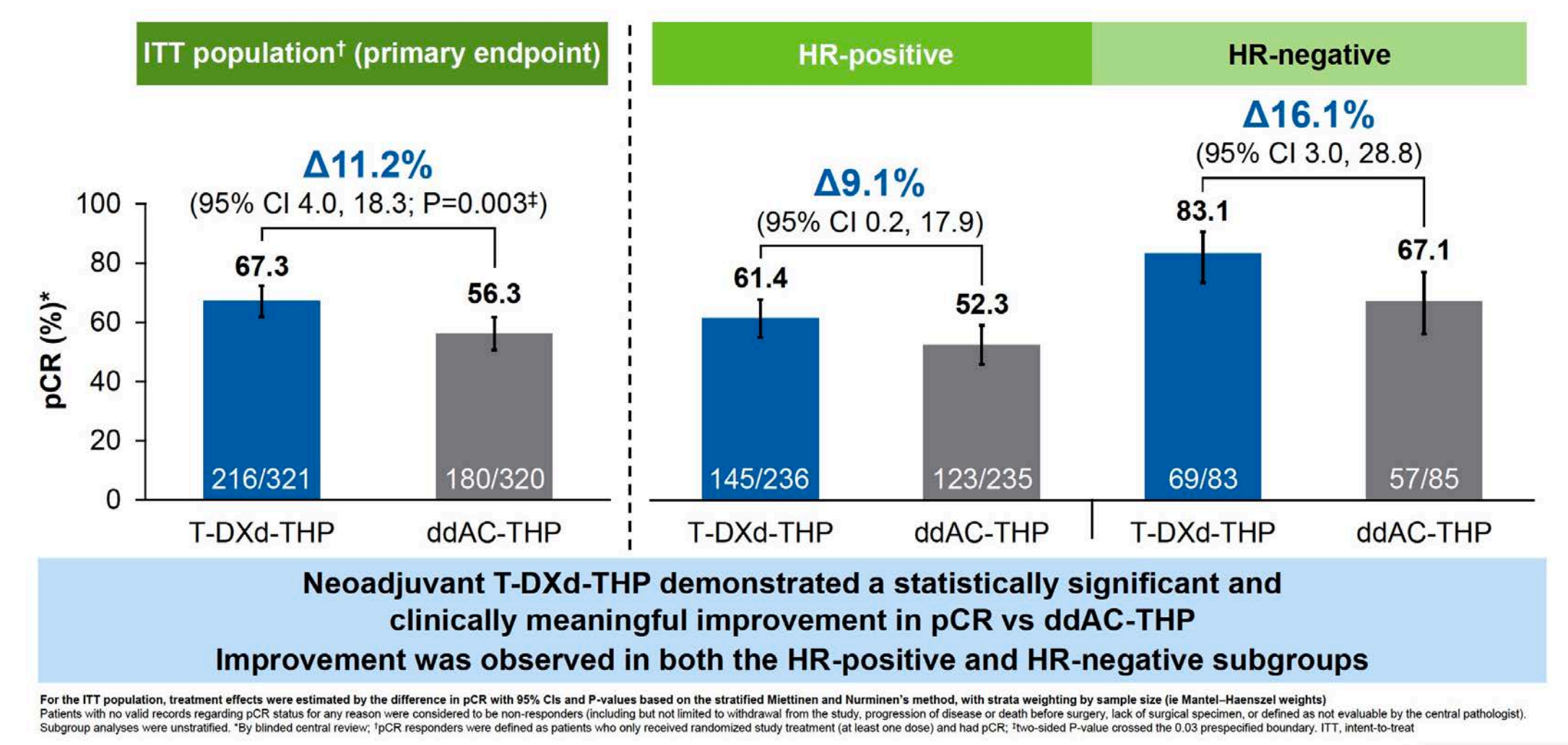


High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); §paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

ddAC = dose-dense doxorubicin and cyclophosphamide; THP = paclitaxel, trastuzumab and pertuzumab

Harbeck N et al. ESMO 2025;Abstract 291O.

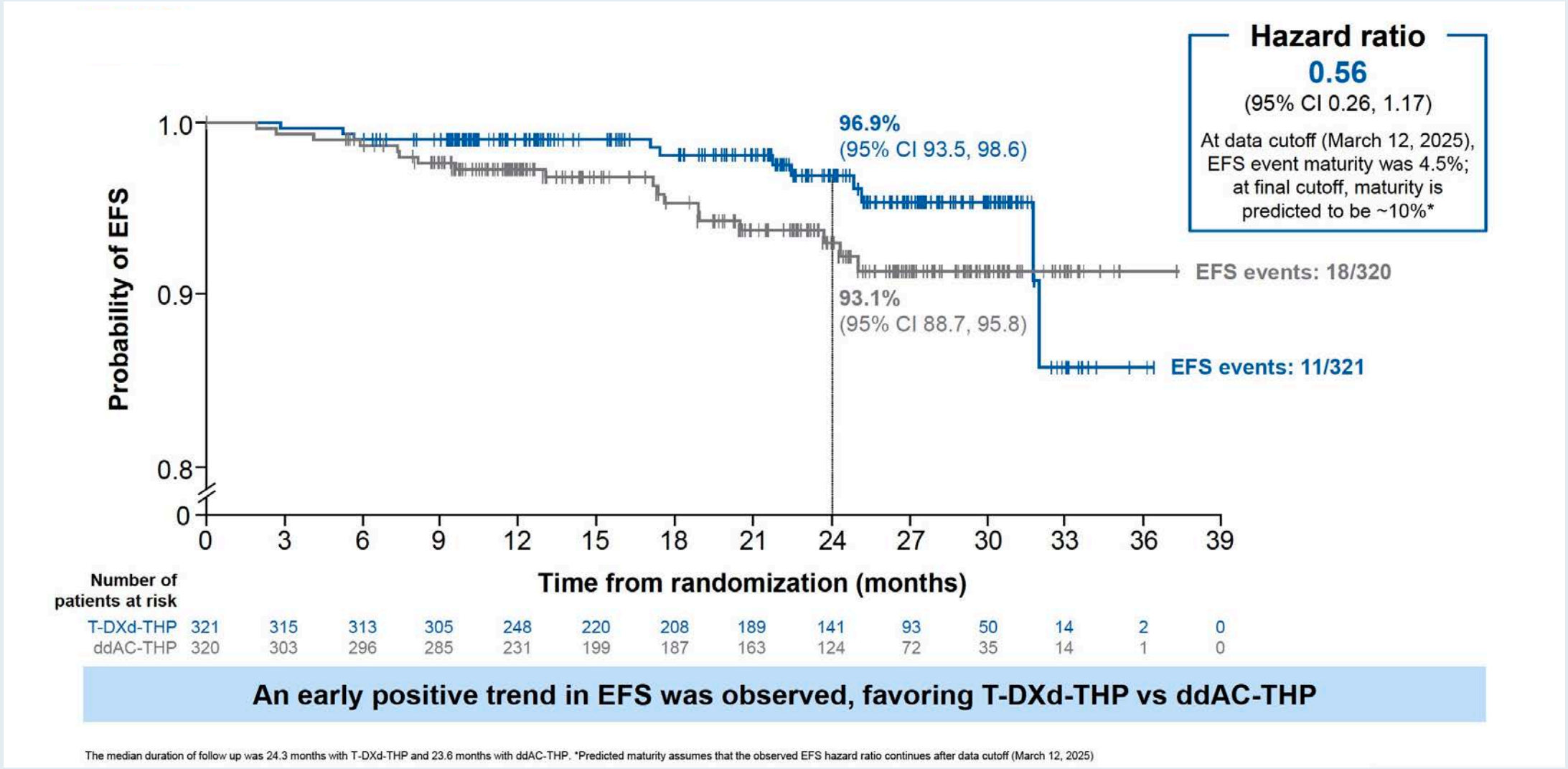
Phase III DESTINY-Breast11: Primary Endpoint (pCR)



pCR = pathologic complete response; ITT = intention-to-treat

Harbeck N et al. ESMO 2025;Abstract 291O.

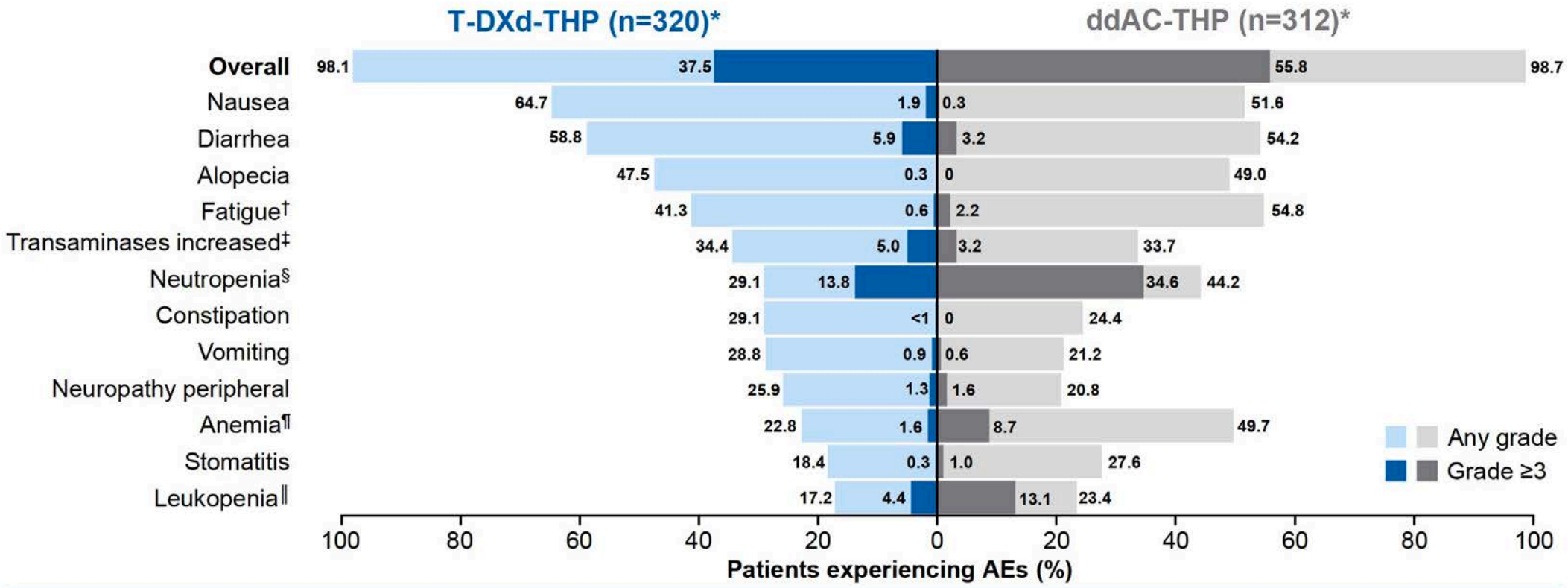
Phase III DESTINY-Breast11: Event-Free Survival (EFS)



The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

Harbeck N et al. ESMO 2025;Abstract 291O.

Phase III DESTINY-Breast11: Common Adverse Events (AEs)



T-DXd-THP had fewer any-grade and Grade ≥3 hematological and fatigue events than ddAC-THP
Aside from nausea, gastrointestinal toxicity was comparable between arms

*Safety analyses included all patients who received at least one dose of any study treatment; †grouped term: fatigue, asthenia, malaise, and lethargy; ‡grouped term: transaminases increased, aspartate transaminase increased, alanine transaminase increased, gamma-glutamyl transferase increased, liver function test abnormal, hypertransaminasemia, hepatic function abnormal, and liver function test increased; §grouped term: neutrophil count decreased and neutropenia; ¶grouped term: hemoglobin decreased, red blood cell count decreased, and anemia and hematocrit decreased; ‖grouped term: white blood cell count decreased and leukopenia. TEAE, treatment-emergent adverse event

Harbeck N et al. ESMO 2025;Abstract 291O.

Phase III DESTINY-Breast11: Authors' Conclusions

- In DESTINY-Breast11, **T-DXd-THP showed the highest reported pCR rate in HER2+ eBC** for a registrational study in the neoadjuvant setting, despite a **high prevalence of HR-positive disease** and a **high-risk population**[1–3*]
- **T-DXd-THP showed a statistically significant and clinically meaningful improvement in pCR rate** vs ddAC-THP: Δ11.2% (95% CI 4.0, 18.3)
  - pCR benefit for T-DXd-THP vs ddAC-THP was independent of HR status and disease stage
- An **early positive trend in EFS** was observed, favoring T-DXd-THP vs ddAC-THP
  - Hazard ratio: 0.56 (95% CI 0.26, 1.17)
- The **safety profile of T-DXd-THP was favorable vs ddAC-THP**
  - Lower rates of Grade ≥3 AEs, serious AEs, and AEs leading to dose interruptions
  - Lower rates of hematological AEs, left-ventricular dysfunction, and fatigue
  - ILD rates were low and similar between arms

pCR rate

67.3%

More than two thirds of patients in the T-DXd-THP arm had a pCR

HR-positive: **61.4%**
HR-negative: **83.1%**

DESTINY-Breast11 results support T-DXd-THP as a more effective and less toxic neoadjuvant treatment compared with ddAC-THP, and it may become a preferred regimen for patients with high-risk HER2+ eBC

*Historical pCR rates (defined by ypT0/is ypN0) from other registrational studies for neoadjuvant SOC treatments in HER2+ eBC ranged from 39.3% to 62.7%, and HR-positive prevalence ranged from 46.7% to 62.4%[1–3]

1. Huober J, et al. *J Clin Oncol*. 2022;40:2946–2956; 2. Hurvitz SA, et al. *Lancet Oncol*. 2018;19:115–126; 3. Gianni L, et al. *Lancet Oncol*. 2012;13:25–32

Harbeck N et al. ESMO 2025;Abstract 291O.

DESTINY-Breast05 Trial

- Geyer CE et al. **Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1)** in patients (pts) with **high-risk human epidermal growth factor receptor 2–positive (HER2+) primary breast cancer (BC)** with residual invasive disease after neoadjuvant therapy (tx): **Interim analysis of DESTINY-Breast05**. ESMO 2025;Abstract LBA1.

Abstract LBA1

BERLIN 2025 ESMO congress

DESTINY Breast05

Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor receptor 2–positive (HER2+) primary breast cancer with residual invasive disease after neoadjuvant therapy: Interim analysis of DESTINY-Breast05

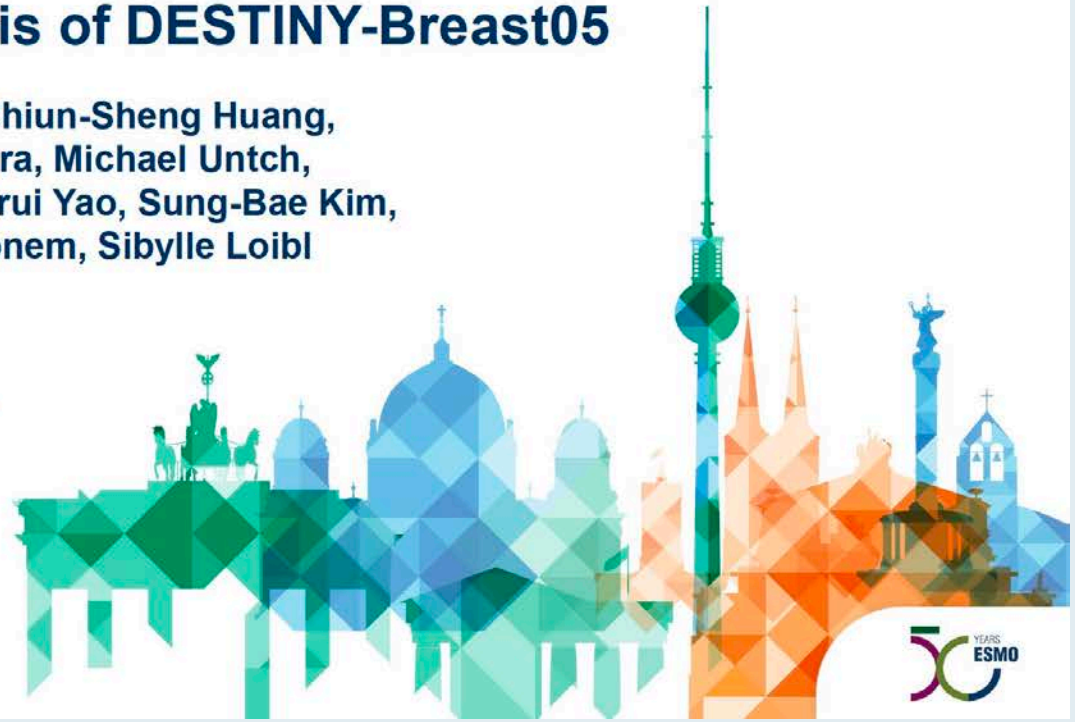
Charles E Geyer Jr,[a,b] Yeon Hee Park, Zhiming Shao, Chiun-Sheng Huang, Carlos Barrios, Jame Abraham, Aleix Prat, Naoki Niikura, Michael Untch, Seock-Ah Im, Wei Li, Huiping Li, Yongsheng Wang, Herui Yao, Sung-Bae Kim, Elton Mathias, Yuta Sato, Wenjing Lu, Hanan Abdel-Monem, Sibylle Loibl

On behalf of the DESTINY-Breast05 investigators

[a]NSABP Foundation, Pittsburgh, PA, USA
[b]University of Pittsburgh Hillman Cancer Center, Pittsburgh, PA, USA

Saturday, October 18, 2025
Presentation LBA1

NSABP National Surgical Adjuvant Breast and Bowel Project · GBG German Breast Group · AGO-B Breast Study Group · SOLTI



50 YEARS ESMO

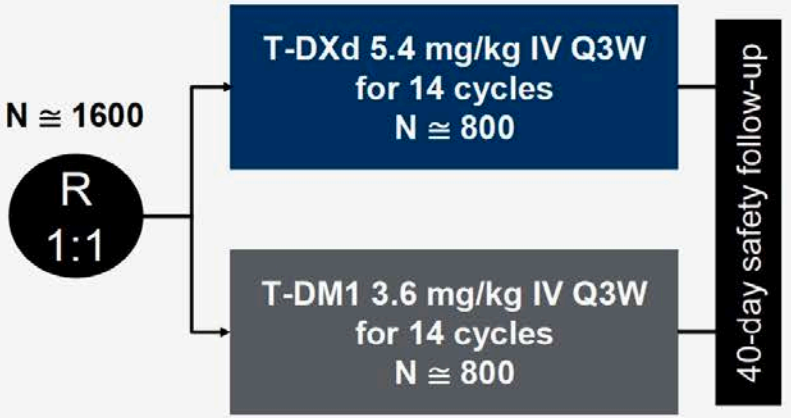
RTP RESEARCH TO PRACTICE

Phase III DESTINY-Breast05 Study Design

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4,N0-3,M0 or cT1-3,N2-3,M0) OR**
  - **Operable eBC (cT1-3,N0-1,M0) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors
- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

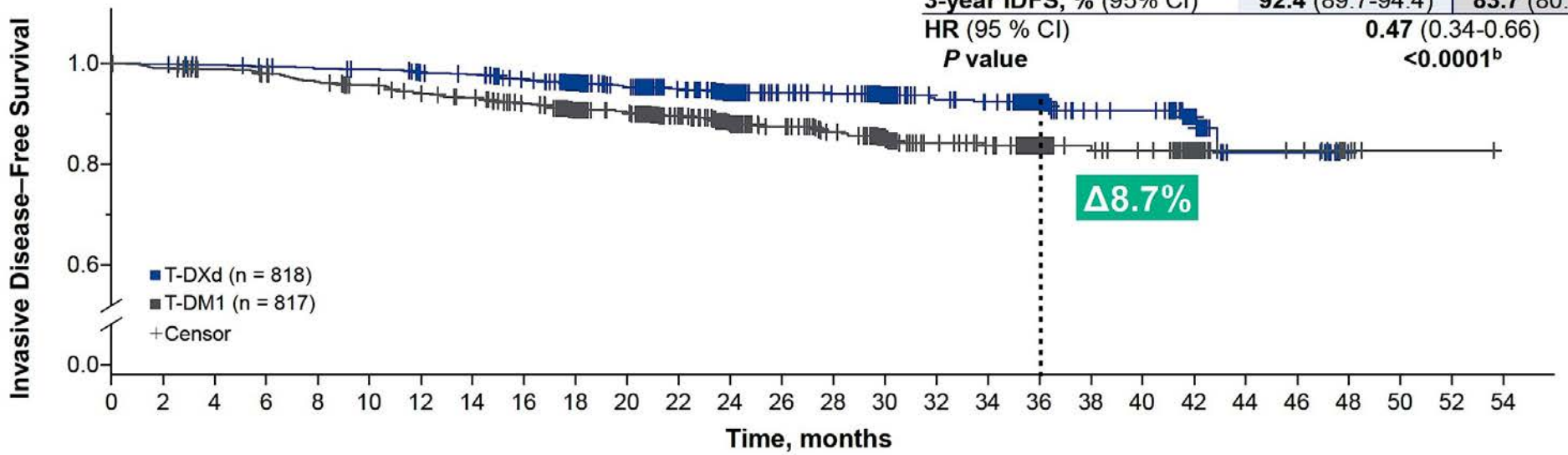
- **Concomitant adjuvant ET was allowed per local practices**
- **If administered, RT could be initiated concurrent with study therapy or completed prior to initiation of study therapy (sequential) per investigator**
- **ILD monitoring program for patients treated with RT**
  - All patients had baseline non-contrast, low dose (LD) chest CT during screening
  - All RT patients (concurrent and sequential) had LD chest CT 6 weeks after start of study therapy, then every 12 weeks while on therapy, and at 40-day follow-up
  - Sequential RT patients had additional LD chest CT after completion of RT prior to start of study therapy

BMFI, brain metastasis–free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Geyer CE et al. ESMO 2025;Abstract LBA1.

Phase III DESTINY-Breast05: Primary Endpoint (IDFS)

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**51** (6.2)	**102** (12.5)
3-year IDFS, % (95% CI)	**92.4** (89.7-94.4)	**83.7** (80.2-86.7)
HR (95 % CI)	**0.47** (0.34-0.66)	
P value	**<0.0001**[b]	



Number at Risk:

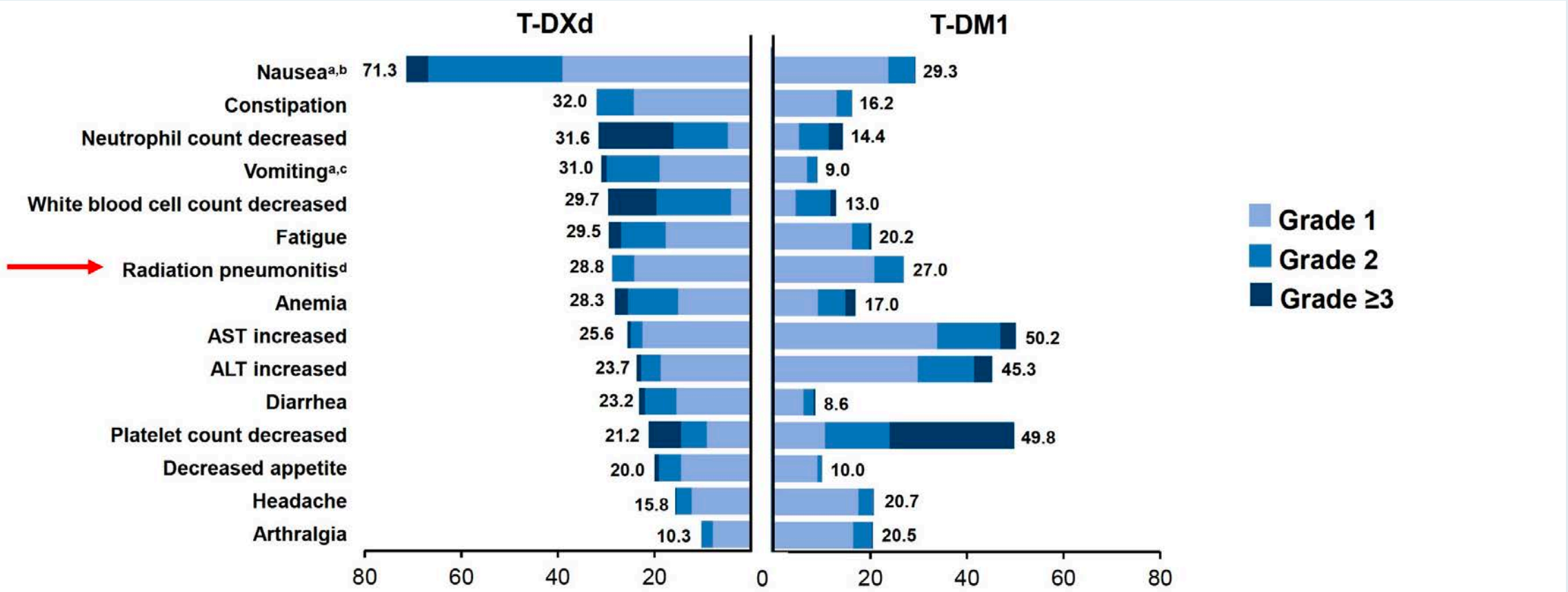
T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Geyer CE et al. ESMO 2025;Abstract LBA1.

Phase III DESTINY-Breast05: Common Adverse Events



ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Prophylactic antiemetics were recommended but not mandatory. [b]In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. [c]In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events. [d]In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1, 4.6% and 6.1% grade 2 events.

Geyer CE et al. ESMO 2025;Abstract LBA1.

Phase III DESTINY-Breast05: Authors' Conclusions

- DESTINY-Breast05 demonstrated **a statistically significant and clinically meaningful improvement in IDFS and DFS with T-DXd vs T-DM1 in high-risk[a] patients with HER2+ eBC and residual invasive disease after NAT**
- **IDFS benefit was consistent across all prespecified subgroups**
- **Benefit in DRFI with T-DXd was also observed**
- **CNS metastases and deaths were numerically fewer with T-DXd vs T-DM1**
- The overall **safety profile** of T-DXd was **manageable with no new signals**
  - >72% of patients completed treatment and was comparable in both arms
  - **Adjudicated drug-related ILD was reported in 9.6% of patients receiving T-DXd, with the majority being grade 1 or 2 and reversible**, suggesting that the risk is manageable with appropriate monitoring and timely intervention

IDFS Benefit T-DXd versus T-DM1

53% reduction in the risk of invasive disease recurrence or death

3-year IDFS rate
92.4% versus 83.7%
HR 0.47
***P* value <0.0001**

Adjuvant T-DXd demonstrated superior efficacy with manageable safety in patients with high-risk HER2+ eBC and residual invasive disease after NAT, representing a potential new standard of care in this post-neoadjuvant setting

DFS, disease-free survival; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease–free survival; ILD, interstitial lung disease; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Defined as cT4, N0-3, M0 or cT1-3, N2-3, M0 at presentation (before NAT) or cT1-3, N0-1, M0, with axillary node–positive disease (ypN1-3) following NAT.

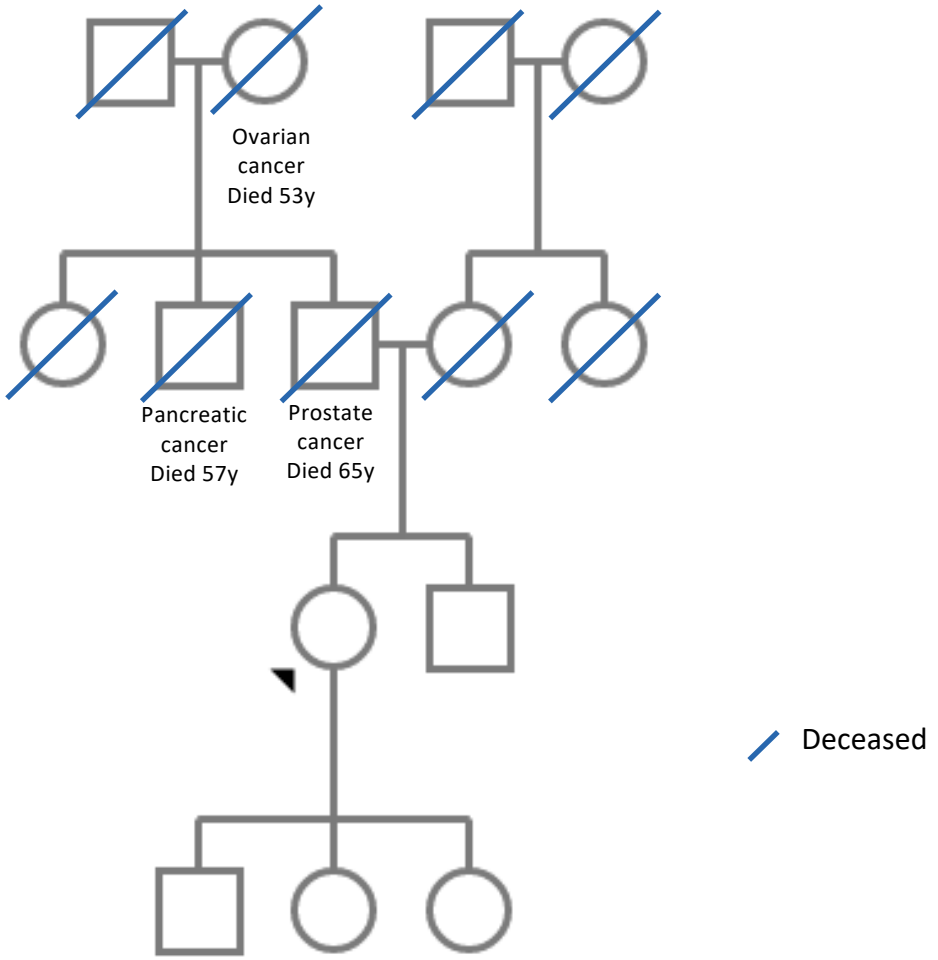
Geyer CE et al. ESMO 2025;Abstract LBA1.

Prof Curigliano: Case Presentation #2

Patient history

Patient profile

- 61-year-old woman
- Caucasian ethnicity
- BMI: 25,3 (overweight)
- G3P3, menopause at 47 y
- Non-smoker, drinks socially
- No relevant major comorbidities
- No allergies
- **Family history of cancer:**
  - Father deceased for prostate cancer (65 years old)
  - Paternal uncle deceased for pancreatic cancer (57 years old)
  - Paternal grandmother deceased for ovarian cancer (53 years old)



BMI: Body mass index; G: gravidity; P: parity; y: years

Prof Curigliano: Case Presentation #2 (Continued)

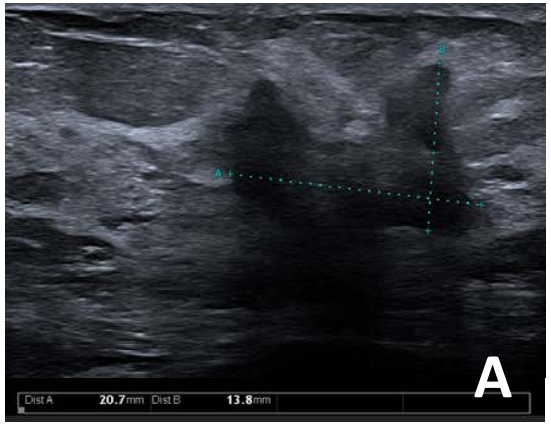
Diagnosis of HR+/HER2+ breast cancer

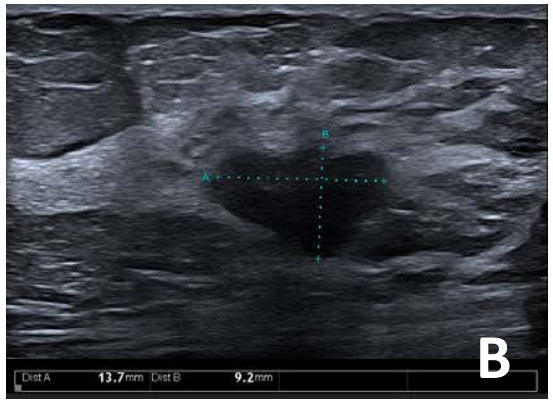
Timeline: Aug 2023

Diagnosis

Initial presentation

- Biannual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 21x14 mm (**A**), in the left supero-external quadrant, and 14x9 mm (**B**), in the superior parareolar site. No axillary lymphadenomegalies. BIRADS: 4c.





BIRADS: Breast Imaging-Reporting and Data System; US: ultrasound

Prof Curigliano: Case Presentation #2 (Continued)

Diagnosis of HR+/HER2+ breast cancer

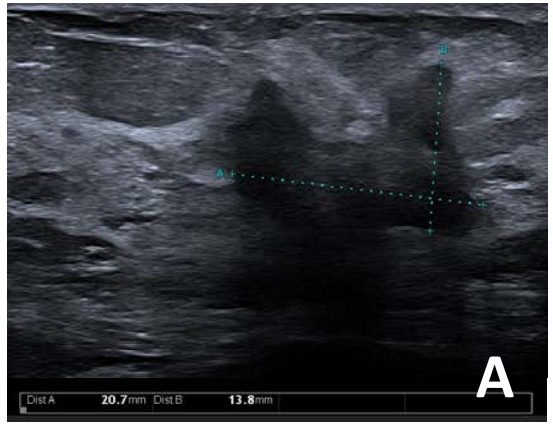
Timeline

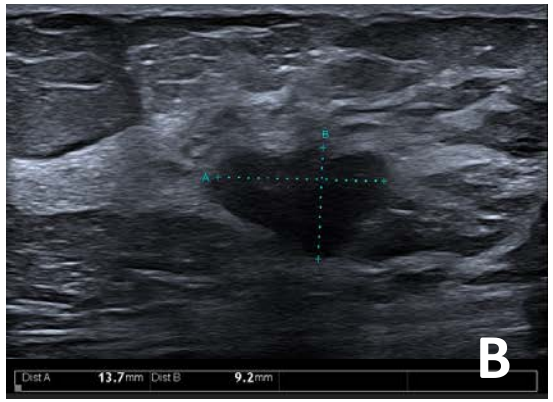
Aug 2023

Diagnosis

Initial presentation

- Biannual screening mammography with evidence of new calcifications.
- Breast US: at left breast, two hypoechogenic nodules measuring 21x14 mm (**A**), in the left supero-external quadrant, and 14x9 mm (**B**), in the superior parareolar site. Axillary lymphadenomegalies. BIRADS: 4c.





Core biopsy (A). Pathology report

- IDC NOS, G2.
- ER (IHC): 65%; PgR (IHC): 5%; Ki67: 40%; HER2 IHCscore: 2+
- ISH test: positive.

FNAC (B). Pathology report

- C5

Stage: cT2 (m) cN1 cM0 (II)

BIRADS: Breast Imaging-Reporting and Data System; ER: estrogen receptor; FNAC, fine-needle aspiration cytology; G: grade; HER2: human epidermal growth factor receptor 2; IDC: invasive ductal carcinoma; IHC: immunohistochemistry; ISH: in situ hybridization; NOS: not otherwise specified; PgR: progesterone receptor; TNM, tumour–node–metastasis; US: ultrasound

Prof Curigliano: Case Presentation #2 (Continued)

Diagnosis of HR+/HER2+ breast cancer

Invasive ductal carcinoma G2 of the left breast
ER: 65%; PgR: 5%; Ki67: 40%; HER2-positive
Stage: cT2 (m) cN1 cM0 (II)

Neoadjuvant pertuzumab and trastuzumab deruxtecan followed by THP in DESTINY 11 trial

+ genetic counseling indicated

ER: estrogen receptor; G: grade; HER2: human epidermal growth factor receptor 2; PgR: progesterone receptor; TNM, tumour–node–metastasis

Prof Curigliano: Case Presentation #2 (Continued)

Surgery

- Neoadjuvant treatment in DESTINY 11

Prof Curigliano: Case Presentation #2 (Continued)

Surgery

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 2 cm

- SLND. Frozen section examination: metastasis of carcinoma with extranodal extension in 2/2 sentinel lymph nodes.

Surgery

Axillary dissection

- Mastectomy indicated
- 2/2 metastatic lymph nodes
- Extranodal extension
- SOC for >2 N+

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano: Case Presentation #2 (Continued)

Surgery

- Left nipple-sparing mastectomy: 4 confluent lumps measuring more than 4 cm
- Left axillary lymph node dissection
- Immediate breast reconstruction

Histology

- IDC NOS, G2. pLVI1
- ER (IHC): 65%; PgR (IHC): 5%; Ki67: 40%; HER2 IHC score: 2+; ISH test: positive

Stage: pT2 (4.2 cm) pN2a (6/16) cM0

Genetic counseling

- Germline mutation of BRCA2: c.6313delA p.(Ile2105Tyrfs) – class 5
- Bilateral prophylactic adnexectomy and right prophylactic mastectomy indicated
- First degree relatives counseling indicated

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano: Case Presentation #2 (Continued)

Surgery

- Which adjuvant therapy?
- Olaparib?
- Continue TDX?
- TDM1?

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Prof Curigliano: Case Presentation #2 (Continued)

Surgery

Adjuvant chemotherapy

- AC x 4 cycles
  - Doxorubicin 60 mg/m^2
  - Cyclophosphamide 600 mg/m^2
  - Followed by TDM1

Which is the best AC schedule?

Standard AC (Q3W)

- Lower toxicity

Dose dense AC (Q2W)

- OS benefit in two clinical trials (CALGB 9741 and GIM2) evaluating the intensification of both anthracyclines and taxanes

ESMO Guidelines 2022; Donker, Lancet Oncol 2014; Sávolt, Eur J Surg Oncol 2017

Agenda

Module 1: HER2-Positive Breast Cancer

Module 2: HR-Positive Breast Cancer

Module 3: Triple-Negative Breast Cancer

RTP RESEARCH TO PRACTICE

monarchE Trial

- Johnston SR et al. **monarchE: Primary overall survival (OS) results** of **adjuvant abemaciclib** + endocrine therapy (ET) for **HR+, HER2-, high-risk early breast cancer (EBC)**. ESMO 2025;Abstract LBA13.

Abstract LBA13

BERLIN 2025 ESMO congress

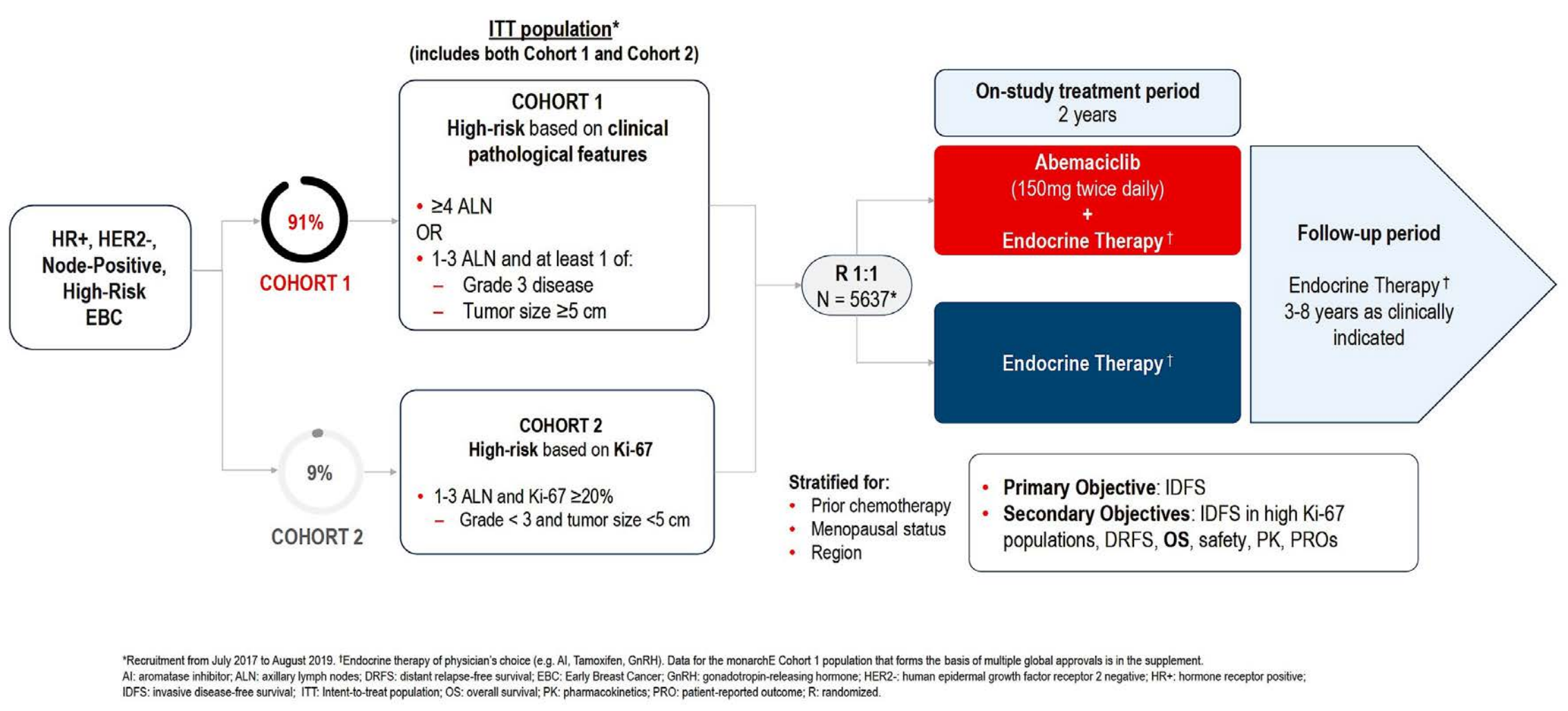
monarchE: Primary overall survival results of adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer

Stephen Johnston, Miguel Martin, Joyce O'Shaughnessy, Roberto Hegg, Sara M. Tolaney, Valentina Guarneri, Lucia Del Mastro, Mario Campone, Joohyuk Sohn, Frances Boyle, Javier Cortes, Hope S. Rugo, Matthew P. Goetz, Erika P. Hamilton, Chiun-Sheng Huang, Elzbieta Senkus, Irfan Cicin, Laura Testa, Patrick Neven, Jens Huober, Zhimin Shao, Ran Wei, Maria Munoz, Belen San Antonio, Ashwin Shahir, Priya Rastogi, Nadia Harbeck

Stephen Johnston, MD, PhD

Breast Unit, The Royal Marsden, NHS Foundation Trust, London, UK

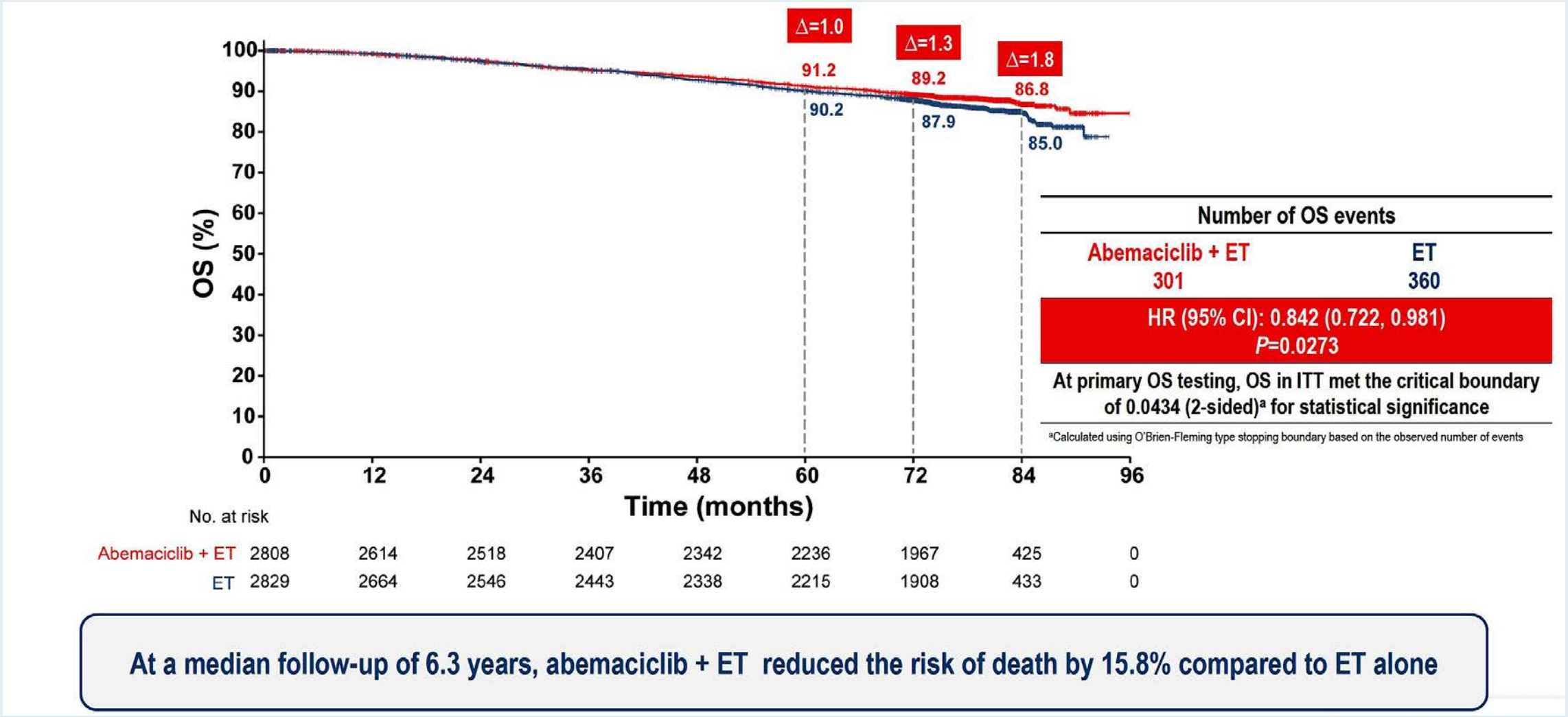
Phase III monarchE Study Design



*Recruitment from July 2017 to August 2019. †Endocrine therapy of physician's choice (e.g. AI, Tamoxifen, GnRH). Data for the monarchE Cohort 1 population that forms the basis of multiple global approvals is in the supplement.
AI: aromatase inhibitor; ALN: axillary lymph nodes; DRFS: distant relapse-free survival; EBC: Early Breast Cancer; GnRH: gonadotropin-releasing hormone; HER2-: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; ITT: Intent-to-treat population; OS: overall survival; PK: pharmacokinetics; PRO: patient-reported outcome; R: randomized.

Johnston SR et al. ESMO 2025;Abstract LBA13.

Phase III monarchE: Long-Term Overall Survival



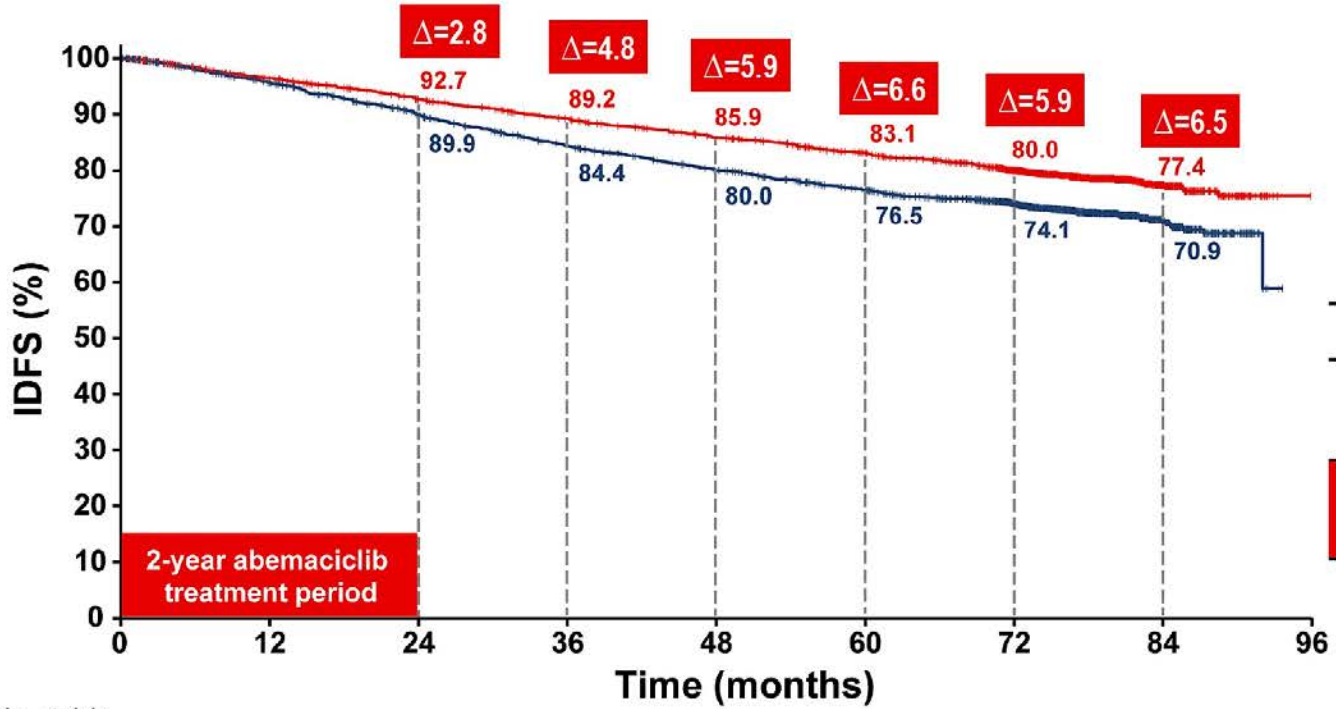
At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

ET = endocrine therapy

Johnston SR et al. ESMO 2025;Abstract LBA13.

RTP RESEARCH TO PRACTICE

Phase III monarchE: Long-Term IDFS



Number of IDFS events	
Abemaciclib + ET	ET
547	722

HR (95% CI): 0.734 (0.657, 0.820)
Nominal *P*<.0001

Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone

Johnston SR et al. ESMO 2025;Abstract LBA13.

Phase III monarchE: Authors' Conclusions

- At the primary OS analysis, **2 years of abemaciclib + ET** demonstrated a **statistically significant and clinically meaningful improvement in OS** in the ITT population
  - With a median follow-up of 76 months (6.3 years), abemaciclib + ET **reduced the risk of death by 15.8%** compared to ET in the ITT population
  - With ~30% **fewer patients in the abemaciclib arm living with metastatic disease**, this is expected to lead to **larger OS benefit with longer follow-up**
- At 7-year landmark analyses, abemaciclib + ET continued to demonstrate **sustained benefit in IDFS and DRFS** reinforcing the consistency and durability of the treatment effect across endpoints
- Consistent OS, IDFS, and DRFS benefits observed in the Cohort 1 population and in all prespecified subgroups
- Safety was consistent with prior reports, and **no new signals** related to delayed toxicities were identified

Abemaciclib is the first CDK4/6 inhibitor to achieve a statistically significant improvement in OS for patients with HR+ HER2-, node-positive, high-risk EBC

Johnston SR et al. ESMO 2025;Abstract LBA13.

RTP RESEARCH TO PRACTICE

Adjuvant Ribociclib

- Crown J et al. **Adjuvant ribociclib** plus nonsteroidal aromatase inhibitor therapy in patients with **HR+/HER2– early breast cancer: NATALEE 5-year outcomes**. ESMO 2025;Abstract LBA14.

Abstract LBA14

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Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor Therapy in Patients With HR+/HER2− Early Breast Cancer: NATALEE 5-Year Outcomes

John Crown[1], Daniil Stroyakovskii[2], Denise A. Yardley[3], Chiun-Sheng Huang[4], Peter A. Fasching[5], Aditya Bardia[6], Stephen Chia[7], Seock-Ah Im[8], Miguel Martin[9], Binghe Xu[10], Carlos H. Barrios[11], Michael Untch[12], Rebecca Moroose[13], Sara A. Hurvitz[14], Gabriel N. Hortobagyi[15], Dennis J. Slamon[16], Frances Visco[17], Gonzalo Spera[18], Zheng Li[19], Sherene Loi[20]

[1]St. Vincent's University Hospital, Dublin, Ireland; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russia; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [5]University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [6]David Geffen School of Medicine at UCLA and the UCLA Health Jonsson Comprehensive Cancer Center; Los Angeles, CA, USA; [7]BC Cancer, Vancouver, BC, Canada; [8]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [9]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [10]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [11]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [12]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [13]Orlando Health Cancer Institute, Orlando, FL, USA; [14]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [15]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [16]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [17]National Breast Cancer Coalition (NBCC), Washington, DC, USA; [18]Translational Research in Oncology (TRIO), Montevideo, Uruguay; [19]Novartis Pharmaceuticals, East Hanover, NJ, USA; [20]Peter MacCallum Cancer Centre, Melbourne, Australia

Speaker: John Crown, M.D.

RTP RESEARCH TO PRACTICE

Phase III NATALEE Study Design

Adult patients with stage II and III HR+/HER2− EBC

- Prior ET allowed up to 12 months
- **Anatomical stage IIA**[a]
  - N0 with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - N1
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

R 1:1

RIB
400 mg/day
3 weeks on/1 week off for **3 y**
+
NSAI
Letrozole or anastrozole[b] for **≥5 y**
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[b] for **≥5 y**
+ goserelin in men and premenopausal women

Primary End Point
iDFS using STEEP criteria

Secondary End Points
- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.

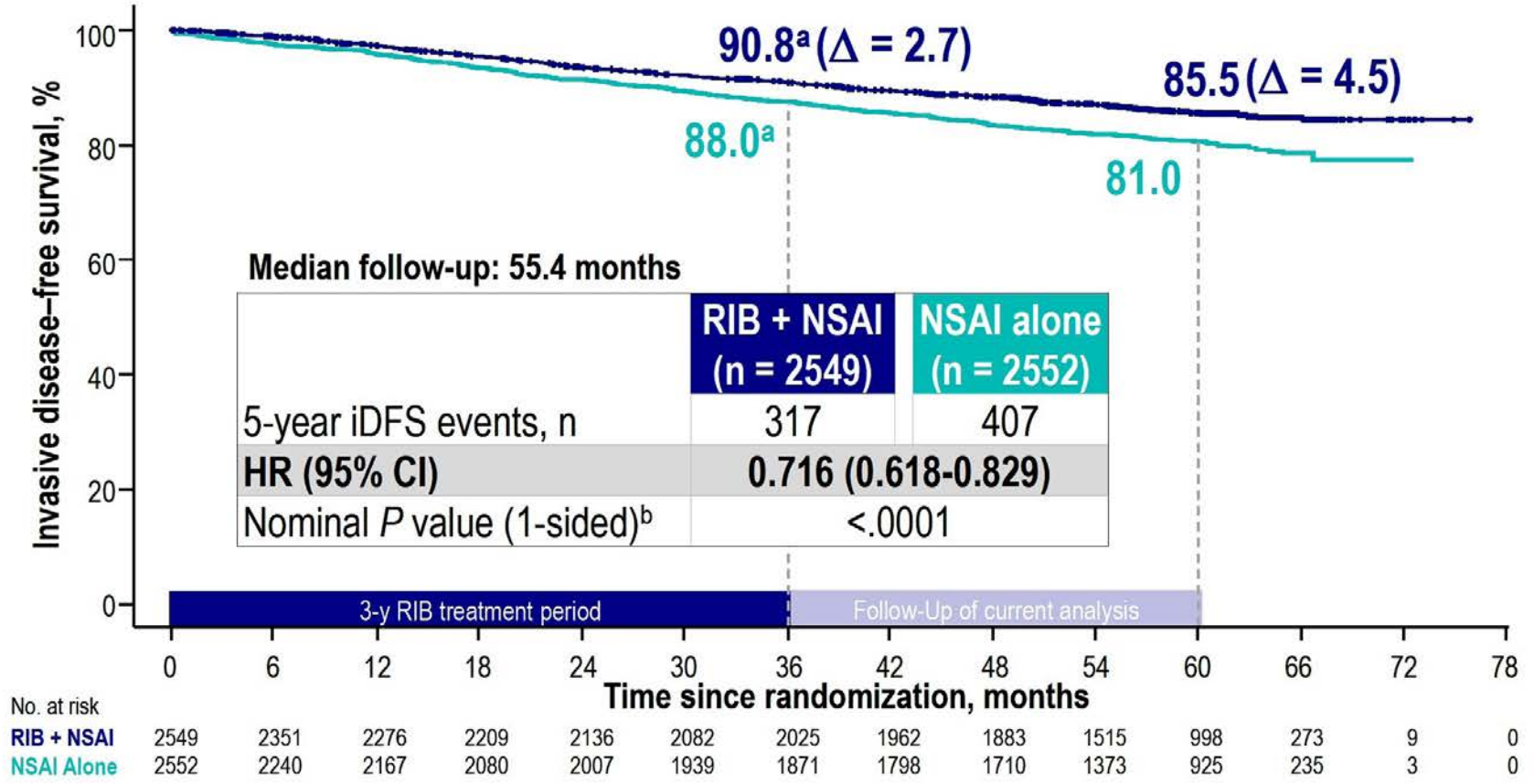
[a] Enrollment of patients with stage II disease was capped at 40%. [b] Per investigator choice.
ctDNA/RNA, circulating tumor DNA/RNA; DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; EBC, early breast cancer; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease–free survival; ITT, intention to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes; RIB, ribociclib; RFS, recurrence-free survival; STEEP, Standardized Definitions for Efficacy End Points.

1. ClinicalTrials.gov. Accessed November 8, 2023. https://clinicaltrials.gov/study/NCT03701334.
2. Slamon D et al. *Ther Adv Med Oncol.* 2023;15:1-16.

Crown J et al. ESMO 2025;Abstract LBA14.

Phase III NATALEE: iDFS (ITT Population)

With 55.4 months of follow-up, RIB continues to demonstrate a durable iDFS benefit

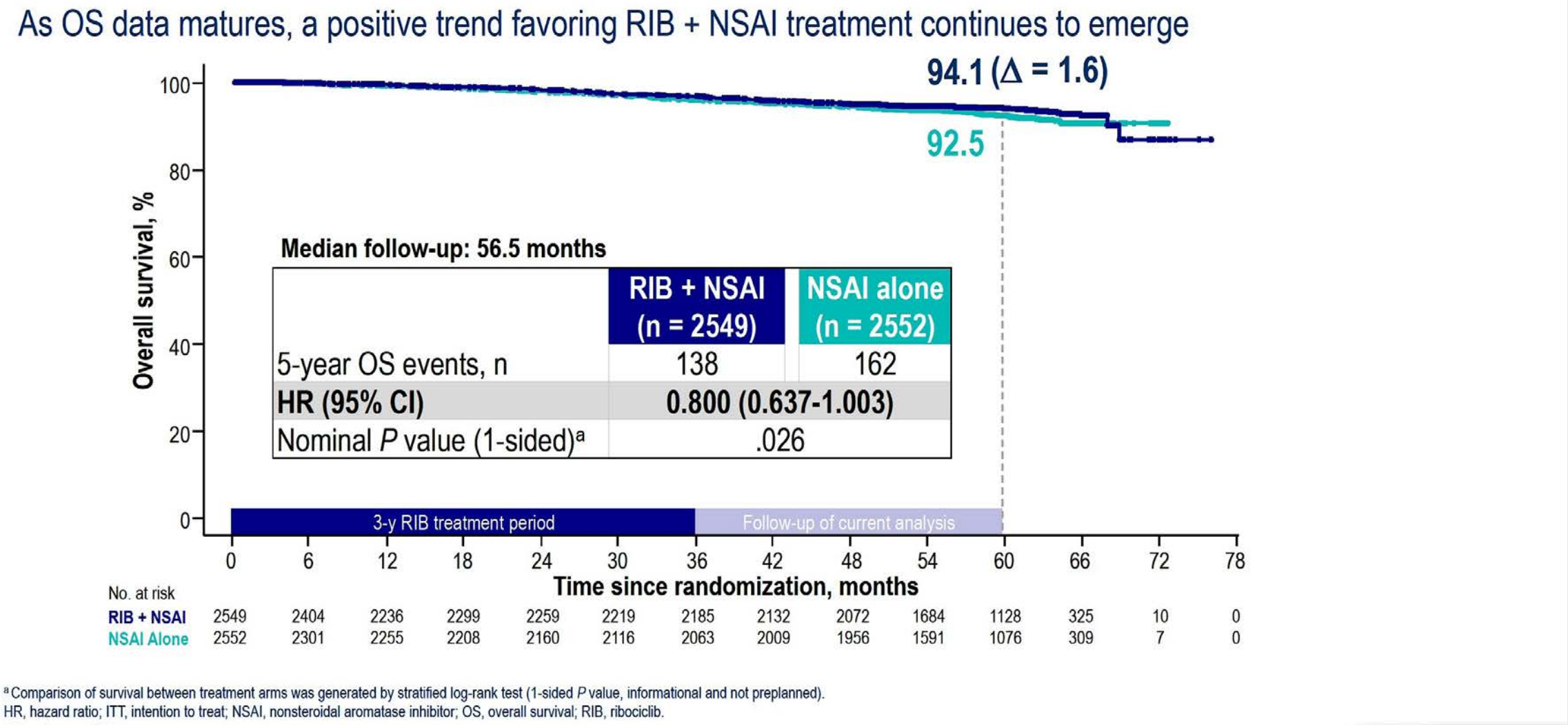


[a] The difference between percentages does not equal 2.7 due to rounding. [b] Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided *P* value, informational and not preplanned).
HR, hazard ratio; IDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Crown J et al. ESMO 2025;Abstract LBA14.

RTP RESEARCH TO PRACTICE

Phase III NATALEE: OS (ITT Population)



[a] Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided *P* value, informational and not preplanned).
HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

Crown J et al. ESMO 2025;Abstract LBA14.

Phase III NATALEE: Authors' Conclusions

- RIB + NSAI demonstrated durable iDFS benefit vs NSAI alone, with a 28% relative reduction in the risk of recurrence or death after a median of 2 years post RIB treatment
  - —Absolute iDFS improvement between treatment arms was Δ4.5% for 5-year rates
- Sustained iDFS benefit with RIB + NSAI was observed across subgroups, including those with high-risk N0 disease, with the upper boundary of the CI for N0 below 1 for the first time
- At the 5-year analysis, RIB + NSAI also demonstrated a clinically meaningful reduction in the risk of distant recurrence or death: 29.1% with DDFS and 30.1% for DRFS
- RIB + NSAI showed a continued numerical trend for improved OS, as data continue to mature
- No new safety signals were identified

At this 5-year follow-up of NATALEE, RIB + NSAI continues to reduce the risk of recurrence beyond the 3-year treatment window, supporting its use as adjuvant therapy in patients with HR+/HER2− EBC at high risk of recurrence, including those with high-risk N0 disease

DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; EBC, early breast cancer; HR+/HER2−, hormone receptor positive, human epidermal growth factor receptor 2 negative; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

Crown J et al. ESMO 2025;Abstract LBA14.

Dr Sharma: Case Presentation #1

62-year-old postmenopausal female with ER/PR-positive/HER2-negative right breast cancer. pT2N1 (3.5 cm grade II IDC, 1/4 positive sentinel LNs, ER = 100%, PR = 30%, HER2 IHC 1+, Ki-67 25%). S/p lumpectomy with SLNB. Oncotype DX® RS 28. Patient receives adjuvant chemotherapy with ddAC followed by weekly paclitaxel and then is started on adjuvant anastrozole along with adjuvant abemaciclib. She was enrolled on institutional protocol of adjuvant abemaciblib dose escalation with starting dose of 100 mg BID for two cycles followed by 150 mg BID. She has been tolerating abemaciclib well for the last 6 months but reports debilitating arthralgias related to anastrozole requiring endocrine therapy switch to tamoxifen.

SERENA-6 Trial: Patient-Reported Outcomes

- Mayer EL et al. **Patient-reported outcomes (PROs)** from the **SERENA-6 trial of camizestrant (CAMI) + CDK4/6 inhibitor (CDK4/6i)** for **emergent *ESR1*m** during first-line (1L) endocrine-based therapy and ahead of disease progression in patients (pts) with **HR+/HER2– advanced breast cancer (ABC)**. ESMO 2025;Abstract 486MO.

Abstract 486MO

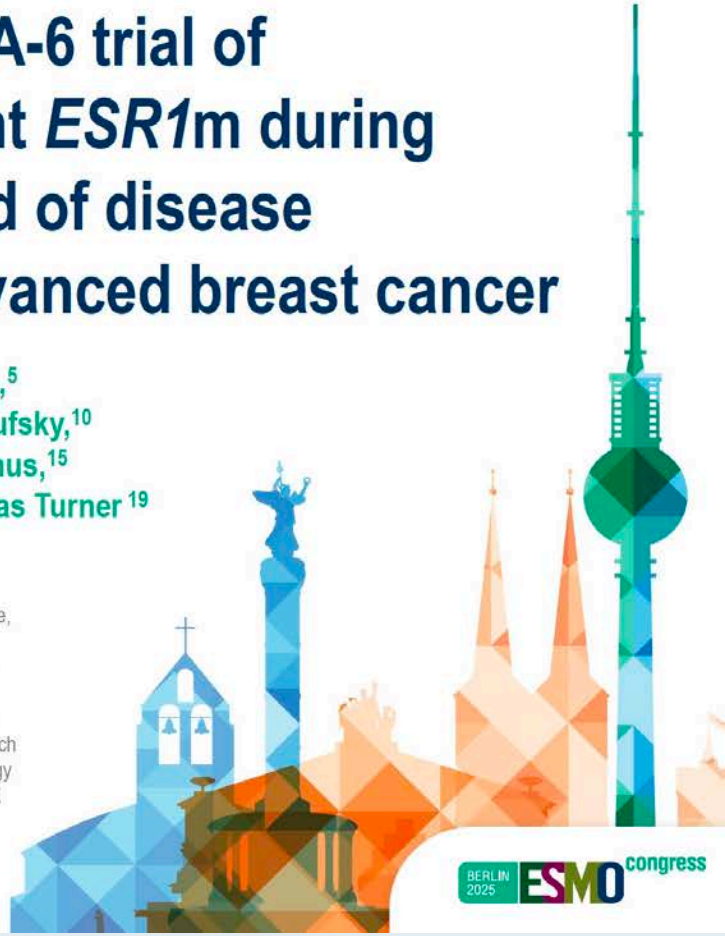
BERLIN 2025 ESMO congress

SERENA-6

Patient-reported outcomes from the SERENA-6 trial of camizestrant + CDK4/6 inhibitor for emergent *ESR1*m during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer

Erica L. Mayer,[1] François-Clément Bidard,[2] Yeon Hee Park,[3] Wolfgang Janni,[4] Cynthia Ma,[5] Massimo Cristofanilli,[6] Giampaolo Bianchini,[7] Hiroji Iwata,[8] Peter A. Fasching,[9] Adam Brufsky,[10] Zbigniew Nowecki,[11] Javier Pascual,[12] Lionel Moreau,[13] Shin-Cheh Chen,[14] Nuri Karadurmus,[15] Cara Arizmendi,[16] Steven Fox,[17] Manuel Selvi Miralles,[17] Cynthia Huang Bartlett,[18] Nicholas Turner [19]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Institut Curie, Paris, France; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Universitätsklinikum Ulm, Ulm, Germany; [5]Washington University School of Medicine, Saint Louis, MO, USA; [6]Weill-Cornell Medicine / New York-Presbyterian Hospital, New York, NY, USA; [7]IRCCS Ospedale San Raffaele, Milan, Italy; [8]Nagoya City University, Nagoya, Japan; [9]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; [10]UMPC Magee-Womens Hospital, Pittsburgh, PA, USA; [11]Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie, Warsaw, Poland; [12]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [13]Pôle Santé République, Clermont-Ferrand, France; [14]Chang Gung Medical Foundation Linkou Branch, Taoyuan City, Taiwan; [15]Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkey; [16]Evinova, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [17]Late Development, Oncology R&D, AstraZeneca, Cambridge, UK; [18]Late Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [19]Royal Marsden Hospital, London, UK



Presented by Erica L. Mayer

RTP RESEARCH TO PRACTICE

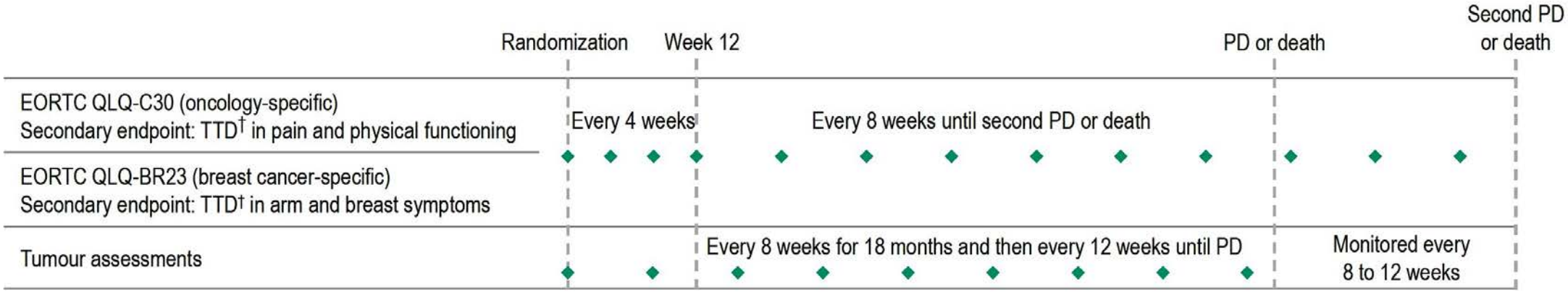
Phase III SERENA-6 Study Design and Patient-Reported Outcomes Assessments

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in circulating tumour DNA (following surveillance) with no evidence of disease progression

R 1:1 N=315

- Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI (n=157)
- Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant (n=158)

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal, or death



- EORTC QLQ-C30 and BR23 assessments were more frequent than tumor assessments
- Overall, compliance rates for the EORTC QLQ-C30 and EORTC QLQ-BR23 were similar between treatment arms

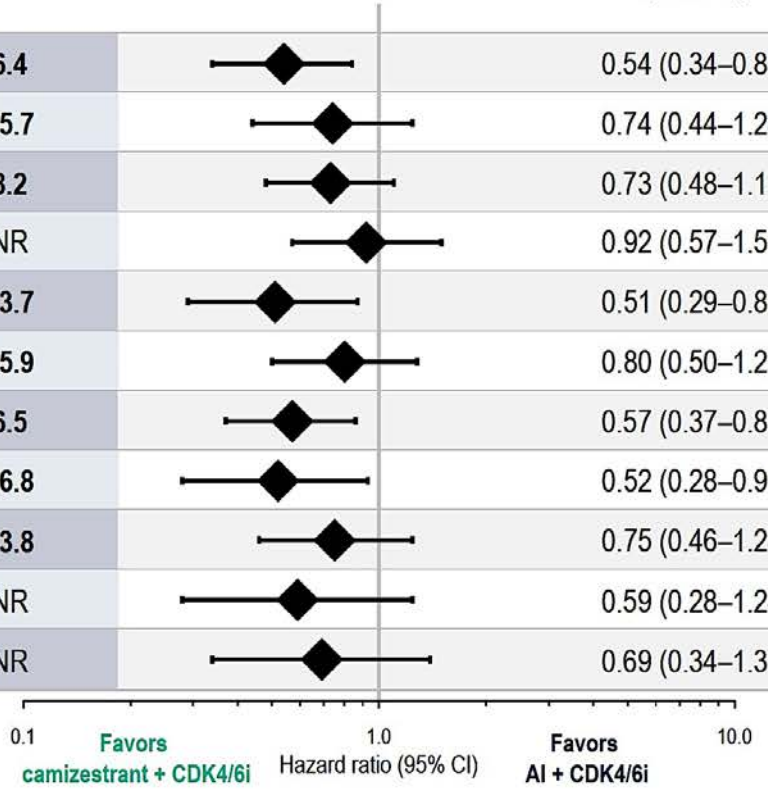
*Pre- or perimenopausal women and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. Overall, compliance rates for the EORTC QLQ-C30 and EORTC QLQ-BR23 were similar between the camizestrant + CDK4/6 inhibitor arm and the AI + CDK4/6 inhibitor arm.
†TTD: time from randomization until first clinically meaningful deterioration confirmed at a subsequent timepoint using study-specific meaningful change thresholds for selected scales (primary analysis).
Data cutoff for analyses reported here: Nov 28, 2024. PD, progressive disease; qd, once daily dose; R, randomized.

Mayer EL et al. ESMO 2025;Abstract 486MO.

RTP RESEARCH TO PRACTICE

Phase III SERENA-6: Time to Deterioration (TTD)

		Deterioration events, n/N		Median TTD* (months)		Hazard ratio (95% CI)
		CAMI + CDK4/6i	AI + CDK4/6i	CAMI + CDK4/6i	AI + CDK4/6i	
EORTC QLQ-C30	GHS/QOL	37/107	49/95	**21.0**	**6.4**	0.54 (0.34–0.84)
	Physical functioning**	33/108	29/95	**23.0**	**15.7**	0.74 (0.44–1.24)
	Role functioning	48/108	47/94	**15.6**	**8.2**	0.73 (0.48–1.10)
	Cognitive functioning	38/107	31/95	**23.0**	NR	0.92 (0.57–1.50)
	Emotional functioning	25/107	32/95	NR	**13.7**	0.51 (0.29–0.87)
	Social functioning	39/107	35/95	**34.1**	**15.9**	0.80 (0.50–1.28)
	Pain**	42/106	49/94	**16.6**	**6.5**	0.57 (0.37–0.86)
	Shortness of breath/ dyspnoea	21/105	29/94	NR	**16.8**	0.52 (0.28–0.93)
	Fatigue	34/104	33/91	NR	**13.8**	0.75 (0.46–1.24)
EORTC QLQ-BR23	Breast symptoms**	13/102	16/92	NR	NR	0.59 (0.28–1.24)
	Arm symptoms**	15/100	18/90	NR	NR	0.69 (0.34–1.39)



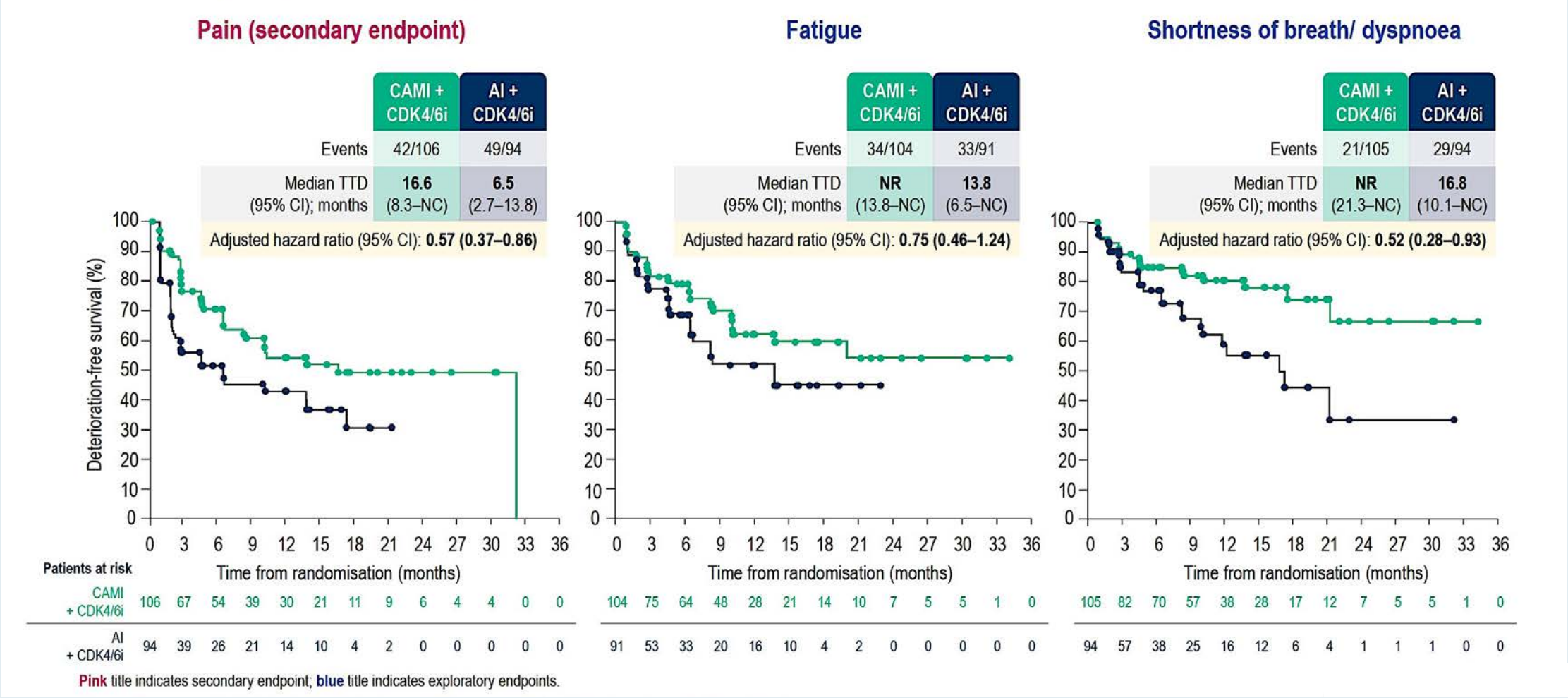
*Time to deterioration defined as time from randomisation to deterioration based on meaningful change thresholds (16.6 for GHS/QoL, role, emotional, cognitive, social functioning, pain and breast symptoms, 22.2 for fatigue and arm symptoms, 13.3 for physical functioning, and 10 for dyspnoea). **Time to deterioration in pain, physical functioning, breast symptoms, and arm symptoms were pre-defined secondary endpoints. Hazard ratios less than 1 favouring CAMI + CDK4/6i. NR, not reached.

CAMI = camizestrant; AI = aromatase inhibitor

Mayer EL et al. ESMO 2025;Abstract 486MO.

RTP RESEARCH TO PRACTICE

Phase III SERENA-6: TTD — Patient-Reported Cancer Symptoms



Mayer EL et al. ESMO 2025;Abstract 486MO.

Phase III SERENA-6: TTD — Patient-Reported Functioning

Physical: ability to perform everyday physical activities **(secondary endpoint)**

	CAMI + CDK4/6i	AI + CDK4/6i
Events	33/108	29/95
Median TTD (95% CI); months	**23.0** (17.4–NC)	**15.7** (8.3–NC)

Adjusted hazard ratio (95% CI): **0.74 (0.44–1.24)**

Role: impact of health on work and daily activities

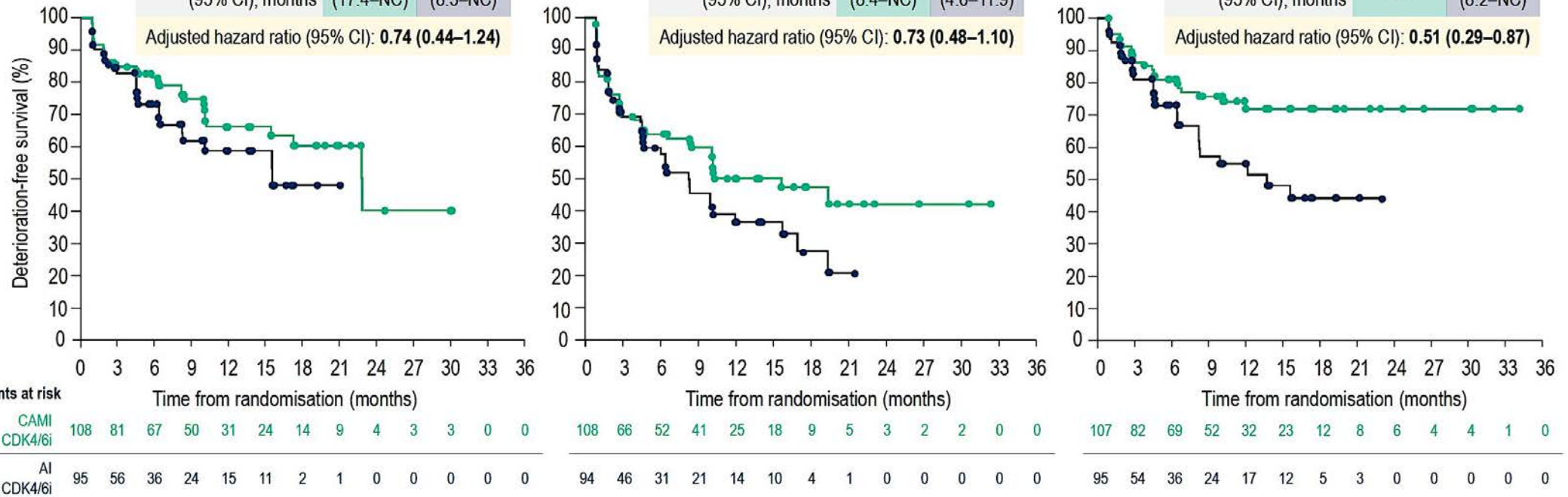
	CAMI + CDK4/6i	AI + CDK4/6i
Events	48/108	47/94
Median TTD (95% CI); months	**15.6** (8.4–NC)	**8.2** (4.6–11.9)

Adjusted hazard ratio (95% CI): **0.73 (0.48–1.10)**

Emotional: feelings of anxiety, depression and irritability

	CAMI + CDK4/6i	AI + CDK4/6i
Events	25/107	32/95
Median TTD (95% CI); months	**NR**	**13.7** (8.2–NC)

Adjusted hazard ratio (95% CI): **0.51 (0.29–0.87)**



Pink title indicates secondary endpoint; **blue** title indicates exploratory endpoints.

Mayer EL et al. ESMO 2025;Abstract 486MO.

RTP RESEARCH TO PRACTICE

Phase III SERENA-6: Authors' Conclusions

- First-line camizestrant with continuation of CDK4/6 inhibitor in patients with emergence of *ESR1*m during AI+CDK4/6 inhibitor therapy, demonstrated consistent benefit in delaying TTD and reducing the risk of deterioration in patient-reported cancer symptoms and functioning
  - These findings support the delay in TTD and reduced risk of deterioration in GHS/QoL reported previously

PRO results further support camizestrant + CDK4/6 inhibitor as a potential new treatment strategy to optimize and improve outcomes in patients with HR+/HER2– ABC and emergence of *ESR1*m, ahead of disease progression, during first-line AI + CDK4/6 inhibitor

GHS = global health status; QoL = quality of life

Mayer EL et al. ESMO 2025;Abstract 486MO.

Survey of 50 General Medical Oncologists: Breast Cancer

Survey Dates: 7/22/25 to 7/25/25

RTP
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Clinical Investigator Survey Participants

Francois-Clement Bidard, MD, PhD

Virginia F Borges, MD, MMSc

Harold J Burstein, MD, PhD

Lisa A Carey, MD, ScM, FASCO

Professor Giuseppe Curigliano, MD, PhD

Angela DeMichele, MD, MSCE

Matthew P Goetz, MD

Stephanie L Graff, MD, FACP

Sara A Hurvitz, MD, FACP

Virginia Kaklamani, MD, DSc

Kevin Kalinsky, MD, MS, FASCO

Ian E Krop, MD, PhD

Kathy D Miller, MD

Shanu Modi, MD

Ruth O'Regan, MD

Joyce O'Shaughnessy, MD

Hope S Rugo, MD

Priyanka Sharma, MD

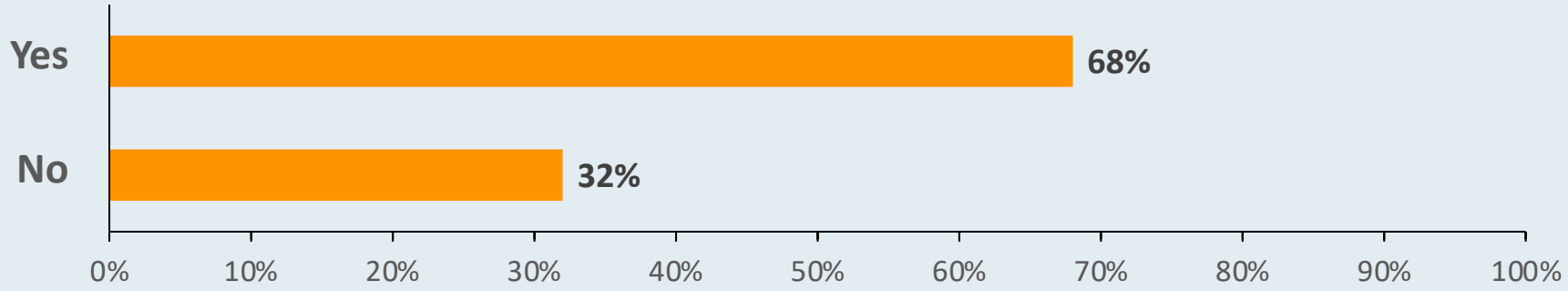
Rebecca Shatsky, MD

Seth Wander, MD, PhD

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, do you believe that the results from the SERENA-6 study justify the routine use of serial ctDNA monitoring for early detection of ESR1 mutations in patients with ER-positive, HER2-negative mBC receiving first-line therapy?

General Medical Oncologists



Clinical Investigators

Survey of 20 US-based clinical investigators and 50 general medical oncologists

RTP RESEARCH TO PRACTICE

Prof Curigliano: Case Presentation #3

The patient

GC, 54-year-old (post-menopausal)

PS ECOG 0, 63 kg, 175 cm

Family history: None

Hypertension, Atrial fibrillation, IBD

Prof Curigliano: Case Presentation #3 (Continued)

Diagnosis

March 2023 Self examination of left breast: lump detected

01.03.23 Mammography + ultrasonography: lump of 43 mm, axillary nodes of 5 cm

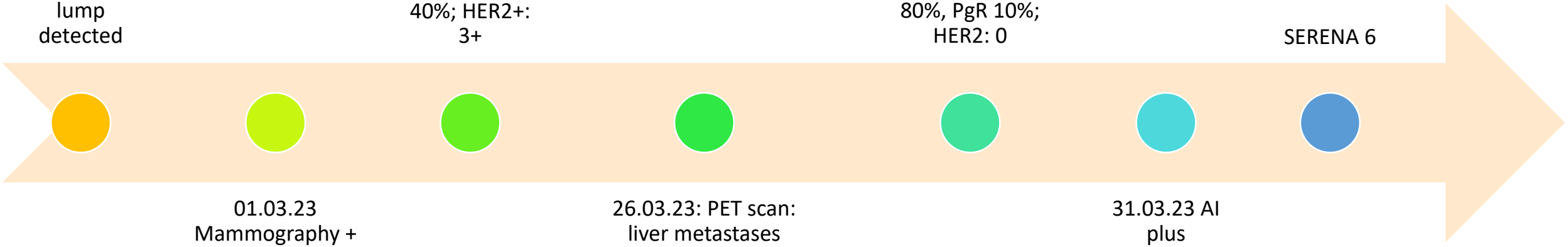
21.03.23 Core biopsy of left breast: ductal infiltrating carcinoma, multifocal, ER: 80%; PgR: 80%; Ki67: 40%; HER2+: 3+

26.03.23: PET scan: liver metastases

29.03.23 Liver biopsy: Breast cancer metastases. ER: 80%, PgR 10%; HER2: 0

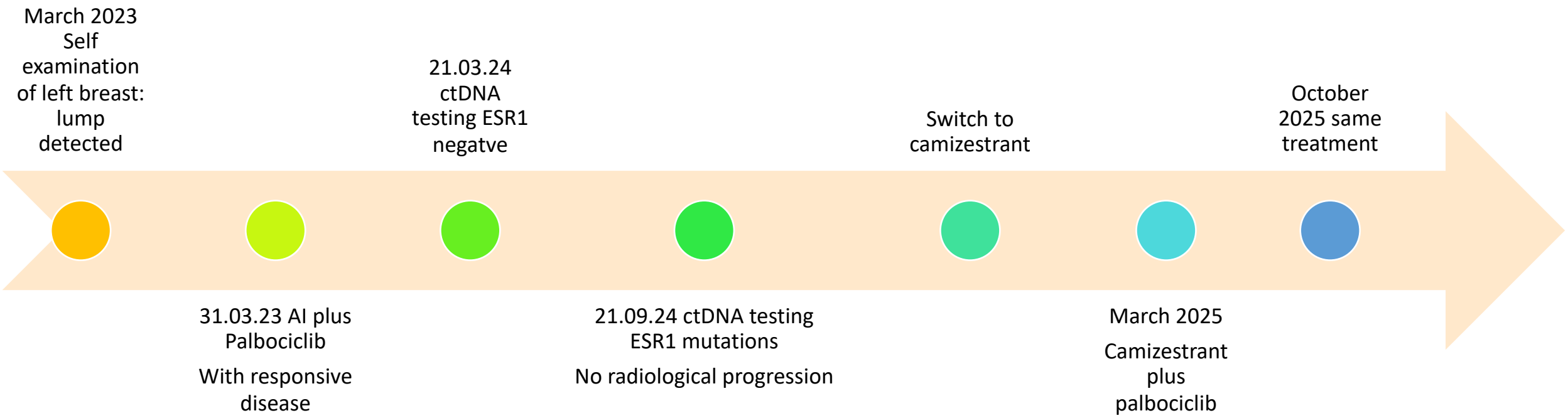
31.03.23 AI plus palbociclib

SERENA 6



Prof Curigliano: Case Presentation #3 (Continued)

Diagnosis



EMBER-3 Trial: Indirect Comparison

- Bidard FC et al. **Imlunestrant plus abemaciclib** versus fulvestrant plus abemaciclib in **estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC)**: An **indirect treatment comparison (ITC) of three phase 3 trial**s. ESMO 2025;Abstract 496P.

Imlunestrant (Imlu) Plus Abemaciclib (Abema) Versus Fulvestrant (Fulv) Plus Abema In Estrogen Receptor–Positive (ER+), Human Epidermal Growth Factor Receptor 2–Negative (HER2-) Advanced Breast Cancer (ABC): An Indirect Treatment Comparison (ITC) of Three Phase 3 Trials

Komal Jhaveri[1], Francois-Clement Bidard[2], Kevin Kalinsky[3], Patrick Neven[4], Hope S. Rugo[5], Sara M. Tolaney[6], Lacey M. Litchfield[7], Christoph Cramer von Laue[7], Sory Traore[7], Francisco Sapunar[7], Yujia Li[7], Joyce O'Shaughnessy[8]

OBJECTIVES

This study aimed to determine the relative efficacy of imlunestrant+abemaciclib versus fulvestrant+abemaciclib through an ITC of the EMBER-3, MONARCH 2, and postMONARCH trials.

ESMO 2025;Abstract 496P

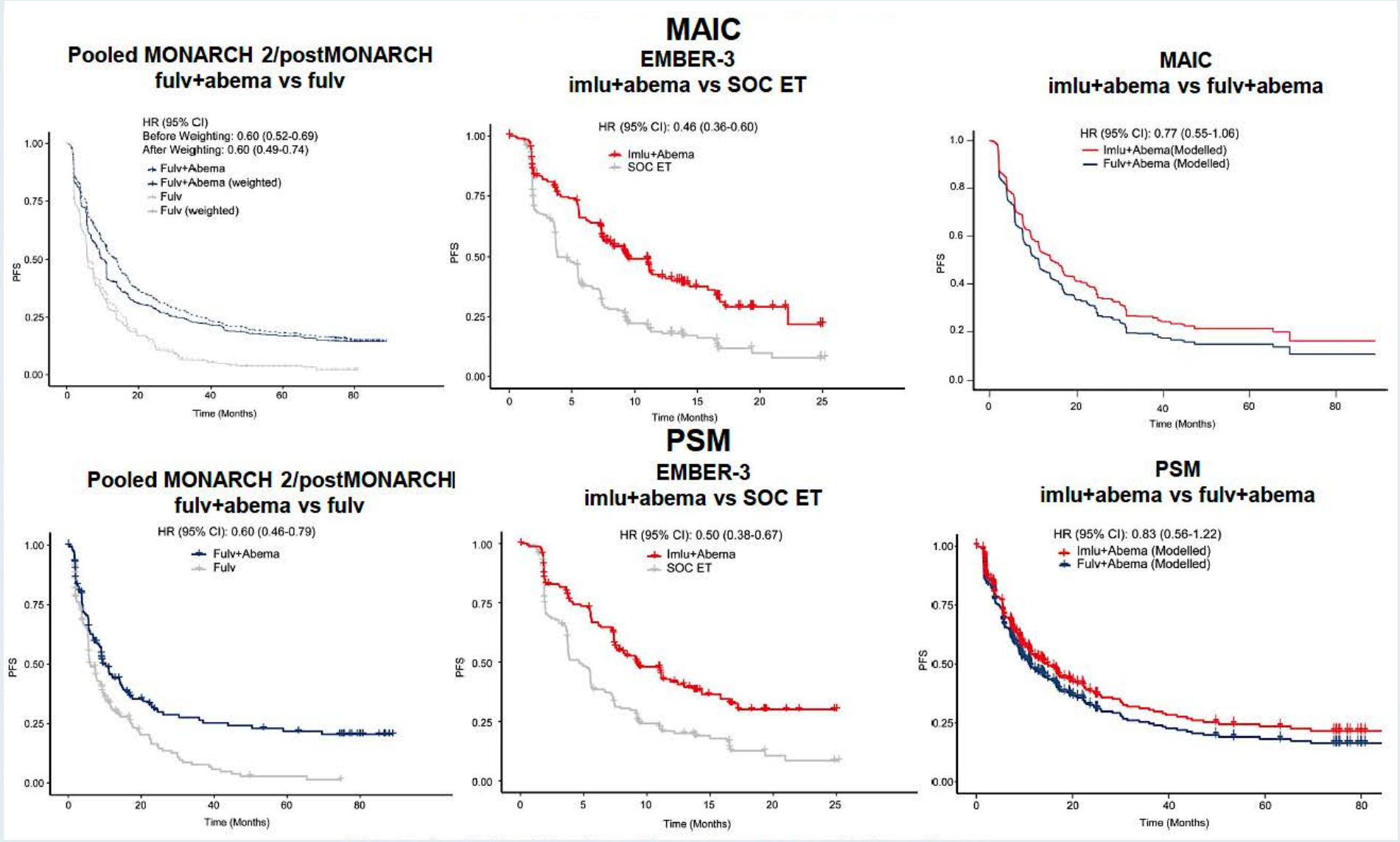
Indirect Treatment Comparison: Phase III Trials Included (HR-Positive, HER2-Negative Advanced Breast Cancer)

	EMBER-3	MONARCH 2	postMONARCH
Design	Open Label	Double Blind	Double Blind
Randomization	1:1:1	2:1	1:1
Enrolment	874†	669	368
Key Inclusion Criteria	Postmenopausal status due to surgical/natural menopause or OFS with a GnRH agonist		
	Disease progression on/after ET in the adjuvant or metastatic setting		
	Prior CDK4/6i allowed	No prior CDK4/6i	Prior CDK4/6i required
	ECOG PS 0-1		
Experimental Arm	Imlu+/-Abema	Fulv+Abema	Fulv+Abema
Comparator Arm	Fulv or Exemestane*	Fulv+Placebo	Fulv+Placebo
Primary Endpoint	Investigator-assessed PFS		
Follow-up Duration (months)	14¥	48 ¥	13 ¥

†213 patients treated with imlu+abema and 330 patients treated with SOC ET (213 patients were concurrently enrolled). An additional arm of 331 patients treated with imlu monotherapy was not relevant to this analysis; *Investigator choice SOC ET (88% fulv); ¥While not exactly comparable, the proportional hazards assumption was met.

Bidard FC et al. ESMO 2025;Abstract 496P.

Kaplan-Meier Plots and Survival Curves for Investigator-Assessed PFS

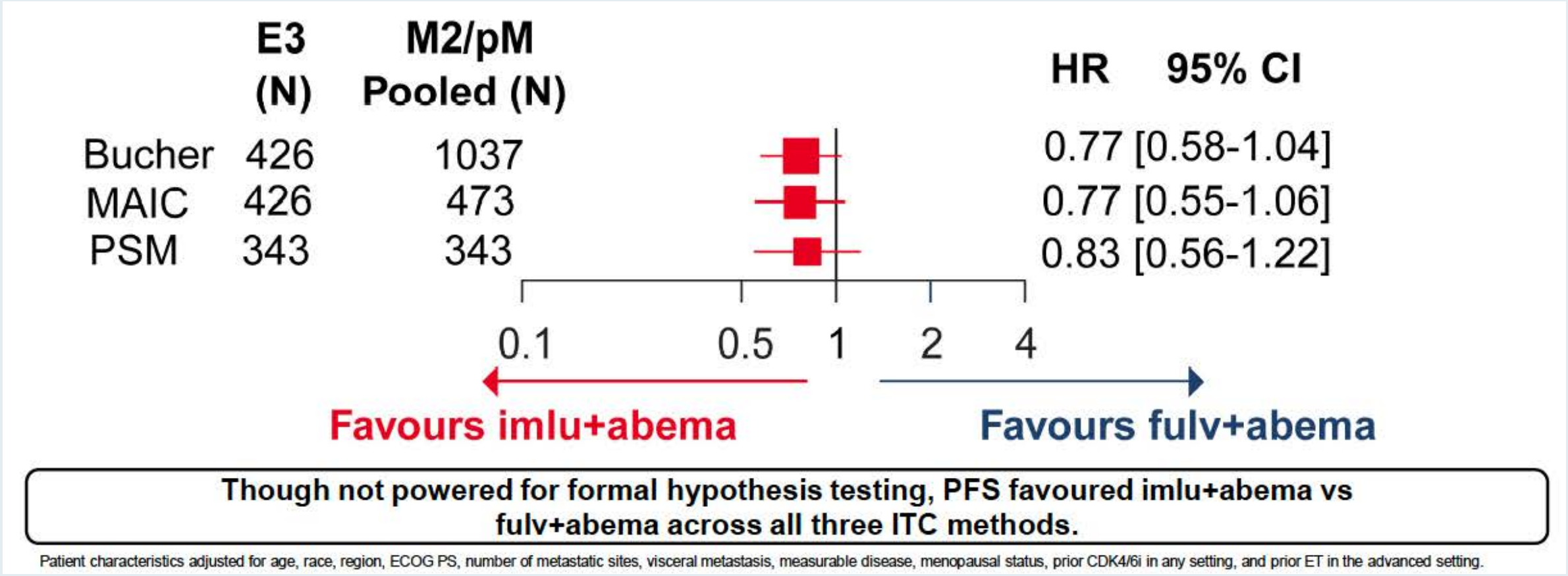


MAIC = matching-adjusted indirect comparison

Bidard FC et al. ESMO 2025;Abstract 496P.

RTP RESEARCH TO PRACTICE

Forest Plot of Imlunestrant with Abemaciclib versus Fulvestrant with Abemaciclib



Bidard FC et al. ESMO 2025;Abstract 496P.

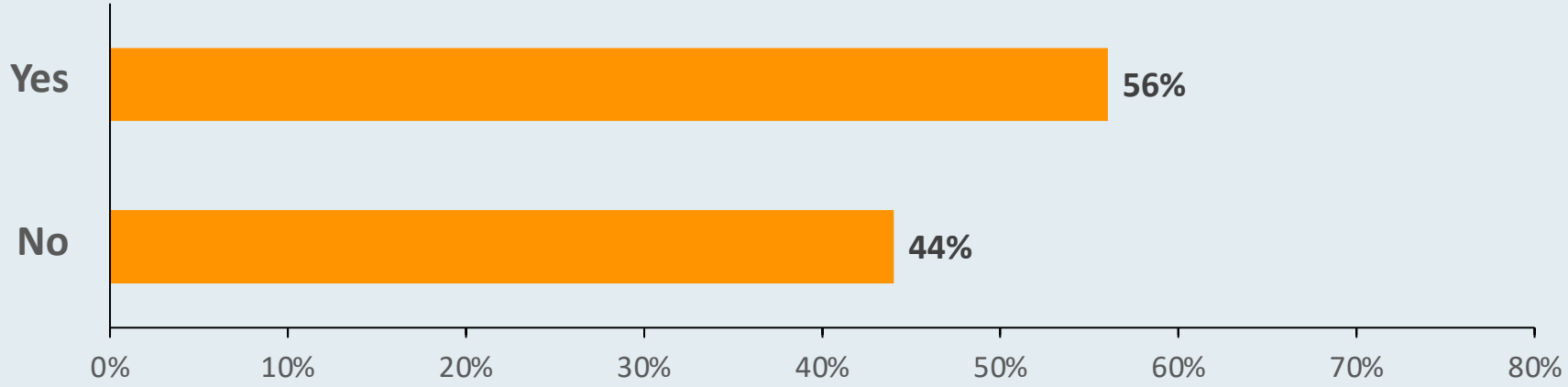
Authors' Conclusions

CONCLUSIONS

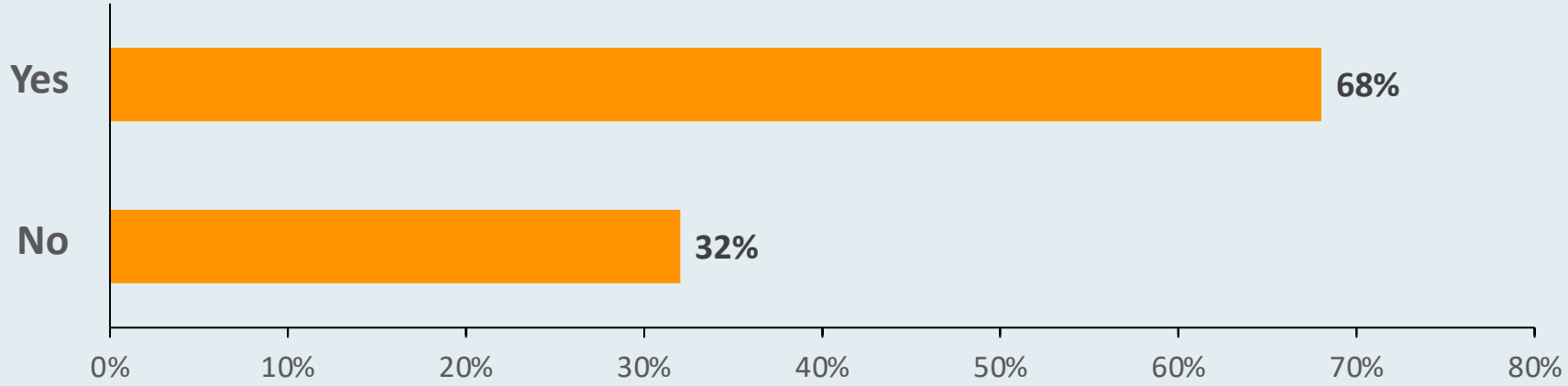
- In this exploratory ITC analysis of patient-level data from three Phase 3 trials, undertaking various approaches, imlunestrant+abemaciclib suggested consistent numerical PFS benefit compared with fulvestrant+abemaciclib in patients with ER+, HER2- ABC previously treated with ET +/- CDK4/6i.
- These results support imlunestrant as a highly effective endocrine partner in combination with abemaciclib, offering patients with endocrine-resistant ER+, HER2– ABC an all-oral targeted combination therapy option.

Bidard FC et al. ESMO 2025;Abstract 496P.

Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib as first-line treatment for ER-positive, HER2-negative mBC?



Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib as second- or later-line treatment for ER-positive, HER2-negative mBC?



Survey of US-based general medical oncologists

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib as first-line treatment for ER-positive, HER2-negative mBC?

Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib as second- or later-line treatment for ER-positive, HER2-negative mBC?

Survey of 20 US-based clinical investigators

RTP RESEARCH TO PRACTICE

Giredestrant

- Mayer EL et al. **Giredestrant (GIRE)**, an oral selective oestrogen receptor (ER) antagonist and degrader, + everolimus (E) in patients (pts) with **ER-positive, HER2-negative advanced breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i): Primary results** of the **phase III evERA BC trial**. ESMO 2025;Abstract LBA16.
- Llombart-Cussac A et al. **Preoperative window-of-opportunity study** with **giredestrant** or tamoxifen (tam) in premenopausal women with **estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) and Ki67≥10% early breast cancer (EBC): The EMPRESS study**. ESMO 2025;Abstract 294MO.

Abstract LBA16

Giredestrant (GIRE), an oral selective oestrogen receptor (ER) antagonist and degrader, + everolimus (E) in patients (pts) with ER-positive, HER2-negative advanced breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i): Primary results of the Phase III evERA BC trial

Erica L. Mayer, Sara M. Tolaney, Miguel Martin, Gregory A. Vidal, Luca Moscetti, Komal L. Jhaveri, Adam Brufsky, William J. Gradishar, Andreas Schneeweiss, Naoki Niikura, Anne Favret, Margarita Alfie, Keun Seok Lee, Sarah Khan, Merilin B. Feldman, Bann-mo Day, Lisa Lam, Walter C. Darbonne, Pablo Perez-Moreno, Hope S. Rugo

Presenting author: Erica L. Mayer, MD, MPH
Dana-Farber Cancer Institute, Boston, MA, USA

Abstract 294MO

BERLIN 2025 ESMO congress

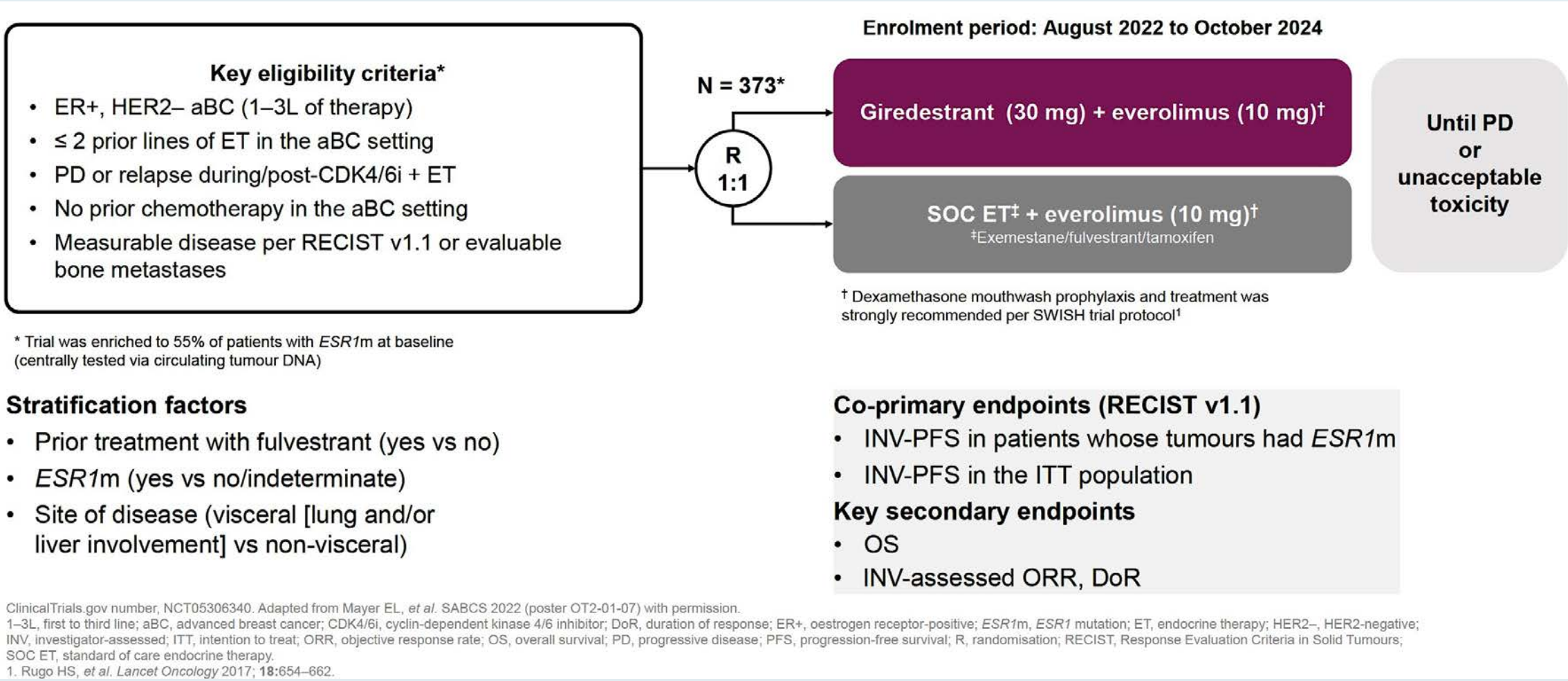
Preoperative window-of-opportunity study with giredestrant or tamoxifen in premenopausal women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative and Ki67≥10% early breast cancer: the EMPRESS study

Antonio Llombart-Cussac, Giuseppe Viale, Manuel Ruiz-Borrego, Vicente Carañana, Elena López-Miranda, María Isabel Blancas, Laia Garrigós, María Gión, Mariana Lopez, Ángel Guerrero, Cristina Saavedra, Juan Miguel Cejalvo, Juan de la Haba, Cinta Albacar, Meritxell Aguiló, José Antonio Guerrero, Pari Skamnioti, Jacques Medioni, José Manuel Pérez-García, Javier Cortés

October, 2025

RTP RESEARCH TO PRACTICE

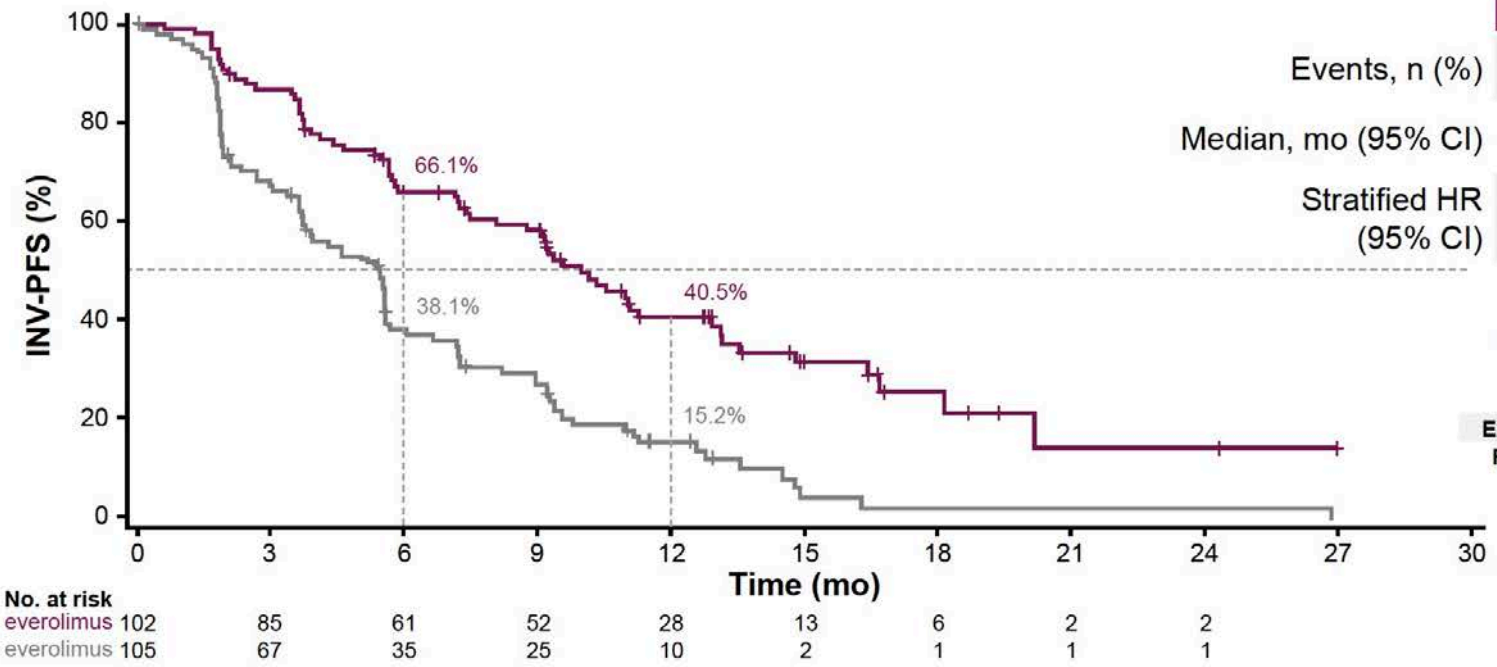
Phase III evERA Breast Cancer Study Design



ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission.
1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.
1. Rugo HS, *et al. Lancet Oncology* 2017; **18**:654–662.

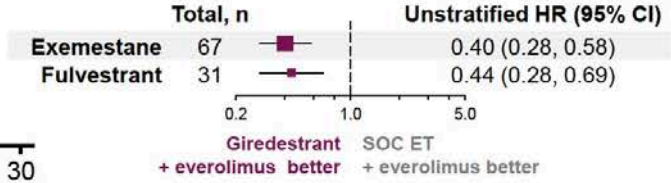
Mayer EL et al. ESMO 2025;Abstract LBA16.

Phase III evERA Breast Cancer Coprimary Endpoint: INV-PFS in the ESR1m Population



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

Exploratory analysis: INV-PFS by SOC ET

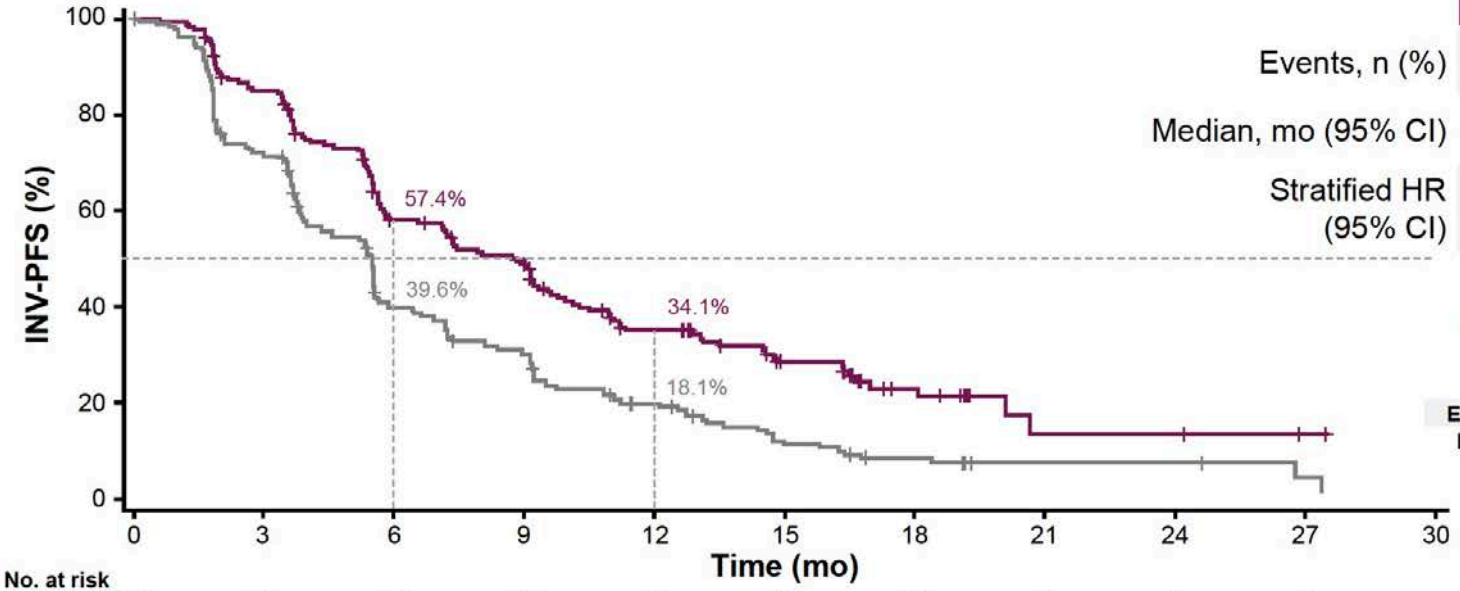


Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71.
CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Mayer EL et al. ESMO 2025;Abstract LBA16.

Phase III evERA Breast Cancer Coprimary Endpoint: INV-PFS in the ITT Population



	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	

Exploratory analysis: INV-PFS by SOC ET

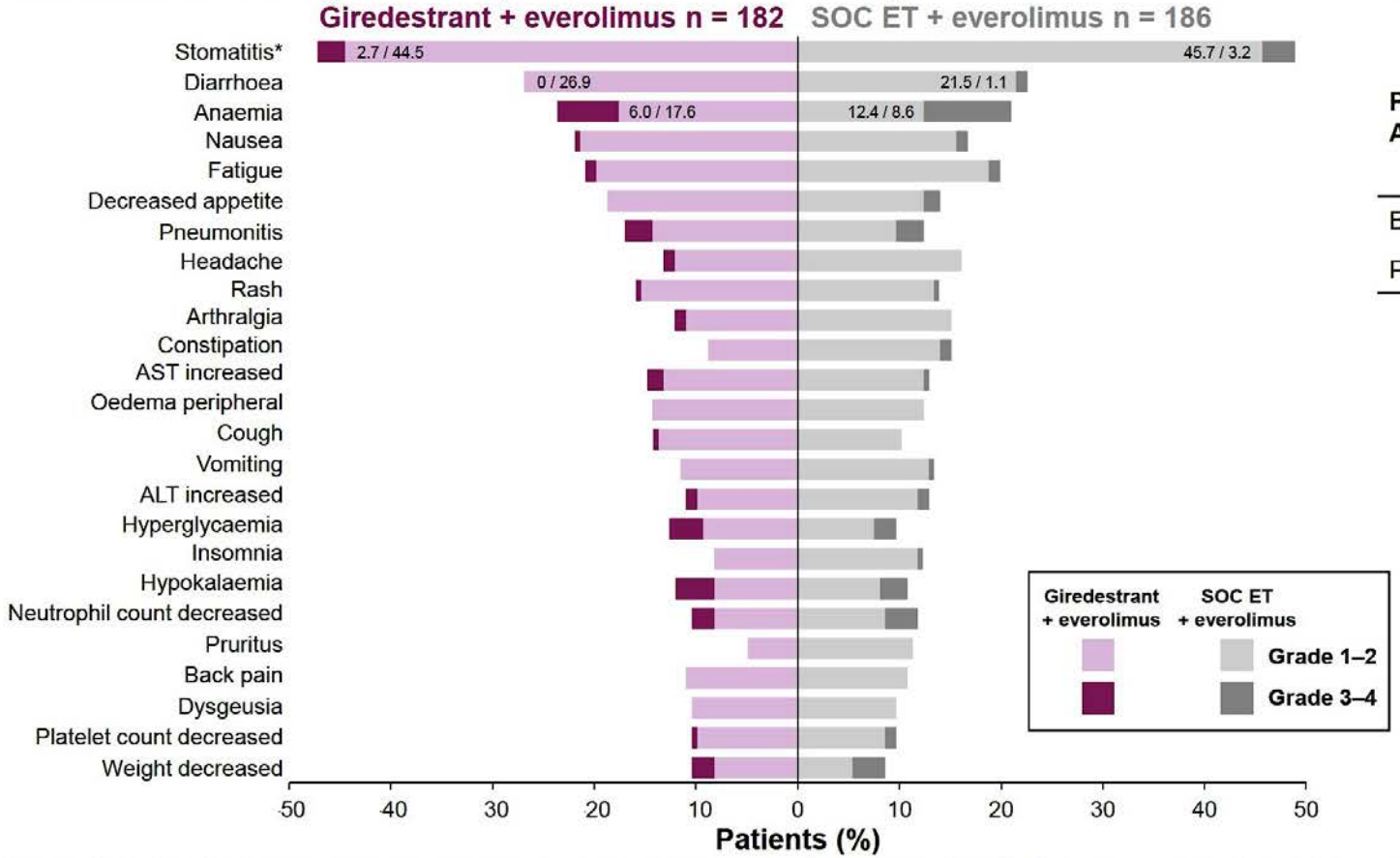
Combination therapy with giredestrant + everolimus led to a clinically meaningful 44% reduction in the risk of progression or death in patients in the ITT population

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 10.32 mo (giredestrant + everolimus) and 7.26 mo (SOC ET + everolimus); stratified HR, 0.66; 95% CI: 0.50, 0.87.
CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; ITT, intention to treat; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Mayer EL et al. ESMO 2025;Abstract LBA16.

Phase III evERA Breast Cancer: Safety Overview

Common TEAEs (≥ 10% of patients in either arm)



Selected AEs

Patients with AE, n	Giredestrant + everolimus n = 182		SOC ET + everolimus n = 186	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Bradycardia†	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Data cutoff: 16 July 2025. * Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol (Rugo HS, *et al. Lancet Oncology* 2017; **18**:654–662).
† Assessed as a medical concept using grouped terms; all events were Grade 1, non-serious and no treatment interruptions/interventions were needed. All events had resolved by data cutoff.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC ET, standard of care endocrine therapy; TEAE, treatment-emergent adverse event.

Mayer EL et al. ESMO 2025;Abstract LBA16.

Phase III evERA Breast Cancer: Authors' Conclusions

- The next-generation oral SERD giredestrant, in combination with everolimus, showed **statistically significant and clinically meaningful improvements in INV-PFS** vs SOC ET + everolimus in ER+, HER2– aBC post-CDK4/6i
  - ***ESR1*m:** 62% reduction in the risk of progression or death (HR **0.38**; median INV-PFS **9.99** vs 5.45 mo)
  - **ITT:** 44% reduction in the risk of progression or death (HR **0.56**; median INV-PFS, **8.77** vs 5.49 mo)
- Consistent benefit with giredestrant + everolimus was seen across key subgroups; ORR and DoR benefits were observed irrespective of *ESR1*m status; OS analyses were immature and favourable
- The safety profile of giredestrant + everolimus was manageable and consistent with the known safety profiles of the individual drugs; there were no unexpected safety findings

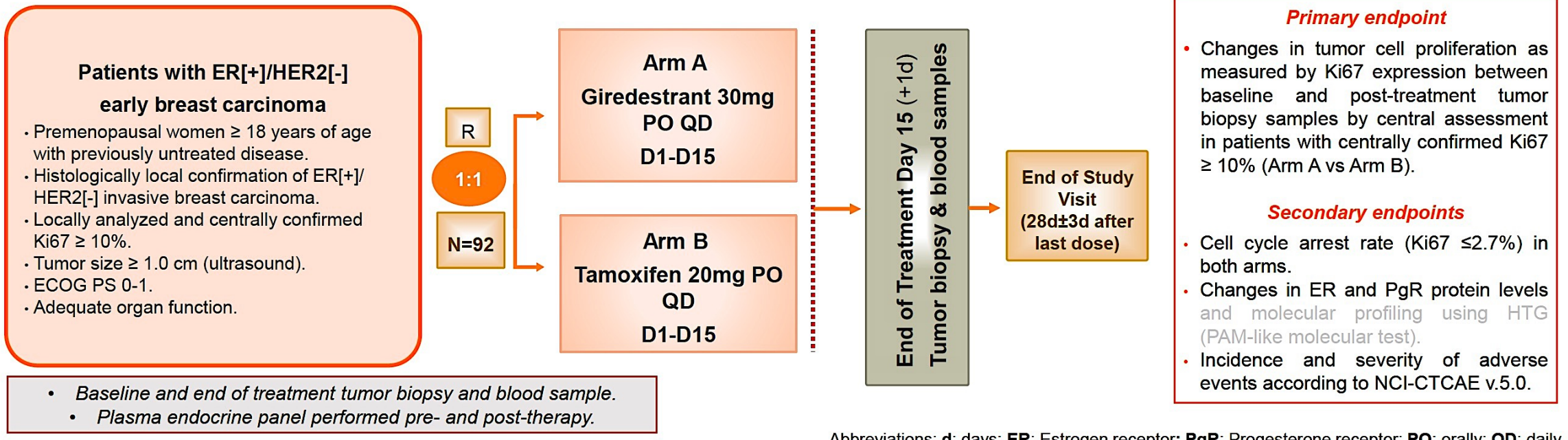
Giredestrant + everolimus may represent a new effective all-oral treatment option in the post-CDK4/6i setting for patients with ER+, HER2– aBC

aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; HER2–, HER2-negative; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; ITT, intention to treat; mo, months; ORR, objective response rate; OS, overall survival; SERD, selective oestrogen receptor antagonist and degrader; SOC ET, standard of care endocrine therapy.

Mayer EL et al. ESMO 2025;Abstract LBA16.

RTP RESEARCH TO PRACTICE

Phase II EMPRESS Study Design

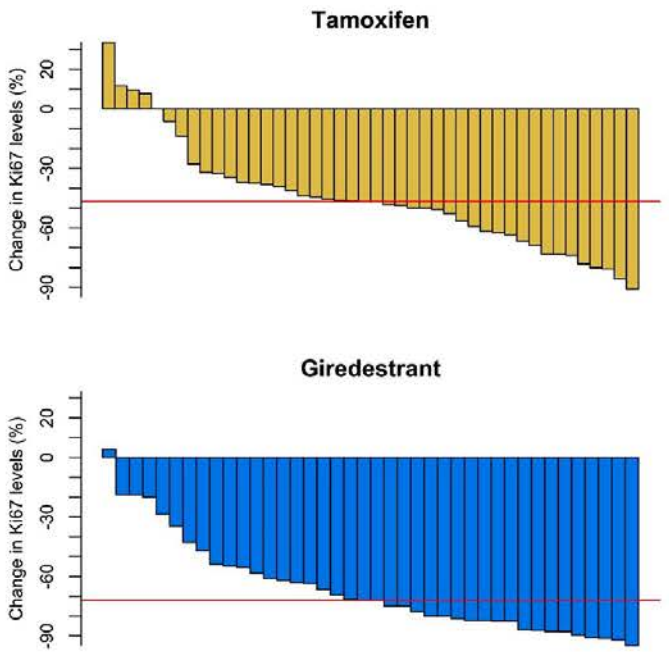


Abbreviations: **d**: days; **ER**: Estrogen receptor; **PgR**: Progesterone receptor; **PO**: orally; **QD**: daily

Llombart-Cussac A et al. ESMO 2025;Abstract 294MO.

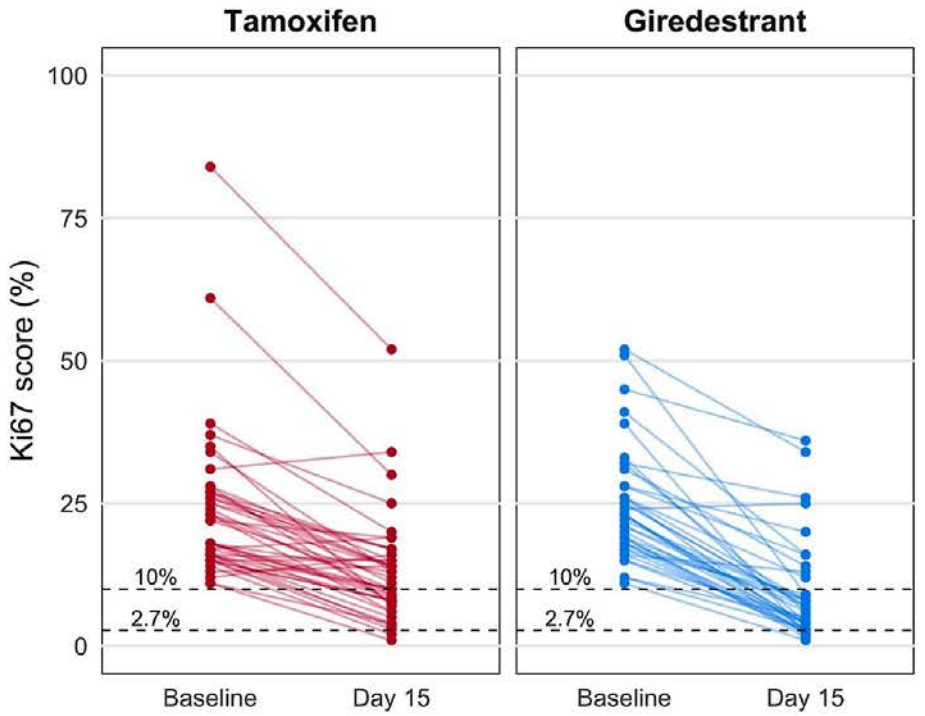
Phase II EMPRESS: Primary Endpoint

Relative change in Ki67 levels



	Tamoxifen	Giredestrant	
Relative reduction % (95% CI)	-51 (-59; -43)	-73 (-78; -66)	**<0.001**

Change in Ki67 levels between baseline and post-treatment



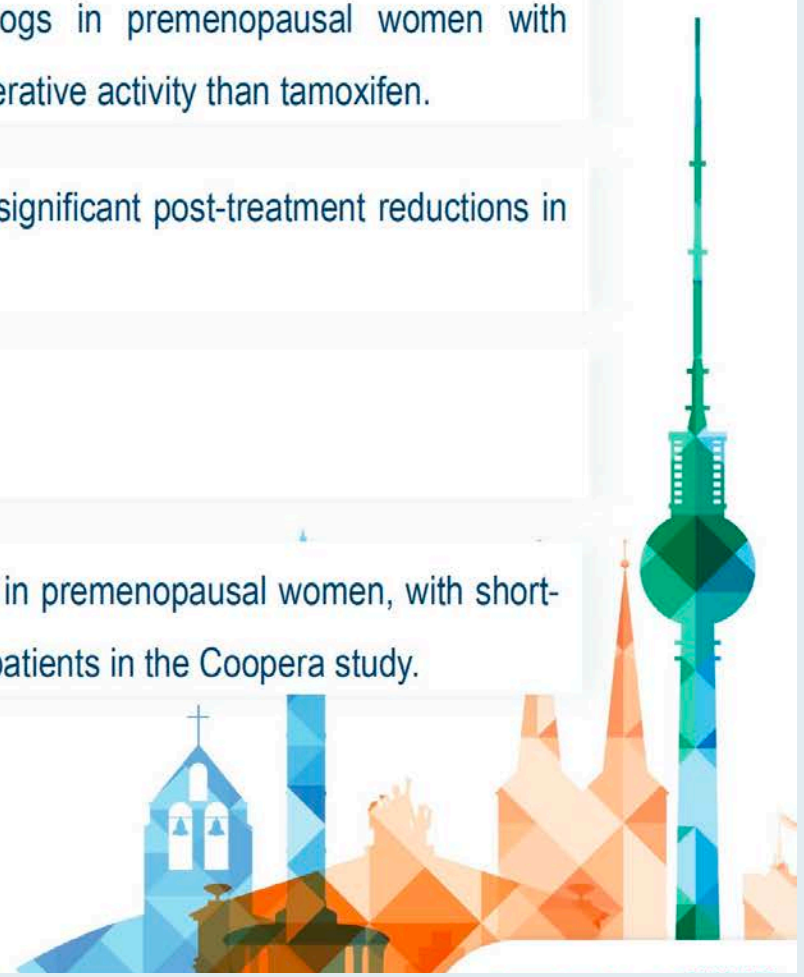
*Efficacy analyses are performed in the modified ITT population, including 44 in the tamoxifen group and 40 patients in the giredestrant group.

Llombart-Cussac A et al. ESMO 2025;Abstract 294MO.

RTP RESEARCH TO PRACTICE

Phase II EMPRESS: Authors' Conclusions

- Preoperative giredestrant, administered for 15 days without GnRH analogs in premenopausal women with ER[+]/HER2[-] early breast cancer, demonstrated statistically superior antiproliferative activity than tamoxifen.
- Giredestrant exerts robust ER antagonism at the tumor level, as reflected by significant post-treatment reductions in Ki67, ER, and PgR expression.
- The toxicity profile was as expected according to each treatment strategy.
- The EMPRESS study demonstrates a robust biological activity for giredestrant in premenopausal women, with short-term antiproliferative effects comparable to those observed in postmenopausal patients in the Coopera study.



Antonio Llombart-Cussac, MD, PhD

Llombart-Cussac A et al. ESMO 2025;Abstract 294MO.

Dr Sharma: Case Presentation #2

- 59-year-old postmenopausal female presents with HR+ *de novo* stage IV breast cancer. She has a 4 cm right breast mass, palpable axillary lymph nodes, 4 osseous lesions and right pleural disease on scans. Biopsy of the breast mass and pleural disease shows invasive breast cancer, ER = 100%, PR = 50%, HER2 IHC 1+.
- She starts on first line treatment with letrozole and ribociclib along with monthly denosumab. This regimen controls her disease for 3 years. Now there is disease progression in the right pleural disease/effusion, and she has two new pulmonary nodules.
- ctDNA testing shows no ESR1 mutation, no PI3K mutation and no other targetable alteration. She enrolls on a clinical trial as part of which she receives everolimus and giredestrant oral therapy. Prophylactic steroid mouth wash is started along with treatment to prevent mucositis. Scans done after 8 weeks of treatment show reduction in the size of two lung lesions. Despite steroid mouthwash, patient has symptomatic mucositis which resolves with one dose level reduction of everolimus. Patient continues on this therapy for 13 months, at which time she is noted to have new liver lesions.

CAPItello-291

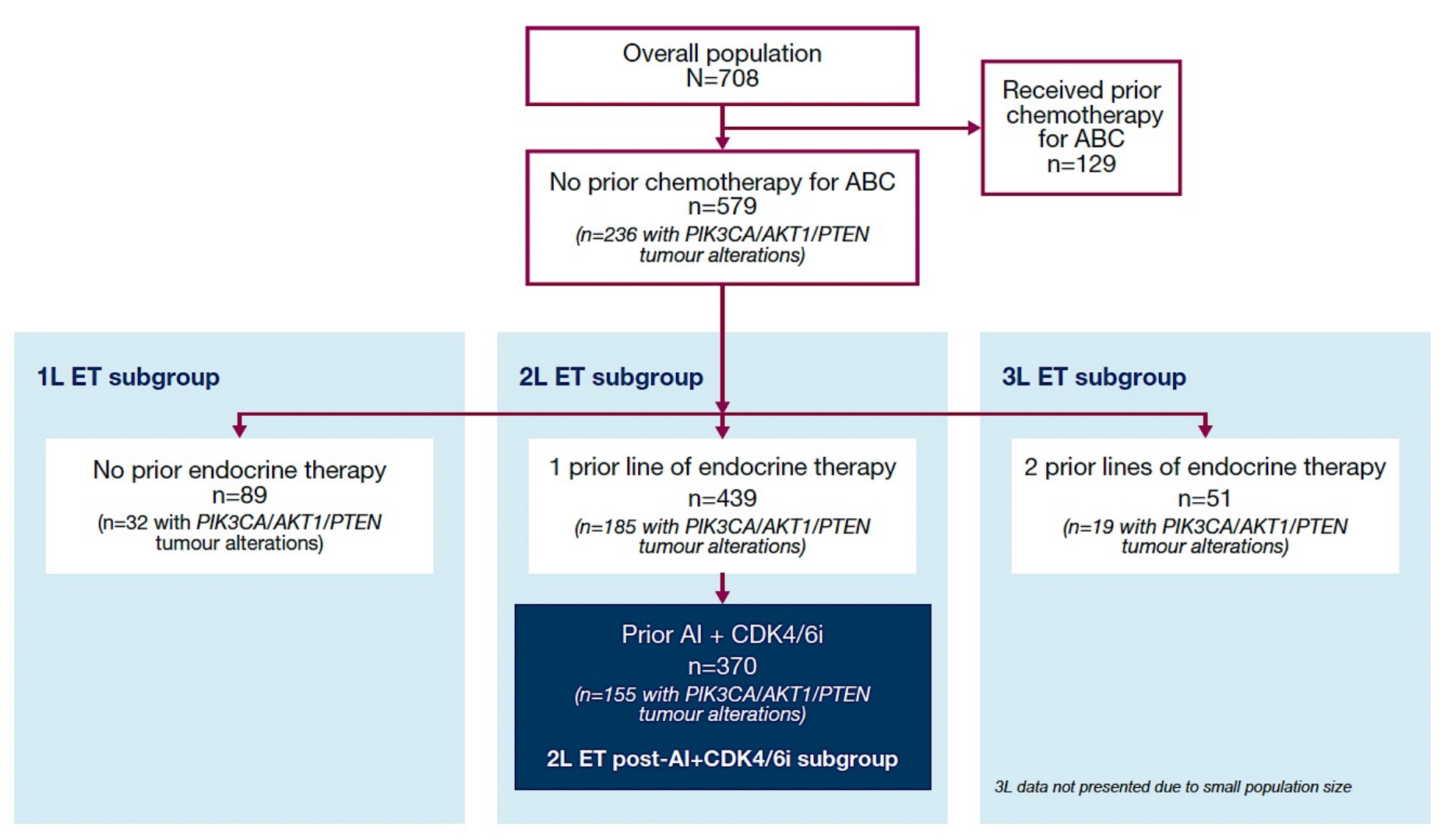
- Rugo HS et al. **Capivasertib** plus fulvestrant as first and second-line endocrine-based therapy in ***PIK3CA/AKT1/PTEN*-altered hormone receptor-positive advanced breast cancer: Subgroup analysis** from the **phase 3 CAPItello-291** trial. ESMO 2025;Abstract 526P.

Poster number: 526P

Capivasertib plus fulvestrant as first- and second-line endocrine-based therapy in *PIK3CA/AKT1/PTEN*-altered hormone receptor-positive advanced breast cancer: Subgroup analysis from the Phase 3 CAPItello-291 trial

Hope S Rugo,[1*] Sibylle Loibl,[2,3] Mafalda Oliveira,[4,5] Sacha J Howell,[6] Florence Dalenc,[7] Javier Cortés,[8,9,10,11,12] Henry L Gomez,[13,14] Xichun Hu,[15] Komal Jhaveri,[16,17] Serafin Morales Murillo,[18] Zbigniew Nowecki,[19] Meena Okera,[20] Yeon Hee Park,[21] Masakazu Toi,[22] Lyudmila Zhukova,[23] Kamal S Saini,[24] Ian Wadsworth,[25] Marta Fulford,[26] Vijay Bhagawati Prasad,[25] Nicholas C Turner[27]

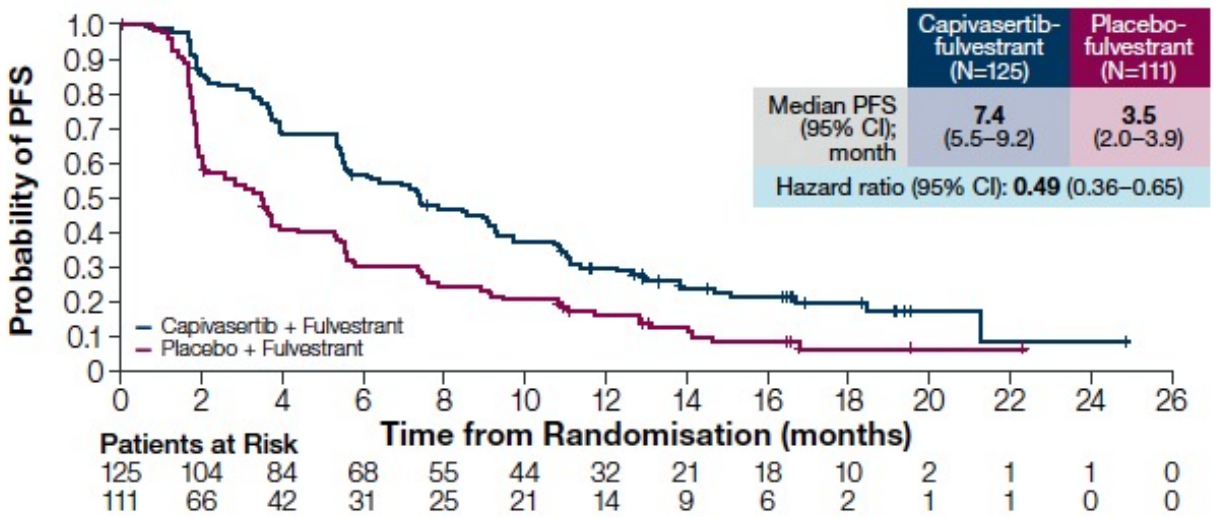
Phase III CAPItello-291 Study: Subgroup Analysis



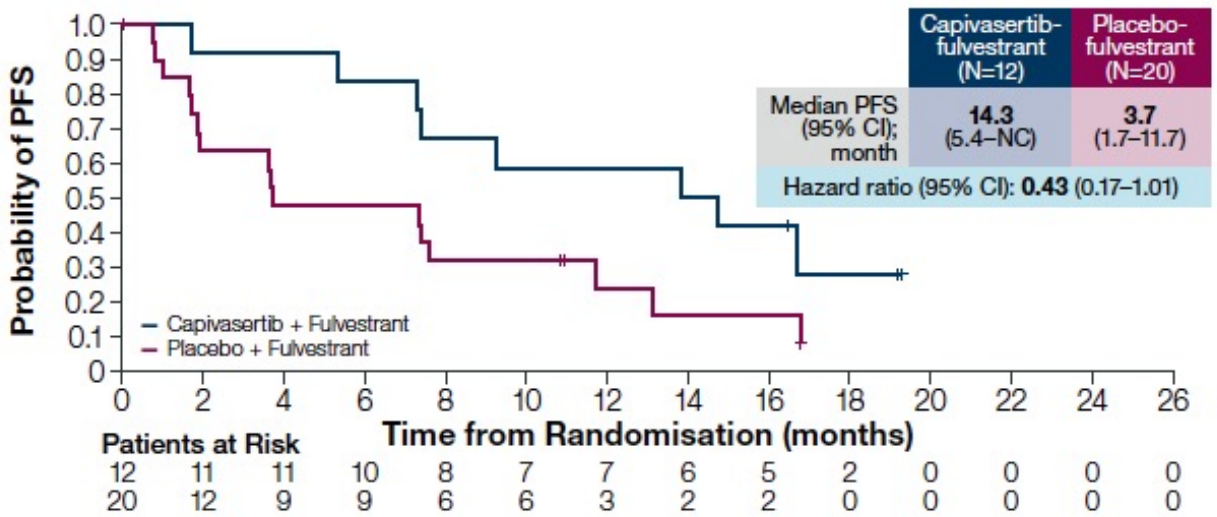
Rugo HS et al. ESMO 2025;Abstract 526P.

Phase III CAPItello-291: PFS — Chemotherapy Naïve, PIK3CA/AKT1/PTEN Altered

Patients



First-line ET subgroup (no prior ET)

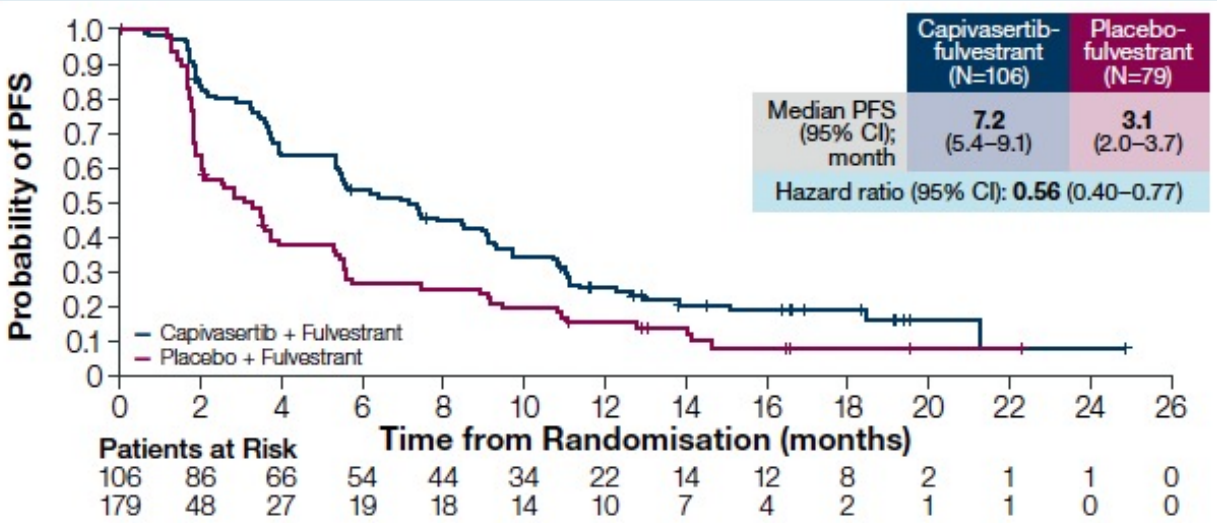


Rugo HS et al. ESMO 2025;Abstract 526P.

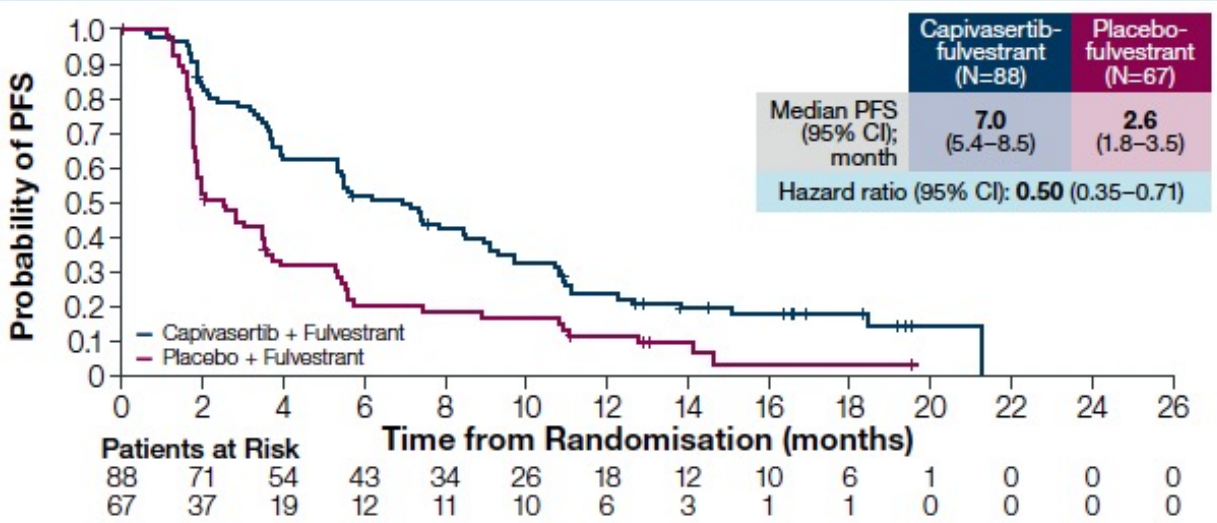
RTP RESEARCH TO PRACTICE

Phase III CAPItello-291: PFS — Chemotherapy Naïve, PIK3CA/AKT1/PTEN Altered (Continued)

Second-line ET subgroup (1 prior ET)



Second-line ET (after AI and CDK4/6i) subgroup



AI = aromatase inhibitor; CDK4/6i = CDK4/6 inhibitor

Rugo HS et al. ESMO 2025;Abstract 526P.

RTP RESEARCH TO PRACTICE

Phase III CAPItello-291: Author's Conclusions

Objective

- To assess the efficacy and safety of capivasertib + fulvestrant in chemotherapy-naive patients with ABC, by the number of prior lines of ET-based therapy

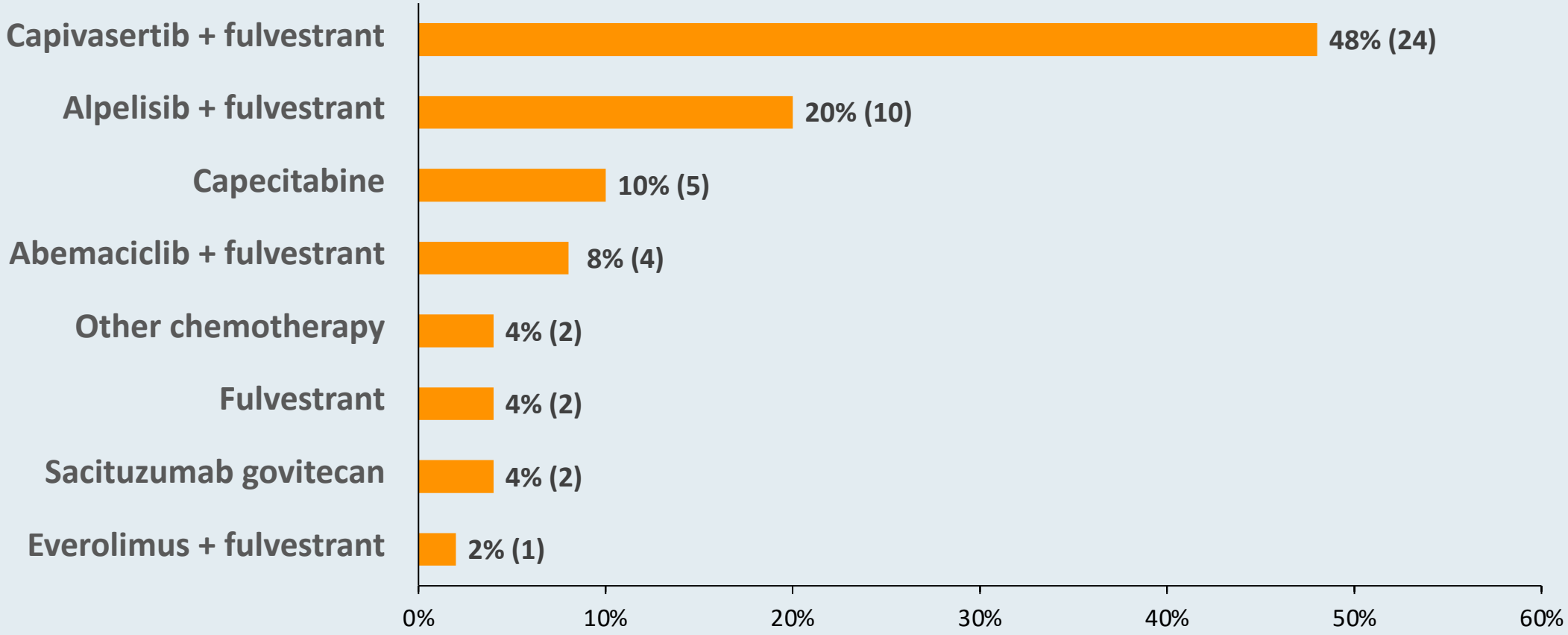
Conclusions

- When used as either 1L (PD <12 months after adjuvant ET) or as 2L treatment, capivasertib + fulvestrant demonstrated a consistent PFS benefit versus placebo + fulvestrant in patients with chemotherapy-naive HR+ ABC harbouring *PIK3CA/AKT1/PTEN* alterations
- Capivasertib + fulvestrant had a generally consistent safety profile across ET lines, with fewer events in select categories of the small 1L subgroup
- Overall, the risk–benefit with capivasertib + fulvestrant appears consistent regardless of treatment line

Rugo HS et al. ESMO 2025;Abstract 526P.

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

ESR1 wild type **PIK3CA mutation**



Survey of 50 US-based general medical oncologists

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

ESR1 wild type **PIK3CA mutation**

Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

Interim analysis of giredestrant (GIRE) + inavolisib▼ (INAVO) in MORPHEUS Breast Cancer (BC): A Phase IB/II study of GIRE treatment (rx) combinations in patients (pts) with estrogen receptor-positive (ER+), HER2-negative, locally advanced/metastatic BC (LA/mBC)

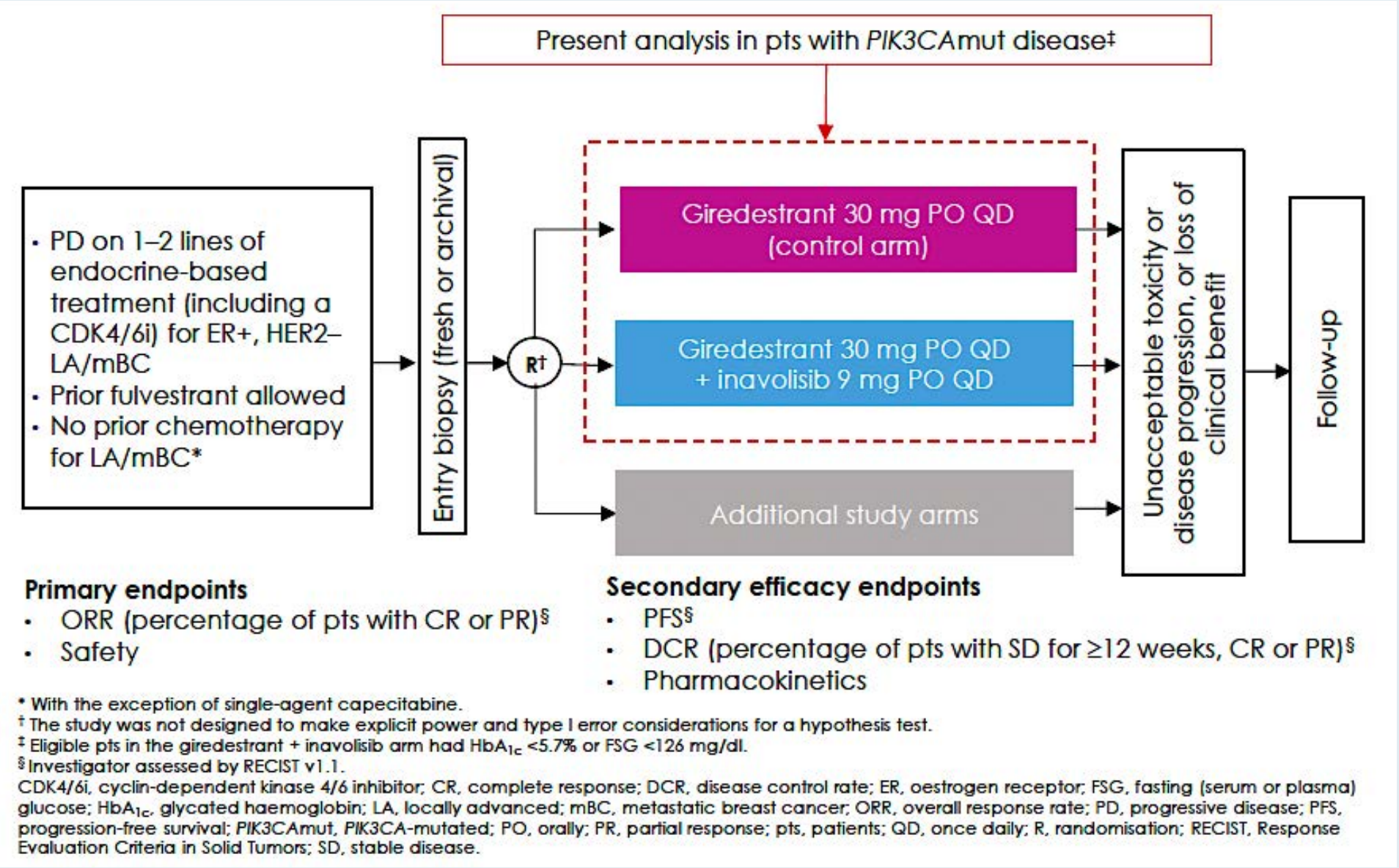
Hope S. Rugo[1], Cristina Saavedra[2], Kyung Hae Jung[3], Melinda L. Telli[4], Amir Sonnenblick[5], Einav Gal-Yam[6], Jing Zhu[7], Annie Collier[7], Aleeza Sheikh[7], Uwe Bader[8], Huy Ngo[7], Richard Schwab[7], Begoña Bermejo De Las Heras[9]

[1]University of California San Francisco, San Francisco, CA, USA; [2]Hospital Universitario Ramón y Cajal, Madrid, Spain; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Stanford University, Stanford, CA, USA; [5]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [6]Institute of Breast Oncology, Oncology Institute, Sheba Medical Center, Ramat Gan, Israel; [7]Genentech, Inc., South San Francisco, CA, USA; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Hospital Clínico Universitario de Valencia, Universidad de Valencia, Valencia, Spain

508P

https://ter.li/u8tar4

Phase Ib/II MORPHEUS BC Study Design



* With the exception of single-agent capecitabine.
† The study was not designed to make explicit power and type I error considerations for a hypothesis test.
‡ Eligible pts in the giredestrant + inavolisib arm had HbA_{1c} <5.7% or FSG <126 mg/dl.
§ Investigator assessed by RECIST v1.1.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; DCR, disease control rate; ER, oestrogen receptor; FSG, fasting (serum or plasma) glucose; HbA_{1c}, glycated haemoglobin; LA, locally advanced; mBC, metastatic breast cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; *PIK3CA*mut, *PIK3CA*-mutated; PO, orally; PR, partial response; pts, patients; QD, once daily; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Rugo HS et al. ESMO 2025;Abstract 508P.

Phase Ib/II MORPHEUS BC: Best Confirmed ORRs

Patients, n (%) (95% CI)	Giredestrant + inavolisib (n = 40)	Giredestrant + inavolisib (*ESR1*mut) (n = 13/38)*,†
Responders (OR)	16 (40.0) (24.9, 56.7)	10 (77.0) (46.2, 95.0)
Complete response	3 (7.5) (1.6, 20.4)	2 (15.4) (1.9, 45.5)
Partial response	13 (32.5) (18.6, 49.1)	8 (61.5) (31.6, 86.1)
Stable disease	22 (55.0) (38.5, 70.7)	2 (15.4) (1.9, 45.5)
Progressive disease	2 (5.0) (0.6, 16.9)	1 (7.7) (0.2, 36.0)
Disease control rate	32 (80.0) (64.4, 91.0)	12 (92.3) (64.0, 99.8)
Clinical benefit rate	28 (70.0) (53.5, 83.4)	11 (84.6) (54.6, 98.1)

* Reported *ESR1*mut response results are limited to F1LCDx liquid biopsy-determined cases; two pts were not evaluable for *ESR1* mutations.
† Notably, these cases carry co-mutations (*PIK3CA* and *ESR1*).
CI, confidence interval; F1LCDx, FoundationOne® Liquid CDx; *ESR1*mut, *ESR1*-mutated; OR, overall response; RECIST, Response Evaluation Criteria in Solid Tumors.

Rugo HS et al. ESMO 2025;Abstract 508P.

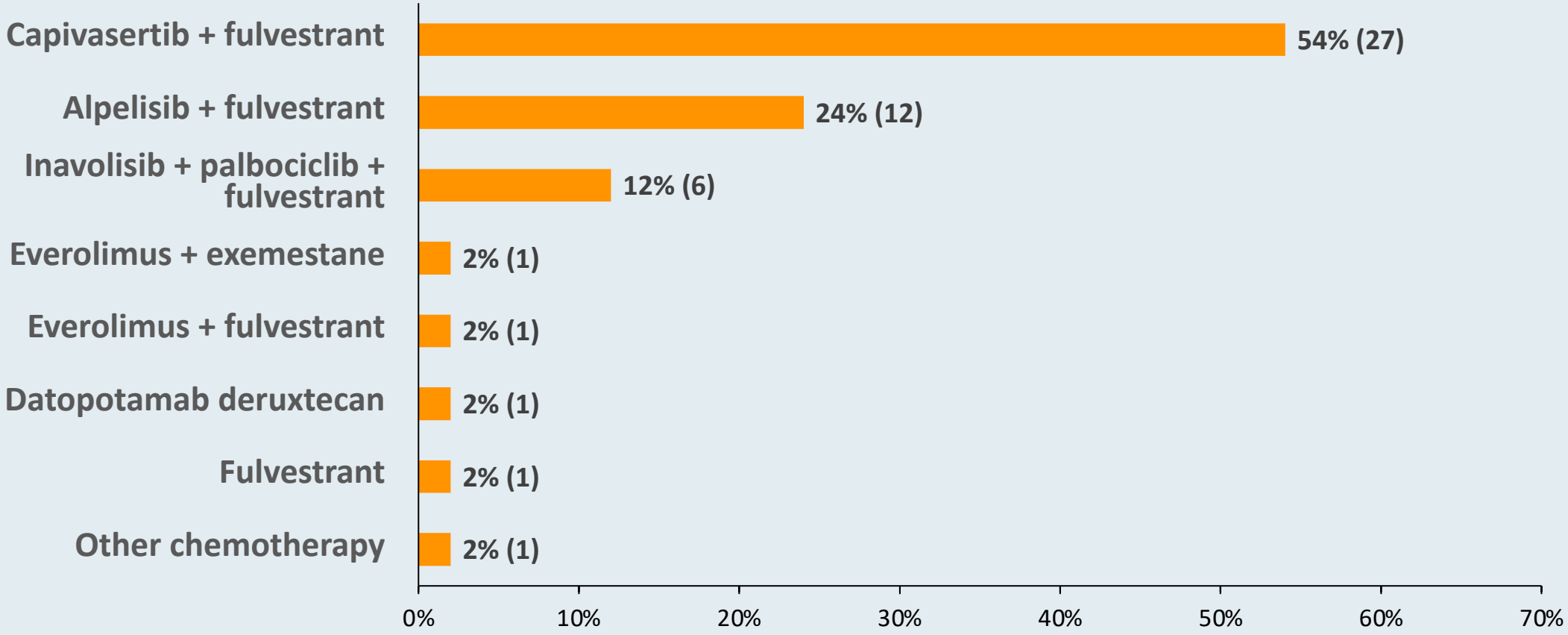
Phase Ib/II MORPHEUS BC: Authors' Conclusions

- Giredestrant + inavolisib showed impressive efficacy in pts with *PIK3CA*mut, ER+, HER2– mBC and prior CDK4/6i treatment, particularly those who also had an *ESR1* mutation, for whom high ORR, DCR and clinical benefit rate were reported.
- The ORR in MORPHEUS BC compares favourably with historical data from BYLieve (alpelisib + fulvestrant; ORR: 23% for pts with measurable disease [PMID: 33794206]), despite BYLieve excluding prior fulvestrant.[18]
- The safety profile of giredestrant + inavolisib was consistent with the known profiles of each agent. Overlapping toxicities (diarrhoea, nausea, vomiting) were manageable. No new safety signals were observed.[19]
- These results support further exploration of giredestrant + inavolisib; the study has been expanded to continue evaluating this combination.

Rugo HS et al. ESMO 2025;Abstract 508P.

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) breast cancer receives adjuvant abemaciclib + anastrozole for 2 years followed by development of biopsy-confirmed ER-positive, HER2-negative (IHC 0/null) metastatic disease with multiple minimally symptomatic bone metastases

ESR1 wild type **PIK3CA mutation**



Survey of 50 US-based general medical oncologists

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) breast cancer receives adjuvant abemaciclib + anastrozole for 2 years followed by development of biopsy-confirmed ER-positive, HER2-negative (IHC 0/null) metastatic disease with multiple minimally symptomatic bone metastases

ESR1 wild type **PIK3CA mutation**

Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

Dr Sharma: Case Presentation #3

65-year-old with pT2N2 HR+ breast cancer. S/p lumpectomy and ALND which showed 2.8 cm grade II IDC with 4/9 involved axillary lymph nodes. ER = 70%, PR = 30%, HER2 IHC 0, Ki-67 38%. Receives adjuvant chemotherapy with ddAC followed by paclitaxel. This is followed by chest wall and RNI irradiation. She starts on adjuvant letrozole but declines adjuvant abemaciclib or ribociclib due to concerns about side effects impacting quality of life and "treatment fatigue".

18 months after initiating letrozole she complains of abdominal pain. CT scans show 7 liver lesions and osseous disease. Biopsy of the liver lesion confirms metastatic breast cancer, ER = 80%, PR = 20%, HER2 IHC 0. Genomic testing on the liver biopsy shows the only abnormality is a PIK3CA mutation (E545K). Labs, including liver function tests, are normal and HbA1c is 5.8.

She starts first-line treatment with inavolisib/palbociclib/fulvestrant. Two weeks after starting the treatment she develops rash on arms and legs (grade 1). She is instructed to start loratadine every day which leads to improvement in the rash. Scans done after 12 weeks show improvement in the liver disease and sclerosis of the osseous lesions. Fasting blood sugar is now 120 and HbA1c is 6.9. She is started on metformin 500 mg every day for hyperglycemia.

VIKTORIA-1

- Hurvitz SA et al. **Gedatolisib (geda) + fulvestrant ± palbociclib (palbo)** vs fulvestrant in patients (pts) with **HR+/ HER2-/*PIK3CA* wild-type (WT) advanced breast cancer (ABC): First results from VIKTORIA-1**. ESMO 2025;Abstract LBA17.

Abstract LBA17

BERLIN 2025 ESMO congress

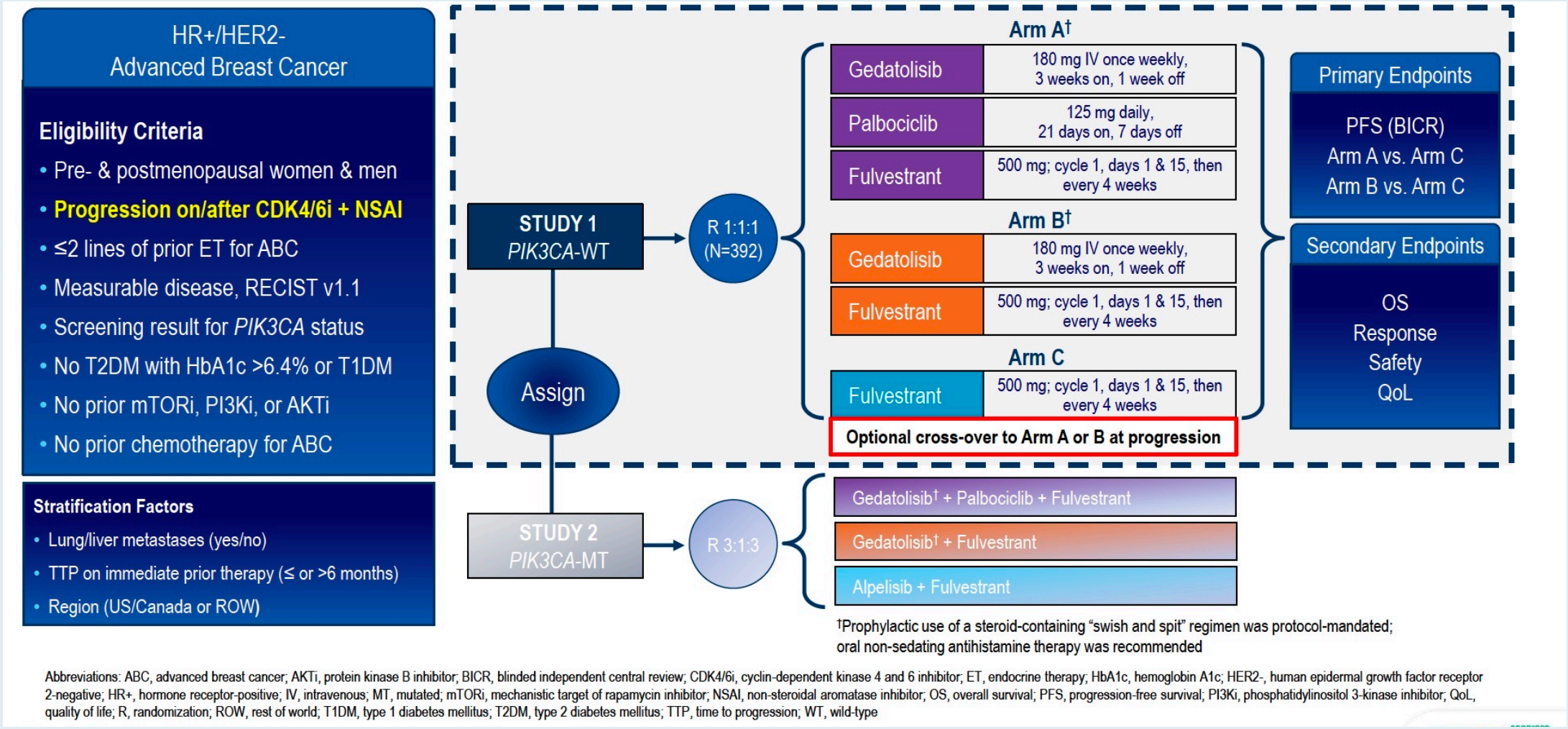
Gedatolisib Plus Fulvestrant, With & Without Palbociclib, vs Fulvestrant in Patients With HR+/HER2-/*PIK3CA* Wild-Type Advanced Breast Cancer: First Results from VIKTORIA-1

Sara A. Hurvitz, Rachel M. Layman, Giuseppe Curigliano, Fabrice André, Massimo Cristofanilli, Sung-Bae Kim, Martin Richardet, Jorge Luis Martínez Rodríguez, Jorge Carlos Nadal, Gun Min Kim, George Emile, Robert Wesolowski, Miguel Martin, Alistair Ring, Sarah C. Mutka, Samuel Suzuki, Brian Sullivan, Igor Gorbatchevsky, Barbara Pistilli

Sara A. Hurvitz
Fred Hutchinson Cancer Center
Seattle, WA, USA
18 October 2025

RTP RESEARCH TO PRACTICE

Phase III VIKTORIA-1 Study Design

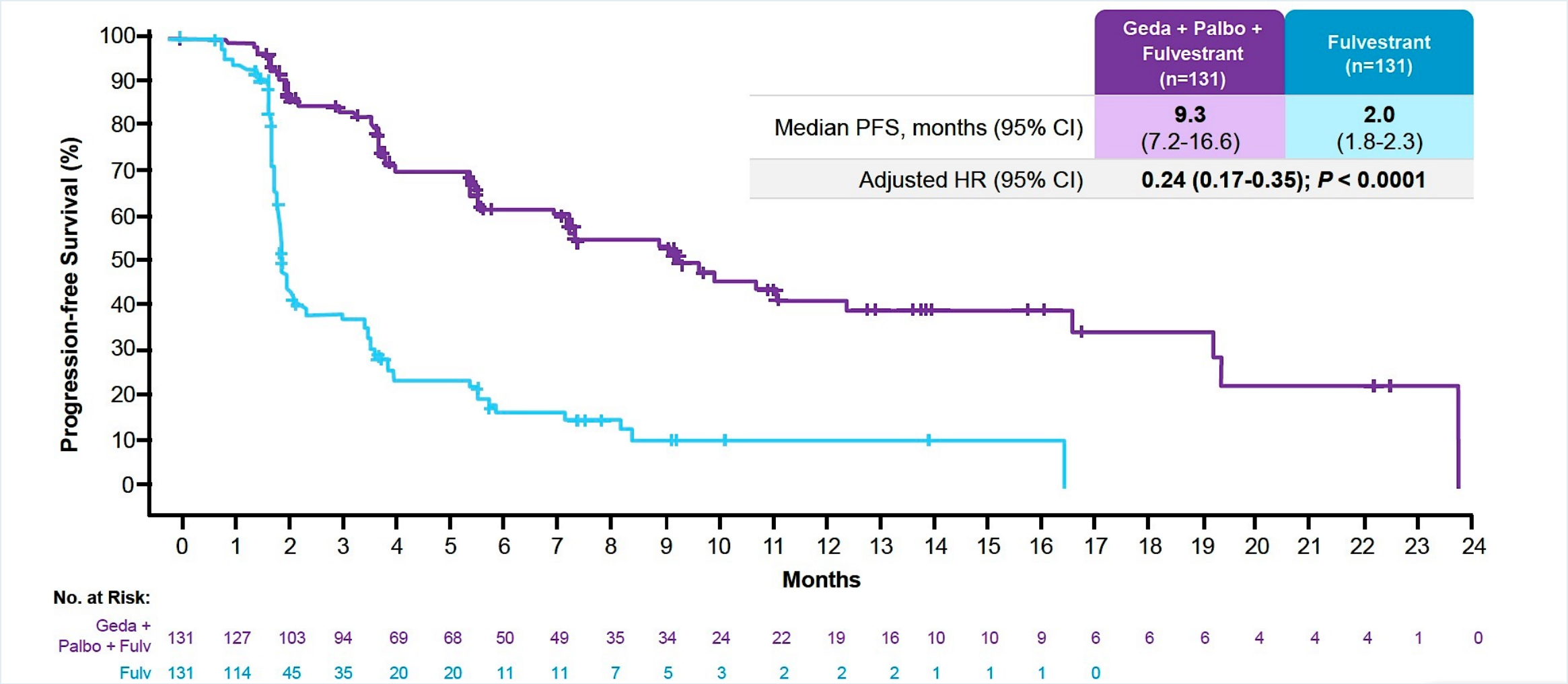


†Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended

Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutated; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, time to progression; WT, wild-type

Hurvitz SA et al. ESMO 2025;Abstract LBA17.

Phase III VIKTORIA-1: PFS with Gedatolisib Triplet versus Fulvestrant



	Geda + Palbo + Fulvestrant (n=131)	Fulvestrant (n=131)
Median PFS, months (95% CI)	**9.3** (7.2-16.6)	**2.0** (1.8-2.3)
Adjusted HR (95% CI)	**0.24 (0.17-0.35); *P* < 0.0001**	

Hurvitz SA et al. ESMO 2025;Abstract LBA17.

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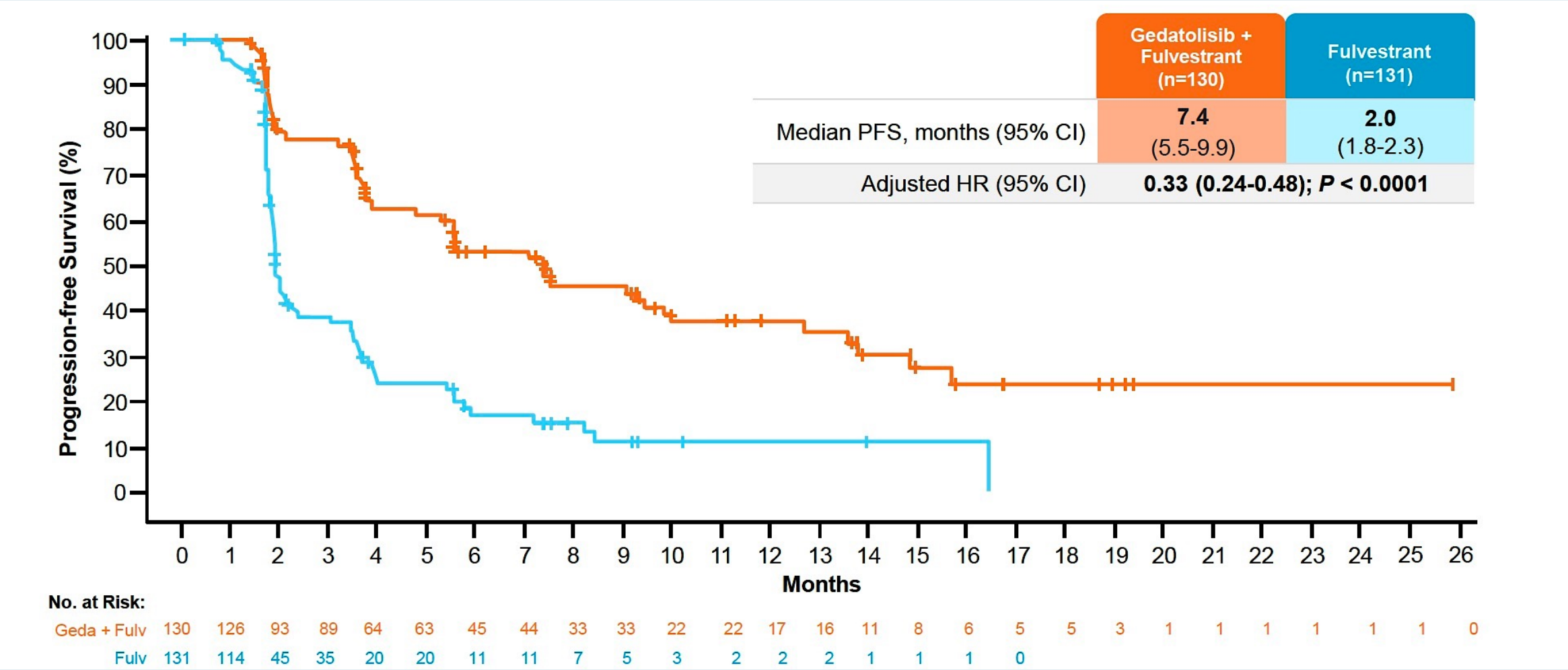
Phase III VIKTORIA-1: PFS with Gedatolisib Doublet versus Fulvestrant



Hurvitz SA et al. ESMO 2025;Abstract LBA17.

RTP RESEARCH TO PRACTICE

Phase III VIKTORIA-1: Safety

SAE and discontinuation, n (%)	Gedatolisib + palbociclib + fulvestrant (n=130)			Gedatolisib + fulvestrant (n=130)			Fulvestrant (n=123)		
Pts with ≥1 SAE	14 (10.8)			12 (9.2)			1 (0.8)		
Study treatment D/C due to TRAE	3 (2.3)			4 (3.1)			0		
Deaths due to TRAE†	2 (1.5)			0			0		
Adverse events, n (%)	**Gedatolisib + palbociclib + fulvestrant (n=130)**			**Gedatolisib + fulvestrant (n=130)**			**Fulvestrant (n=123)**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Stomatitis‡	**90 (69.2)**	**25 (19.2)**	**0**	**74 (56.9)**	**16 (12.3)**	**0**	**0**	**0**	**0**
Neutropenia‡	85 (65.4)	68 (52.3)	13 (10.0)	2 (1.5)	0	1 (0.8)	1 (0.8)	1 (0.8)	0
Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
Rash‡	**36 (27.7)**	**6 (4.6)**	**0**	**42 (32.3)**	**7 (5.4)**	**0**	**0**	**0**	**0**
Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
Diarrhea§	**22 (16.9)**	**2 (1.5)**	**0**	**16 (12.3)**	**1 (0.8)**	**0**	**0**	**0**	**0**
Hyperglycemia‡,§	**12 (9.2)**	**3 (2.3)**	**0**	**15 (11.5)**	**3 (2.3)**	**0**	**0**	**0**	**0**

Abbreviations: D/C, discontinued; Pts, patients; SAE, serious adverse event; TRAE, treatment-related adverse event (per investigator)
*Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
†Grade 5 events include one considered related to palbociclib (pneumonia) and one due to hepatic failure in a patient with multiple liver metastases considered related to all three drugs (and likely associated with disease)
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms shown; if a patient experienced multiple terms, it was counted once for the highest grade.
§Additional events of clinical importance

Hurvitz SA et al. ESMO 2025;Abstract LBA17.

Phase III VIKTORIA-1: Authors' Conclusions

- **VIKTORIA-1 is the first study to demonstrate a statistically significant and clinically meaningful improvement in PFS with PAM inhibition in patients with *PIK3CA*-WT disease, all of whom received prior CDK4/6i**
  - Gedatolisib triplet, mPFS 9.3 months (HR, 0.24; 95% CI, 0.17-0.35; $P < 0.0001$)
  - Gedatolisib doublet, mPFS 7.4 months (HR, 0.33; 95% CI, 0.24-0.48; $P < 0.0001$)
- **Efficacy of gedatolisib-based therapy was comparable regardless of which prior CDK4/6i was used**
- Adverse events associated with gedatolisib in VIKTORIA-1 were mainly Grade 1 or 2 in severity
  - **Hyperglycemia was low** (9.2% for triplet, 11.5% for doublet), **as was diarrhea** (16.9% and 12.3%, respectively), which is unexpected for a drug targeting the PAM pathway
  - Study treatment discontinuation due to TRAEs was reported in 2.3% (triplet) and 3.1% (doublet) of patients
- **These results validate the PAM pathway as a molecular driver in *PIK3CA*-WT disease**

Gedatolisib plus fulvestrant, with or without palbociclib, represents a potential new standard of care for patients with HR+, HER2-negative, *PIK3CA*-WT ABC whose disease progressed on or after treatment with a CDK4/6 inhibitor

WT = wild type

Hurvitz SA et al. ESMO 2025;Abstract LBA17.

RTP RESEARCH TO PRACTICE

Sacituzumab Tirumotecan

- Li M et al. **Sacituzumab tirumotecan (sac-TMT)** vs investigator's choice of chemotherapy (ICC) in **previously treated locally advanced or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Results** from the randomized, multi-center **phase 3 OptiTROP-Breast02 study**. ESMO 2025;Abstract LBA23.

Abstract LBA23

BERLIN 2025 ESMO congress

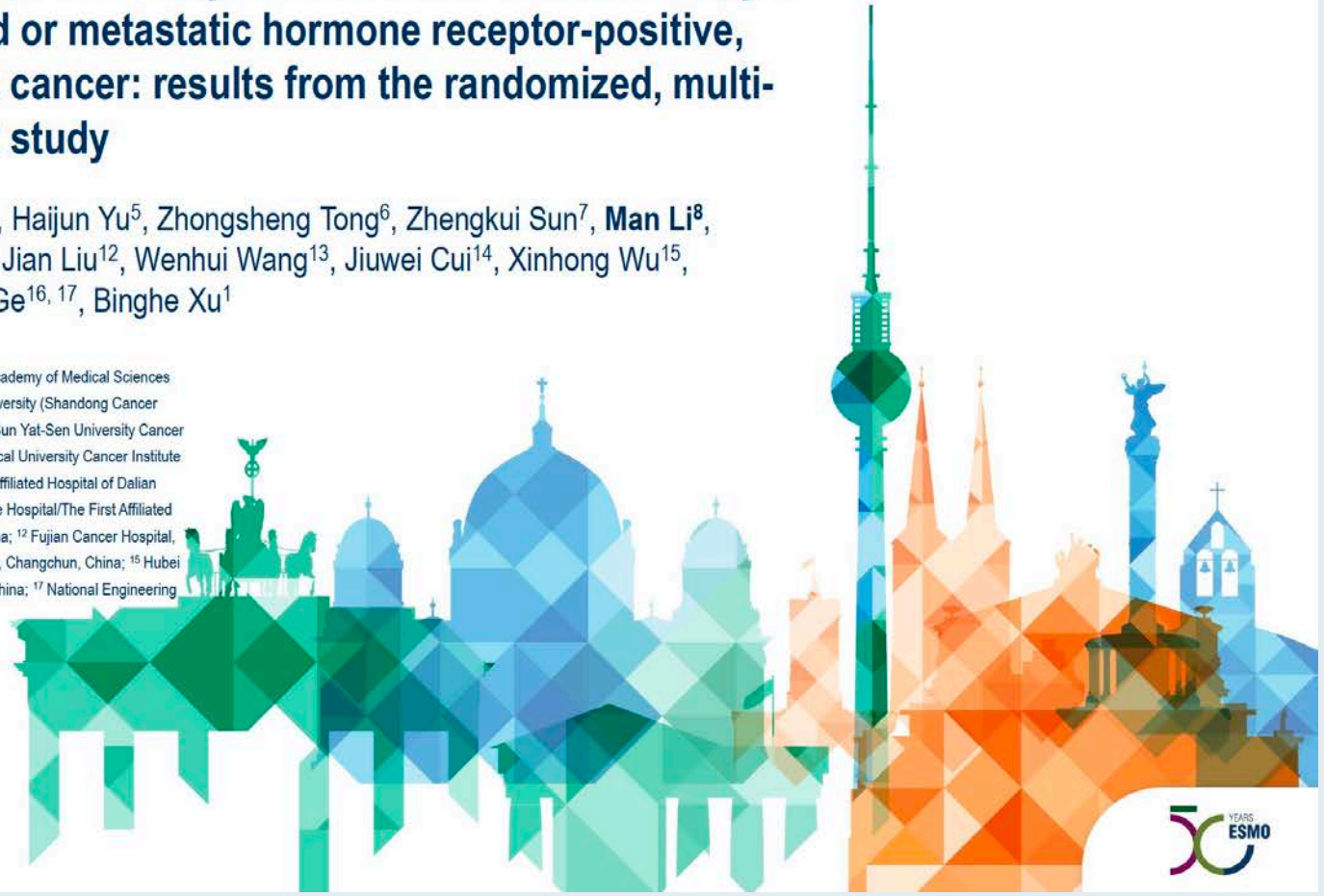
Sacituzumab tirumotecan (sac-TMT) vs investigator's choice of chemotherapy in previously treated locally advanced or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer: results from the randomized, multi-center phase 3 OptiTROP-Breast02 study

Ying Fan[1], Huihui Li[2], Hao Wang[3], Shusen Wang[4], Haijun Yu[5], Zhongsheng Tong[6], Zhengkui Sun[7], **Man Li[8]**, Xiying Shao[9], Yongmei Yin[10], Quchang Ouyang[11], Jian Liu[12], Wenhui Wang[13], Jiuwei Cui[14], Xinhong Wu[15], Gesha Liu[16], Yina Diao[16], Xiaoping Jin[16], Junyou Ge[16, 17], Binghe Xu[1]

[1] National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2] Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China; [3] Sichuan Cancer Hospital, Chengdu, China; [4] Sun Yat-Sen University Cancer Center, Guangzhou, China; [5] Zhongnan Hospital of Wuhan University, Wuhan, China; [6] Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [7] Jiangxi Provincial Cancer Hospital, Nanchang, China; [8] The Second Affiliated Hospital of Dalian Medical University, Dalian, China; [9] Zhejiang Cancer Hospital, Hangzhou, China; [10] Jiangsu Province Hospital/The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; [11] Hunan Cancer Hospital, Changsha, China; [12] Fujian Cancer Hospital, Fuzhou, China; [13] Weifang People's Hospital, Weifang, China; [14] The First Hospital of Jilin University, Changchun, China; [15] Hubei Cancer Hospital, Wuhan, China; [16] Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China; [17] National Engineering Research Center of Targeted Biologics, Chengdu, China.

Presenter: Professor Man Li

The Second Affiliated Hospital of Dalian Medical University, Dalian, China



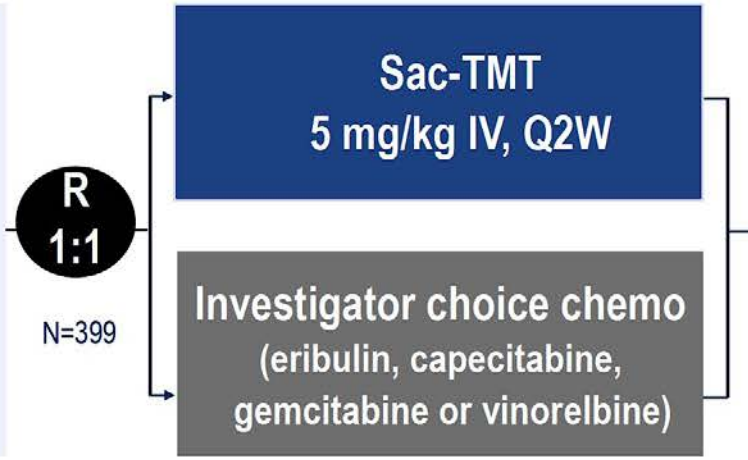
Sat, 18.10.2025

RTP RESEARCH TO PRACTICE

Phase III OptiTROP-Breast02 Study Design

Key Eligibility

- HR+/HER2- BC*
- Prior 1 - 4 lines of chemotherapy
- At least one endocrine therapy, CDK 4/6 inhibitor, and taxane in any setting



Primary endpoints

- PFS by BICR per RECIST v1.1

Secondary endpoints

- PFS (investigator assessed)
- OS
- ORR, DCR and DoR

Stratification Factors:

1. Lines of chemotherapy (1 vs >1)
2. HER2 status (zero vs low) *
3. Endocrine therapy ≥ 6 months (yes vs no) †

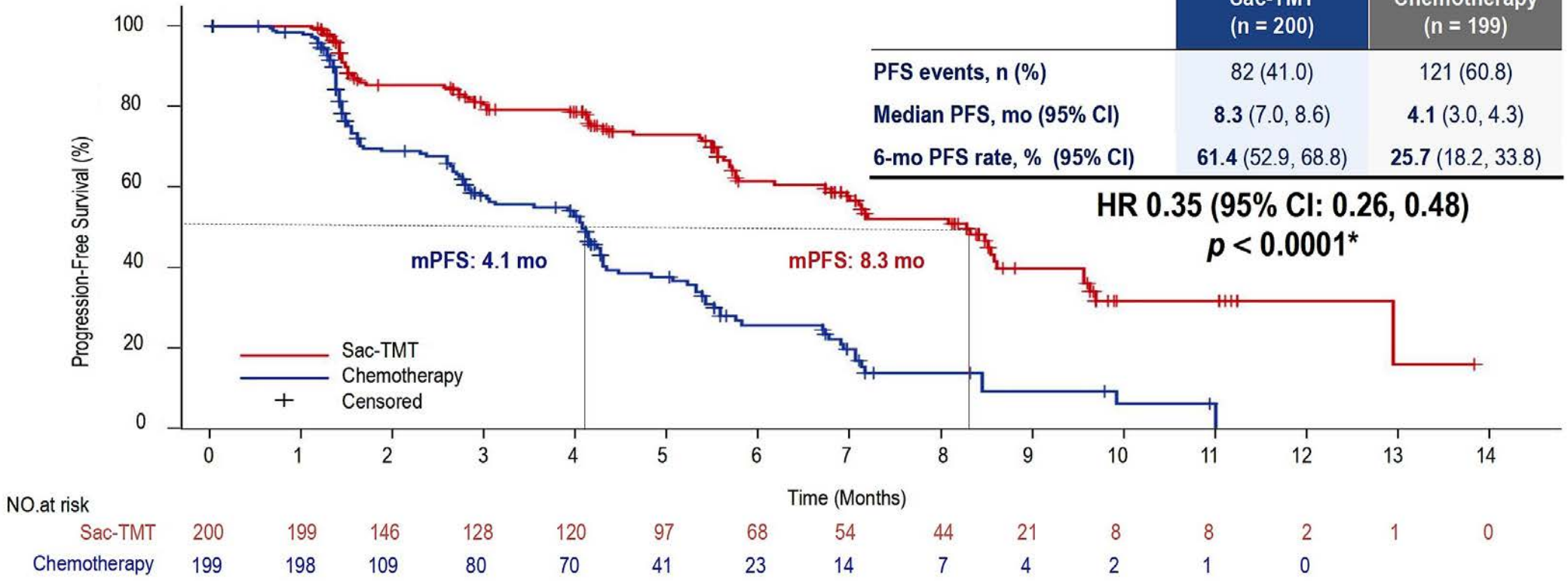
Statistical considerations:

- **Pre-specified IA for PFS** was performed when all patients had the opportunity to have 1 post-baseline scan and at least 188 PFS events were occurred
- **Pre-specified IA for OS:** approximately 165 OS events occurred
- Lan-DeMets O'Brien-Fleming α-spending function for both PFS and OS IA

*HER2- BC includes two subtypes: HER2-zero and HER2-low. HER2-zero: No staining, or barely perceptible staining with a proportion > 0% but ≤ 10%; HER2-low defined as IHC1+, or IHC2+/ISH-negative. † If no prior endocrine therapy in advanced setting, assess if (neo)adjuvant endocrine therapy duration ≥ 2 years.
BC, breast cancer; BICR, blinded independent central review; CDK 4/6, cyclin dependent kinase 4/6; DCR, disease control rate; DoR, duration of response; IA, interim analysis; OS, overall survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Li M et al. ESMO 2025;Abstract LBA23.

Phase III OptiTROP-Breast02: PFS by BICR



	Sac-TMT (n = 200)	Chemotherapy (n = 199)
PFS events, n (%)	82 (41.0)	121 (60.8)
Median PFS, mo (95% CI)	**8.3** (7.0, 8.6)	**4.1** (3.0, 4.3)
6-mo PFS rate, % (95% CI)	**61.4** (52.9, 68.8)	**25.7** (18.2, 33.8)

HR 0.35 (95% CI: 0.26, 0.48)
p* < 0.0001

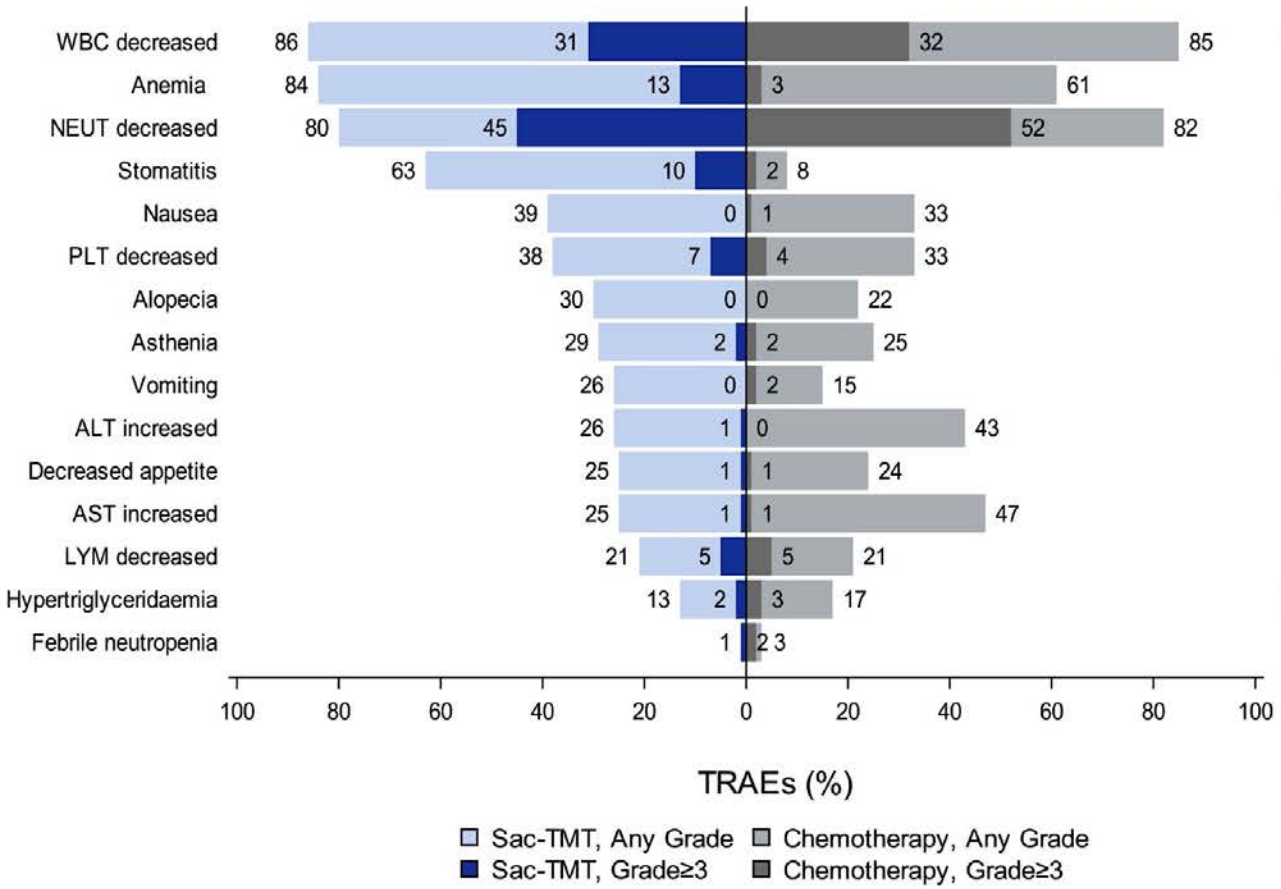
The investigator-assessed PFS was consistent with BICR: HR 0.39 (95% CI: 0.30, 0.52)

* Based on pre-specified PFS IA, one-sided *P* value was less than the pre-specified efficacy boundary to achieve statistically significant improvement (one-sided alpha level of 0.010 determined by the O'Brien-Fleming alpha spending function).

BICR = blinded independent central review

Li M et al. ESMO 2025;Abstract LBA23.

Phase III OptiTROP-Breast02: Safety



- The most common TRAEs for both sac-TMT and chemotherapy were hematologic toxicities.
- Grade ≥ 3 diarrhea occurred in **1.0%** of patients in the sac-TMT group.
- Low ocular surface toxicity (11.5% dry eyes, 4.0% corneal disease, all grade 1-2) observed in the sac-TMT group.
- ILD/pneumonitis occurred in **1.5% and 1.0%** of patients (**all grade 1-2**) in the sac-TMT and chemotherapy groups.

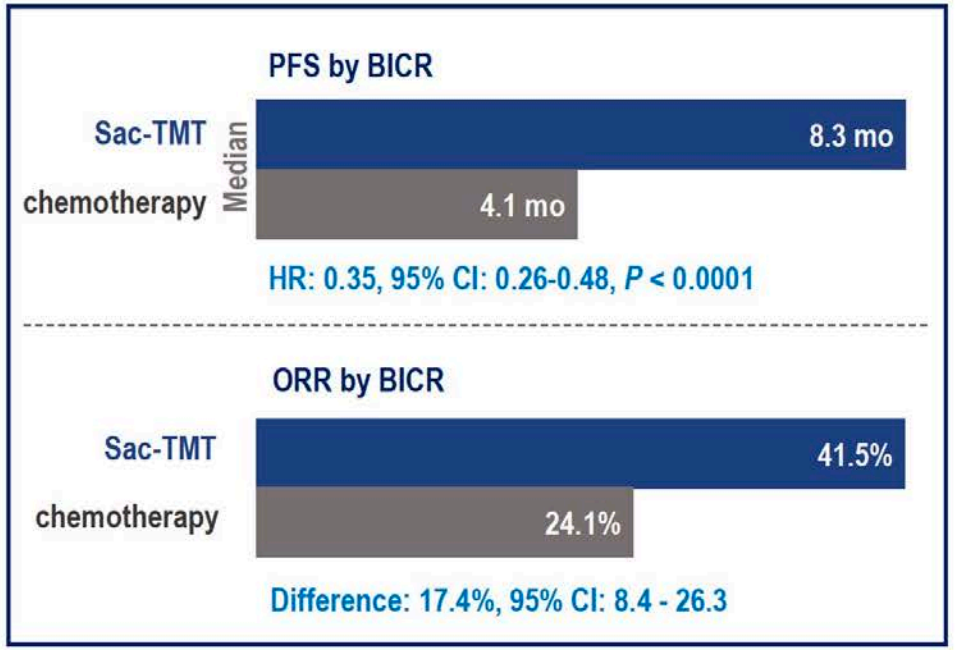
* Summary of TRAEs that occurred in either treatment group at an incidence of ≥ 20% for any grade or ≥ 2% for grade ≥ 3.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; LYM, lymphocyte count; NEUT, neutrophil count; PLT, platelet count; WBC, white blood cell.

TRAEs = treatment-related adverse events

Li M et al. ESMO 2025;Abstract LBA23.

Phase III OptiTROP-Breast02: Authors' Conclusions

- Sac-TMT demonstrated statistically significant and clinically meaningful improvement in PFS compared to chemotherapy.
  - PFS benefit was observed across all predefined subgroups.
  - PFS by BICR HR: 0.35 (95% CI: 0.26-0.48, P < 0.0001).
- Positive OS trend was observed with sac-TMT.
  - OS HR 0.33; (95% CI, 0.18, 0.61).
- Sac-TMT demonstrated a manageable safety profile, with no new safety signals.
- Phase 3 studies of sac-TMT (as monotherapy and/or in combination with pembrolizumab) in chemotherapy naïve HR+/HER2- breast cancer are ongoing globally (NCT06312176) and in China (NCT07071337).



The OptiTROP-Breast02 study supports sac-TMT as a new treatment option for patients with HR+/HER2- breast cancer following endocrine-based therapy and chemotherapy

Li M et al. ESMO 2025;Abstract LBA23.

RTP RESEARCH TO PRACTICE

ER-Positive, HER2 (0 or low), mBC: Sequencing of Systemic Therapies Post Endocrine Treatment

ER-positive, HER2-low

- T-DXd versus TROP2-targeted ADC (sacituzumab govitecan, datopotamab deruxtecan)
- Capecitabine
- Other chemotherapy

ER-positive, HER2-negative

- Sacituzumab govitecan versus datopotamab deruxtecan
- Capecitabine
- Other chemotherapy

Clinical factors:

- PS, comorbidities
- Tumor-related symptoms
- Visceral, CNS disease
- Prior systemic treatment

Agenda

Module 1: HER2-Positive Breast Cancer

Module 2: HR-Positive Breast Cancer

Module 3: Triple-Negative Breast Cancer

RTP
RESEARCH
TO PRACTICE

Neoadjuvant Durvalumab for TNBC

- Loibl S et al. **Durvalumab** in combination with neoadjuvant chemotherapy in **early triple-negative breast cancer (TNBC) – Long-term analysis** from the **GeparNuevo trial**. ESMO 2025;Abstract 292MO.

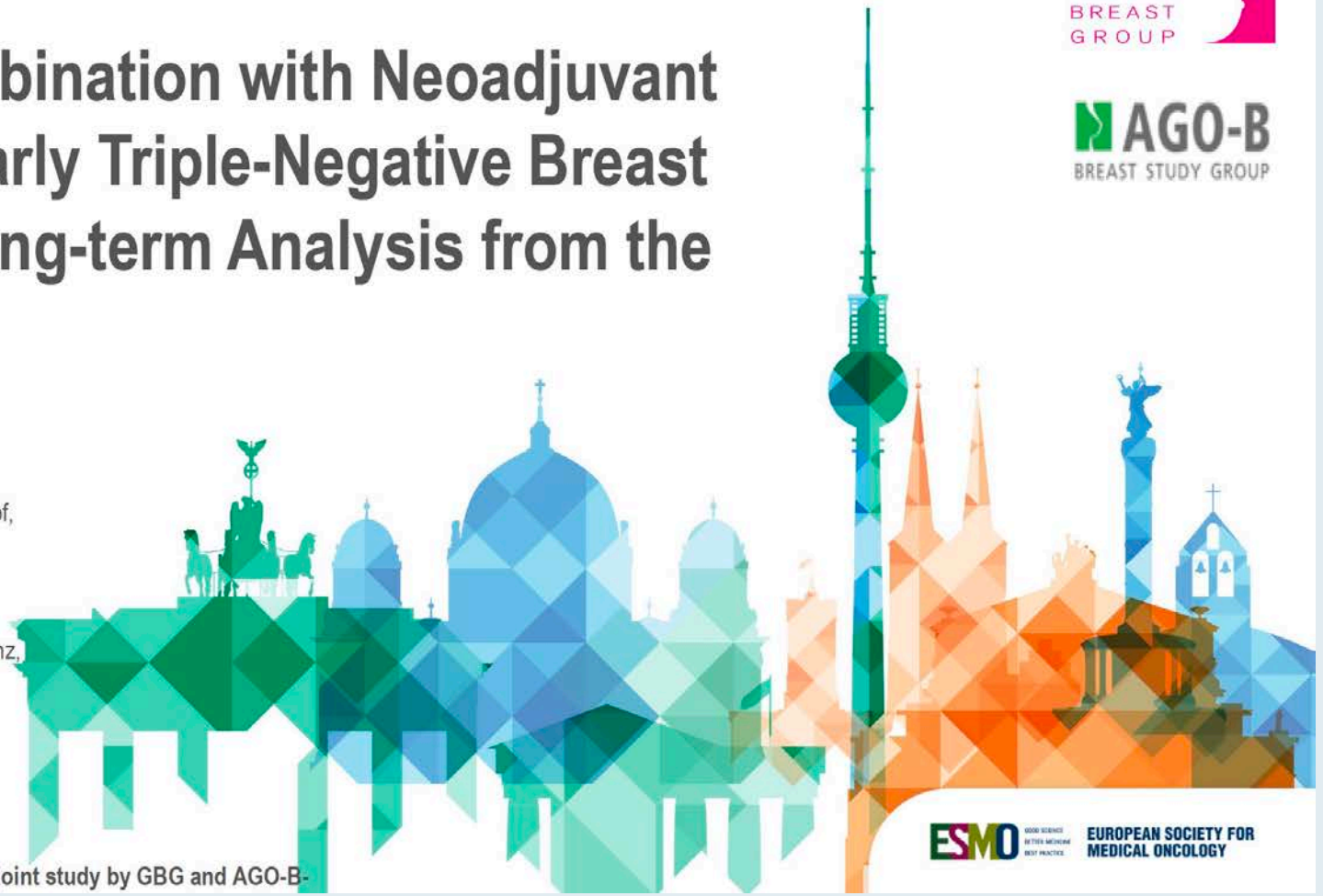
Abstract 292MO

BERLIN 2025 ESMO congress

Durvalumab in Combination with Neoadjuvant Chemotherapy in Early Triple-Negative Breast Cancer (TNBC) – Long-term Analysis from the GeparNuevo Trial

Sibylle Loibl, Michael Untch, Jens Huober, Vanessa Schaser, Michael Braun, Carsten Denkert, Andreas Hartkopf, Jens-Uwe Blohmer, Claus Hanusch, Theresa Link, Mattea Reinisch, Dirk-Michael Zahm, Rudolf Weide, Vesna Bjelic-Radisic, Peter Staib, Hans Tesch, Kerstin Rhiem, Ralf Lorenz, Julia Rey, Andreas Schneeweiss

GBG Forschungs GmbH; Neu-Isenburg, Germany
Goethe University Frankfurt



-This is a joint study by GBG and AGO-B-

Gepar Nuevo

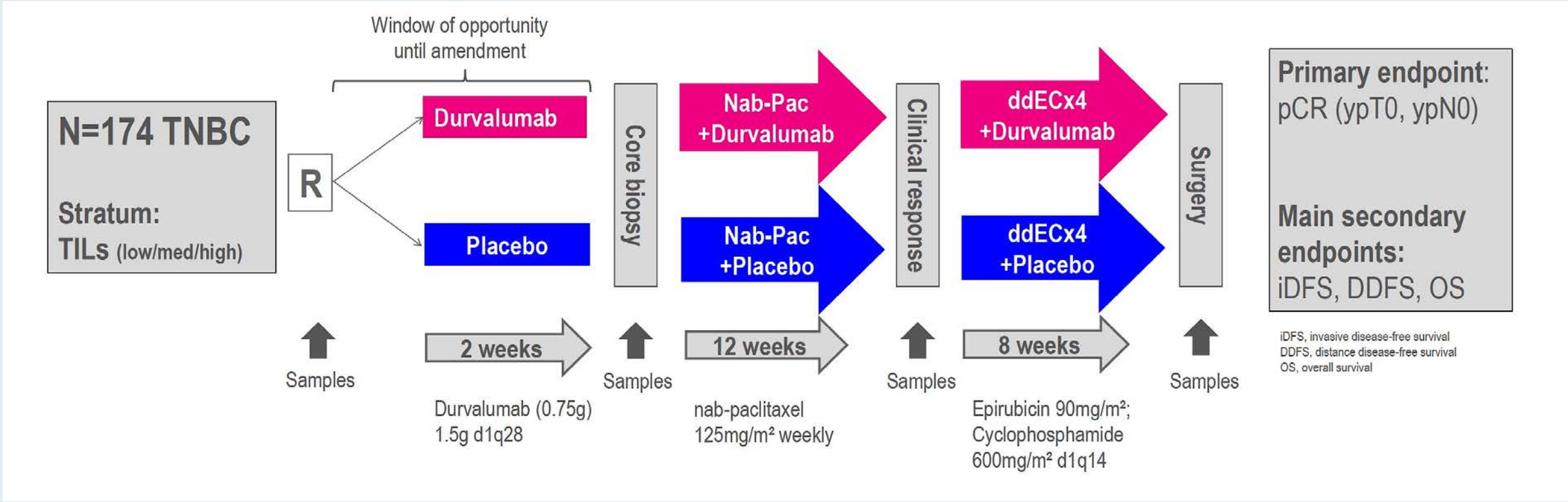
GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

ESMO EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

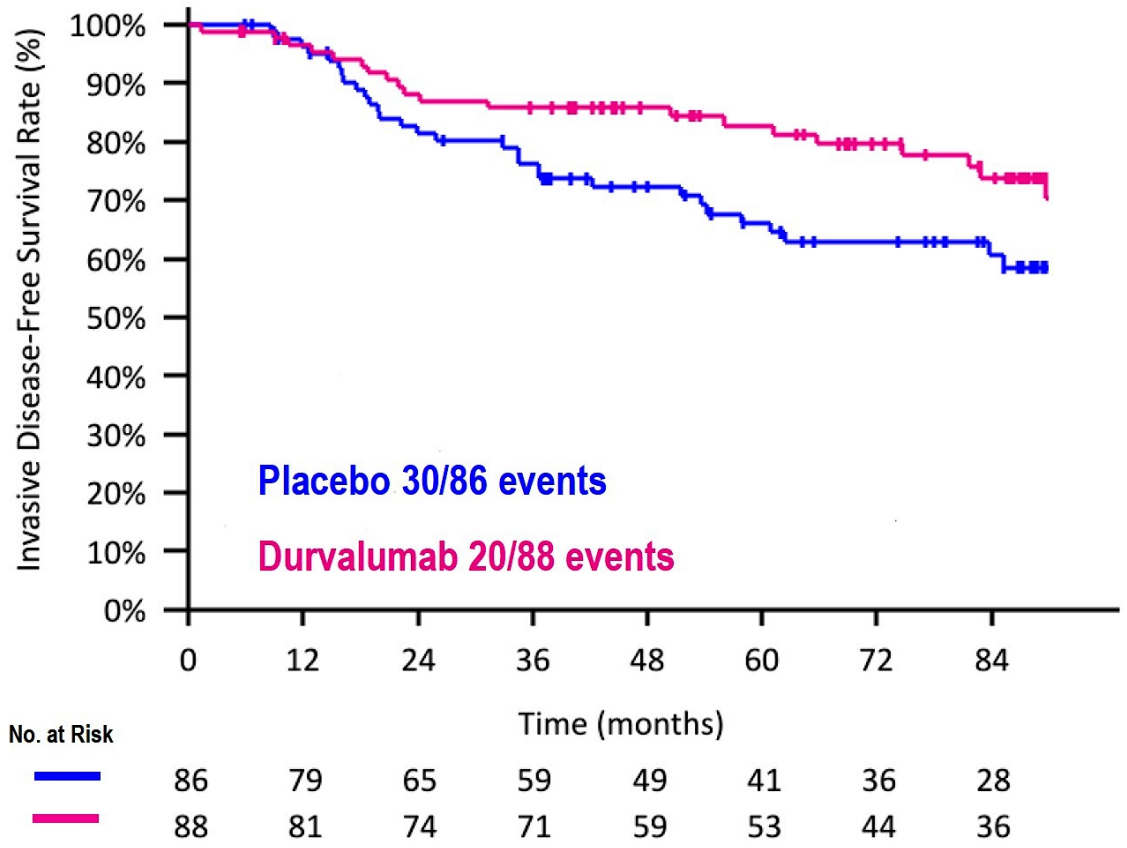
RTP RESEARCH TO PRACTICE

Phase II GeparNuevo Study Design



Loibl S et al. ESMO 2025;Abstract 292MO.

Phase II GeparNuevo: Updated IDFS



Median follow-up 86.4 (range 4.9-103) months

	Placebo	Durvalumab
6-year iDFS (95% CI)	62.8% (50.7%, 72.8%)	79.6% (68.7%, 87.1%)
7-year iDFS (95% CI)	60.7% (48.2%, 71.0%)	73.7% (61.4%, 82.6%)
HR 0.56 (0.32-0.99) Log-rank *p*=0.043		

Loibl S et al. ESMO 2025;Abstract 292MO.

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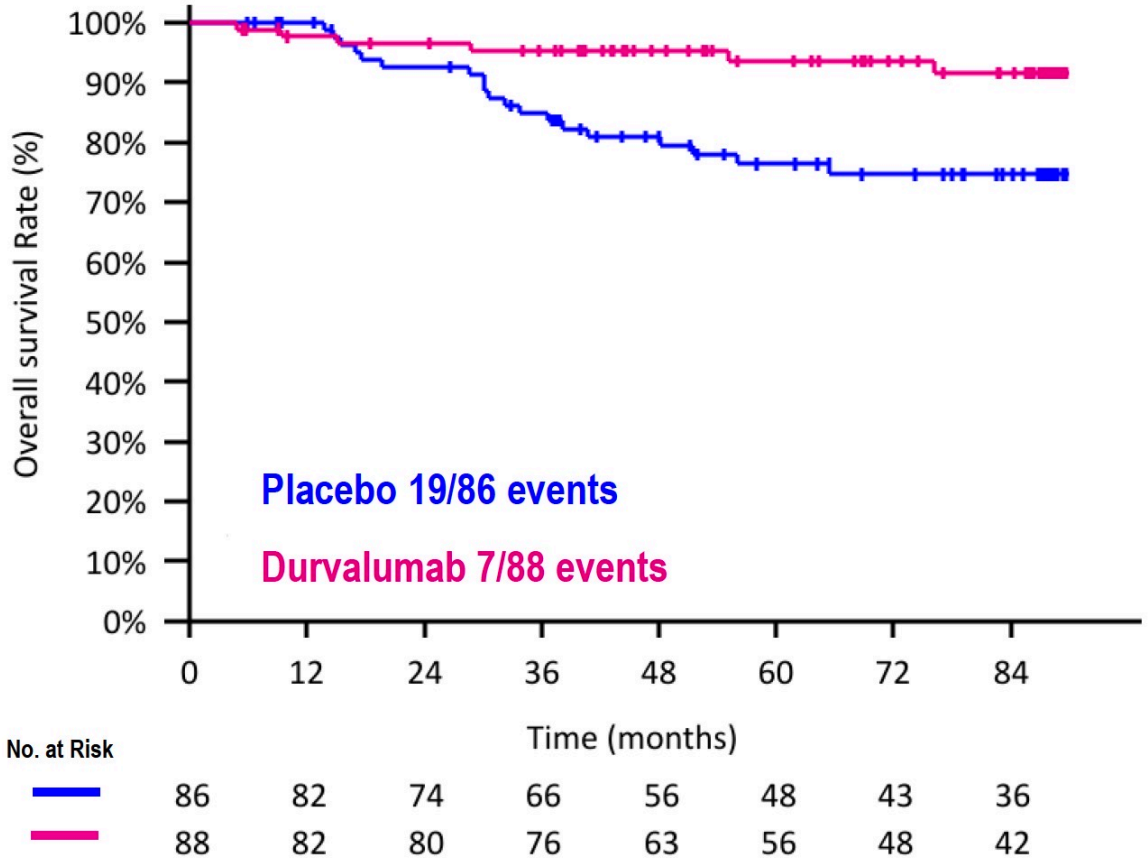
Phase II GeparNuevo: 7-Year Overall Survival



Median follow-up 86.4 (range 4.9-103) months

	Placebo	Durvalumab
6-year IDFS (95% CI)	74.7% (63.0%, 83.1%)	93.6% (85.2%, 97.3%)
7-year IDFS (95% CI)	74.7% (63.0%, 83.1%)	91.6% (81.8%, 96.2%)
HR 0.33 (0.14-0.79) Log-rank *p*=0.009		

Loibl S et al. ESMO 2025;Abstract 292MO.

RTP RESEARCH TO PRACTICE

Phase II GeparNuevo: Authors' Conclusions

- The addition of the checkpoint inhibitor (CPI) durvalumab to carboplatinum-free, but dose-dense NACT in patients with early TNBC resulted in statistically significant improvement of iDFS, DDFS, and OS despite no administration of adjuvant CPI.
- 7-year follow-up data confirm earlier results:
  - Survival benefit observed irrespective of pCR
  - Patients with TILs in the residual tumor have an excellent outcome.
- As in the NSABP-B58/GeparDouze study – there is a significant interaction with the nodal status.
- GeparNuevo raises two questions:
  - Shall patients with cN0 receive a CPI?
  - Do patients need to continue after surgery with the CPI?
- GeparNuevo is the only trial to prove survival benefit in the presence of dose-dense NACT without carboplatinum and the only trial to report survival benefit for a PD-L1 inhibitor.

NACT = neoadjuvant chemotherapy; TIL = tumor-infiltrating lymphocyte

Loibl S et al. ESMO 2025;Abstract 292MO.

ASCENT-03

- Cortés JC et al. **Primary results from ASCENT-03:** A randomized phase 3 study of **sacituzumab govitecan (SG)** vs chemotherapy (chemo) in patients (pts) with previously **untreated advanced triple-negative breast cancer (TNBC)** who are **unable to receive PD-(L)1 inhibitors (PD-[L]1i)**. ESMO 2025;Abstract LBA20.

Abstract LBA20

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Primary Results From ASCENT-03: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Chemotherapy in Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer Who Are Unable to Receive PD-(L)1 Inhibitors

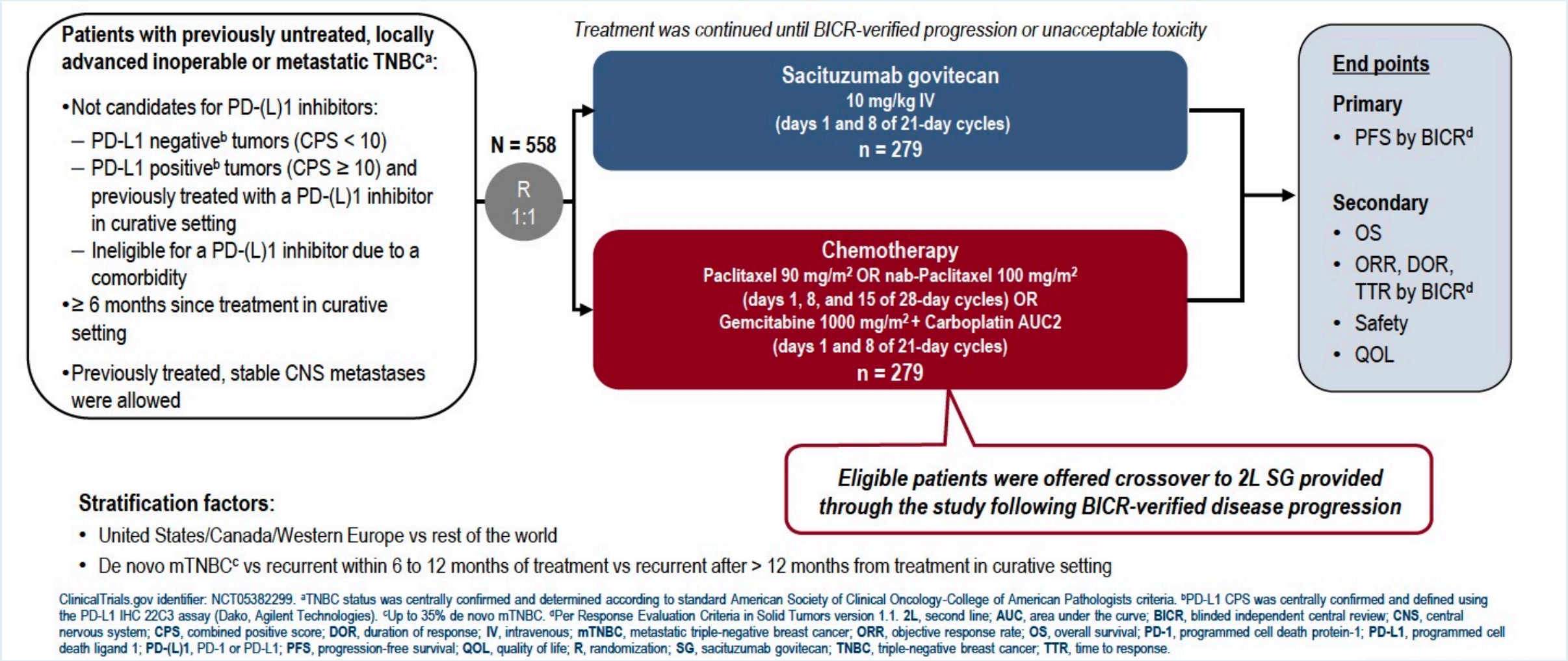
Javier Cortés[1-5], Aditya Bardia[6], Kevin Punie[7], Carlos Barrios[8], Sara Hurvitz[9], Andreas Schneeweiss[10], Joohyuk Sohn[11], Eriko Tokunaga[12], Adam Brufsky[13], Yeon Hee Park[14], Binghe Xu[15], Roberto Hegg[16], Mafalda Oliveira[17], Alessandra Fabi[18], Natalya Vaksman[19], Theresa Valdez[19], Xinrui Zhang[19], Catherine Lai[19], Sara M Tolaney[20]

[1]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; [2]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain; [3]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid, Spain; [4]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [5]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, USA; [6]David Geffen School of Medicine, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [7]Ziekenhuis Aan de Stroom, Antwerp, Belgium; [8]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [9]Department of Medicine, UW Medicine, Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA USA; [10]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [11]Yonsei Cancer Center, Seoul, Republic of Korea; [12]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [13]Magee-Womens Hospital and the Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [14]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [15]Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [16]University of São Paulo, São Paulo, Brazil; [17]Vall d'Hebron University Hospital, Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [18]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [19]Gilead Sciences Inc., Foster City, CA, USA; [20]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Sunday, October 19, 2025; 9:15-9:25 am
LBA 20

RTP RESEARCH TO PRACTICE

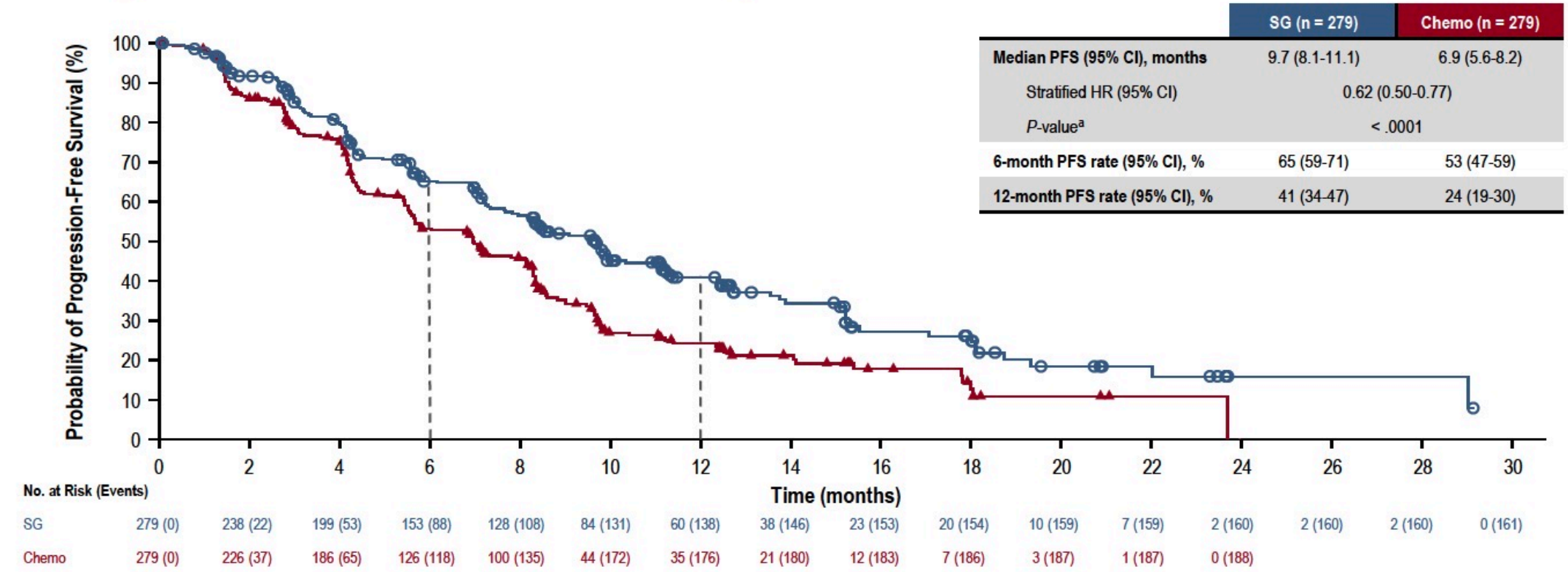
Phase III ASCENT-03 Study Design



ClinicalTrials.gov identifier: NCT05382299. [a]TNBC status was centrally confirmed and determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]PD-L1 CPS was centrally confirmed and defined using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies). [c]Up to 35% de novo mTNBC. [d]Per Response Evaluation Criteria in Solid Tumors version 1.1. **2L**, second line; **AUC**, area under the curve; **BICR**, blinded independent central review; **CNS**, central nervous system; **CPS**, combined positive score; **DOR**, duration of response; **IV**, intravenous; **mTNBC**, metastatic triple-negative breast cancer; **ORR**, objective response rate; **OS**, overall survival; **PD-1**, programmed cell death protein-1; **PD-L1**, programmed cell death ligand 1; **PD-(L)1**, PD-1 or PD-L1; **PFS**, progression-free survival; **QOL**, quality of life; **R**, randomization; **SG**, sacituzumab govitecan; **TNBC**, triple-negative breast cancer; **TTR**, time to response.

Cortés JC et al. ESMO 2025;Abstract LBA20.

Phase III ASCENT-03: PFS by BICR



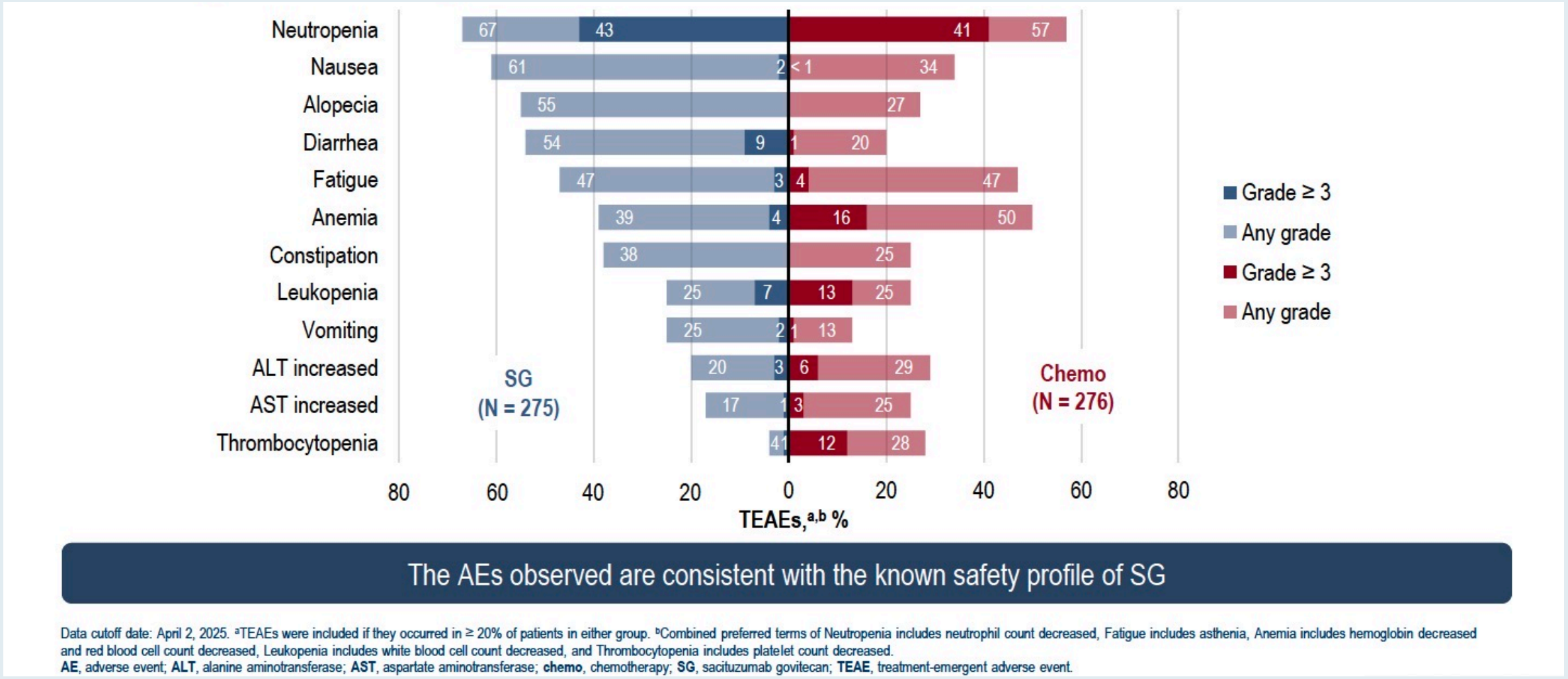
	SG (n = 279)	Chemo (n = 279)
Median PFS (95% CI), months	9.7 (8.1-11.1)	6.9 (5.6-8.2)
Stratified HR (95% CI)	0.62 (0.50-0.77)	
P-value[a]	< .0001	
6-month PFS rate (95% CI), %	65 (59-71)	53 (47-59)
12-month PFS rate (95% CI), %	41 (34-47)	24 (19-30)

SG demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo by BICR analysis, with a 38% reduction in risk of disease progression or death

Data cutoff date: April 2, 2025. [a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; **chemo**, chemotherapy; **HR**, hazard ratio; **PFS**, progression-free survival; **SG**, sacituzumab govitecan.

Cortés JC et al. ESMO 2025;Abstract LBA20.

Phase III ASCENT-03: Common AEs



The AEs observed are consistent with the known safety profile of SG

Data cutoff date: April 2, 2025. [a]TEAEs were included if they occurred in ≥ 20% of patients in either group. [b]Combined preferred terms of Neutropenia includes neutrophil count decreased, Fatigue includes asthenia, Anemia includes hemoglobin decreased and red blood cell count decreased, Leukopenia includes white blood cell count decreased, and Thrombocytopenia includes platelet count decreased.
AE, adverse event; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **chemo**, chemotherapy; **SG**, sacituzumab govitecan; **TEAE**, treatment-emergent adverse event.

Cortés JC et al. ESMO 2025;Abstract LBA20.

Phase III ASCENT-03: Authors' Conclusions

- SG led to a statistically significant and clinically meaningful improvement in PFS vs chemo (median, 9.7 vs 6.9 months; HR, 0.62)
  - PFS benefit was observed across key prespecified subgroups

PFS by BICR

38% reduction in risk of progression or death

- ORR was similar between treatment groups; however, duration of response was longer with SG vs chemo
- OS was immature at the time of the analysis and PFS2 was improved with SG vs chemo

PFS2 per investigator

Median PFS2 was 4.2 months longer with SG vs chemo

- Safety of SG was consistent with its known profile; use of prophylactic G-CSF is advised as appropriate
- Rates of treatment discontinuations (4% vs 12%) were lower with SG vs chemo

Treatment Discontinuation

Lower rate of treatment discontinuation due to TEAEs with SG vs chemo

ASCENT-03 data support SG as a potential new standard of care for patients with previously untreated mTNBC who are not candidates for a PD-(L)1 inhibitor

Data cutoff date: April 2, 2025. **Chemo**, chemotherapy; **G-CSF**, granulocyte-colony stimulation factor; **HR**, hazard ratio; **mTNBC**; metastatic triple-negative breast cancer; **ORR**, objective response rate; **OS**, overall survival; **PD-1**, programmed cell death protein-1; **PD-L1**, programmed cell death ligand 1; **PD-(L)1**, PD-1 or PD-L1; **PFS**, progression-free survival; **SG**, sacituzumab govitecan; **TEAEs**, treatment-emergent adverse events.

Cortés JC et al. ESMO 2025;Abstract LBA20.

RTP RESEARCH TO PRACTICE

ASCENT-04 Patient Reported Outcomes

- de Azambuja E et al. **Patient-reported outcomes (PROs)** with **sacituzumab govitecan (SG)** + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in patients (pts) with previously **untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC)** in the **phase 3 ASCENT-04/KEYNOTE-D19 study**. ESMO 2025;Abstract LBA22.

Abstract LBA22

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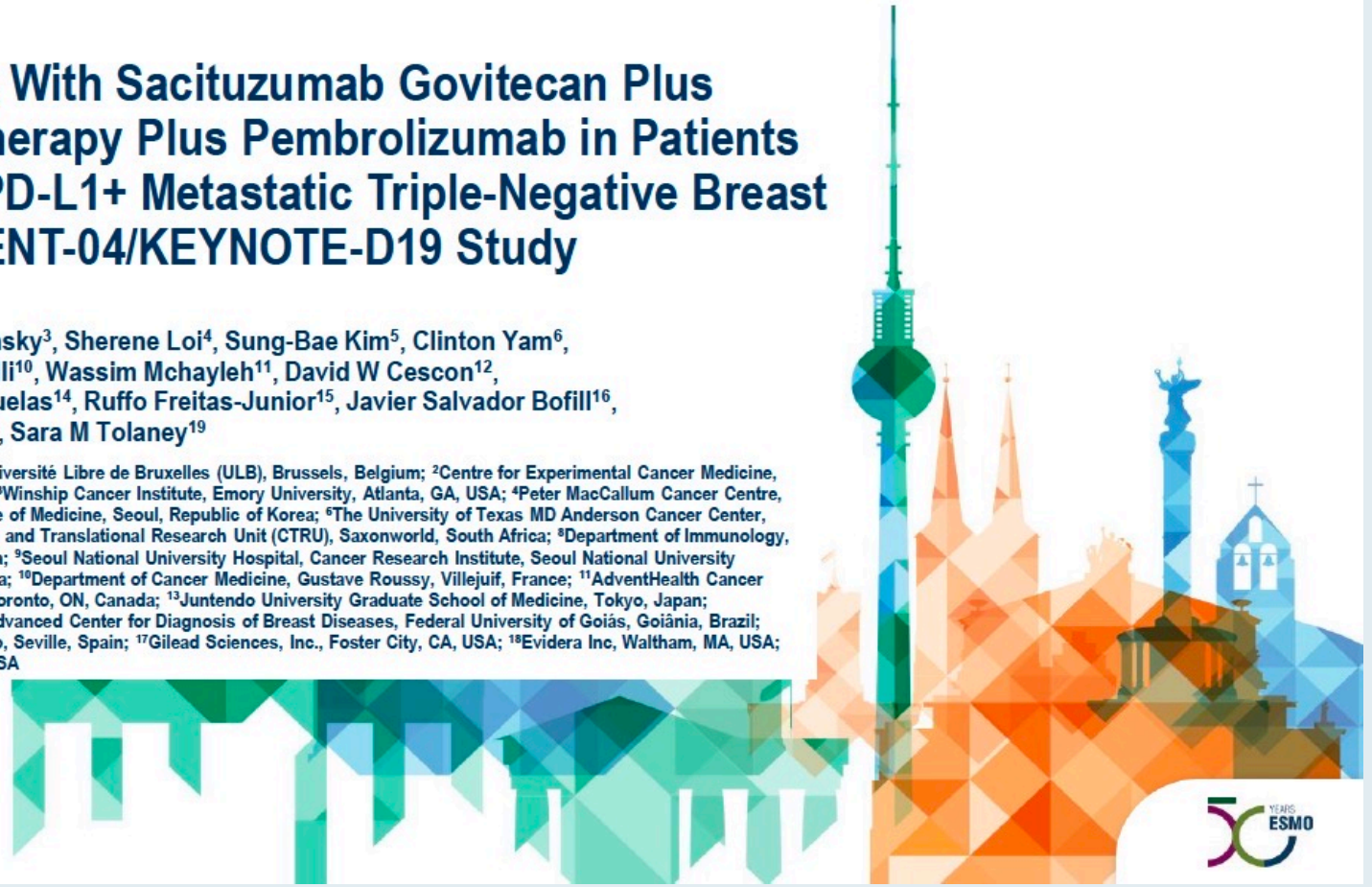
Patient-Reported Outcomes With Sacituzumab Govitecan Plus Pembrolizumab vs Chemotherapy Plus Pembrolizumab in Patients With Previously Untreated PD-L1+ Metastatic Triple-Negative Breast Cancer in the Phase 3 ASCENT-04/KEYNOTE-D19 Study

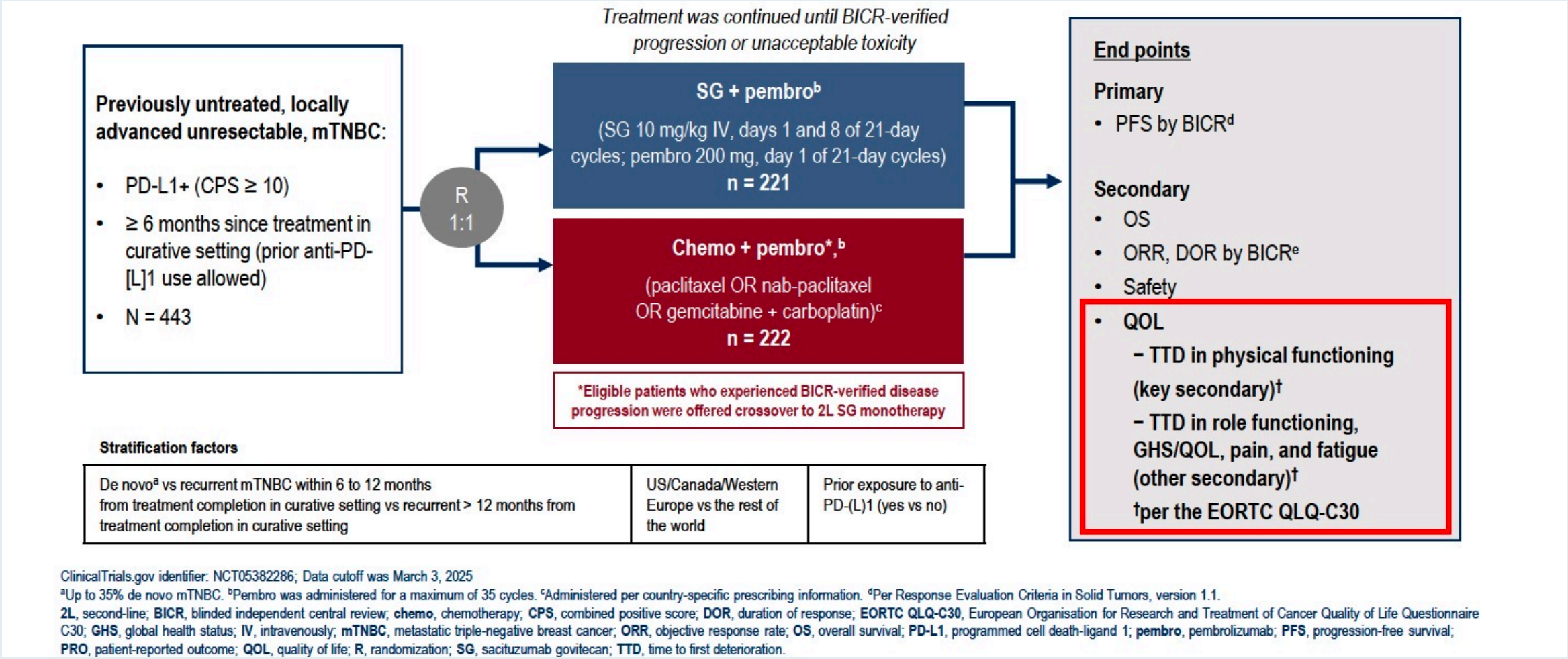
Evandro de Azambuja[1], Peter Schmid[2], Kevin Kalinsky[3], Sherene Loi[4], Sung-Bae Kim[5], Clinton Yam[6], Bernardo Rapoport[7,8], Seock-Ah Im[9], Barbara Pistilli[10], Wassim Mchayleh[11], David W Cescon[12], Junichiro Watanabe[13], Manuel Alejandro Lara Bañuelas[14], Ruffo Freitas-Junior[15], Javier Salvador Bofill[16], Xue Wang[17], Yiran Zhang[17], Ling Shi[18], Ann Chen[17], Sara M Tolaney[19]

[1]Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B) and Université Libre de Bruxelles (ULB), Brussels, Belgium; [2]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]The Medical Oncology Centre of Rosebank, Clinical and Translational Research Unit (CTRU), Saxonworld, South Africa; [8]Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [9]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [10]Department of Cancer Medicine, Gustave Roussy, Villejuif, France; [11]AdventHealth Cancer Institute, Orlando, FL, USA; [12]Princess Margaret Cancer Centre, UHN, Toronto, ON, Canada; [13]Juntendo University Graduate School of Medicine, Tokyo, Japan; [14]SCIENTIA Investigación Clínica S.C., Chihuahua, Mexico; [15]CORA – Advanced Center for Diagnosis of Breast Diseases, Federal University of Goiás, Goiânia, Brazil; [16]Medical Oncology Department, Hospital Universitario Virgen del Rocio, Seville, Spain; [17]Gilead Sciences, Inc., Foster City, CA, USA; [18]Evidera Inc, Waltham, MA, USA; [19]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA



Monday, October 20, 2025; 10:15 – 10:20 AM
LBA 22

Phase III ASCENT-04/KEYNOTE-D19 Study Design



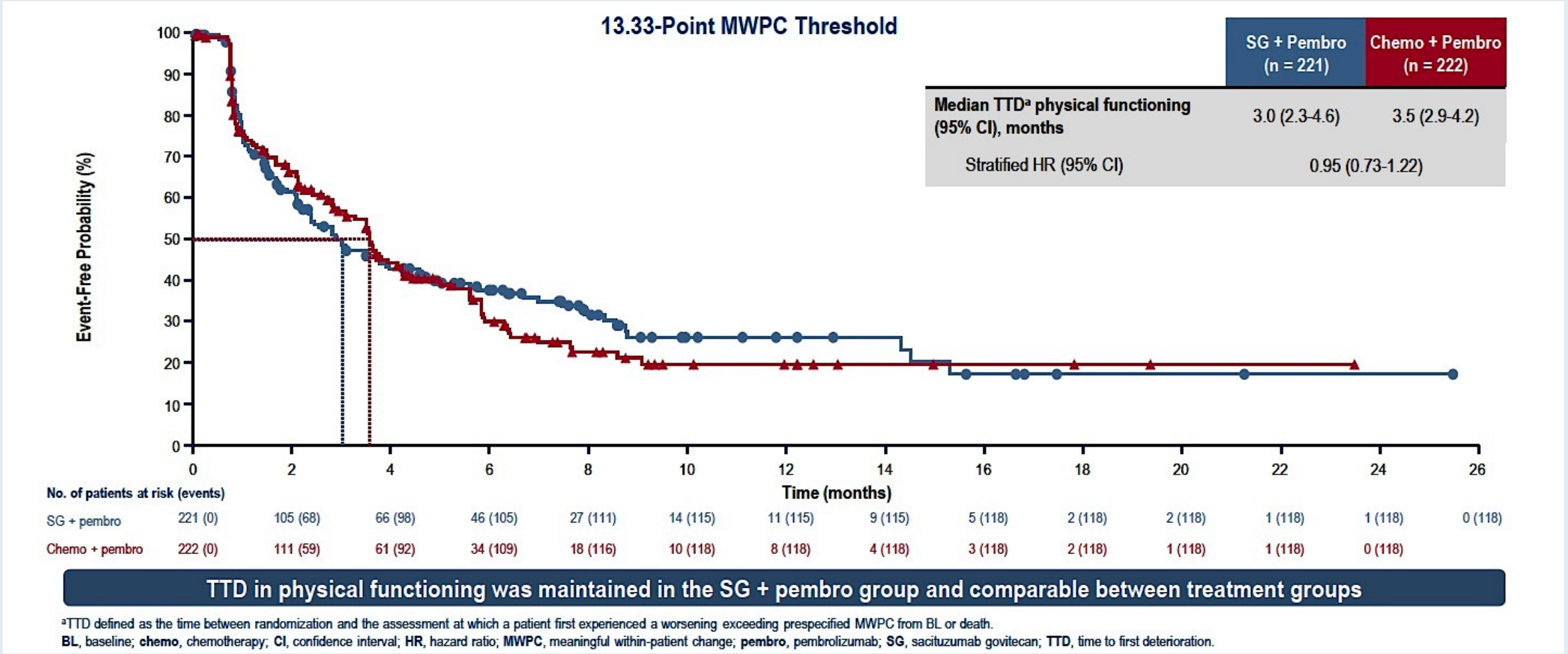
ClinicalTrials.gov identifier: NCT05382286; Data cutoff was March 3, 2025

[a]Up to 35% de novo mTNBC. [b]Pembro was administered for a maximum of 35 cycles. [c]Administered per country-specific prescribing information. [d]Per Response Evaluation Criteria in Solid Tumors, version 1.1.

2L, second-line; **BICR**, blinded independent central review; **chemo**, chemotherapy; **CPS**, combined positive score; **DOR**, duration of response; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; **GHS**, global health status; **IV**, intravenously; **mTNBC**, metastatic triple-negative breast cancer; **ORR**, objective response rate; **OS**, overall survival; **PD-L1**, programmed cell death-ligand 1; **pembro**, pembrolizumab; **PFS**, progression-free survival; **PRO**, patient-reported outcome; **QOL**, quality of life; **R**, randomization; **SG**, sacituzumab govitecan; **TTD**, time to first deterioration.

de Azambuja E et al. ESMO 2025;Abstract LBA22.

Phase III ASCENT-04/KEYNOTE-D19: Time to First Deterioration in Physical Function



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Median TTD[a] physical functioning (95% CI), months	3.0 (2.3-4.6)	3.5 (2.9-4.2)
Stratified HR (95% CI)	0.95 (0.73-1.22)	

TTD in physical functioning was maintained in the SG + pembro group and comparable between treatment groups

[a]TTD defined as the time between randomization and the assessment at which a patient first experienced a worsening exceeding prespecified MWPC from BL or death.

BL, baseline; **chemo**, chemotherapy; **CI**, confidence interval; **HR**, hazard ratio; **MWPC**, meaningful within-patient change; **pembro**, pembrolizumab; **SG**, sacituzumab govitecan; **TTD**, time to first deterioration.

de Azambuja E et al. ESMO 2025;Abstract LBA22.

RTP RESEARCH TO PRACTICE

Phase III ASCENT-04/KEYNOTE-D19: Authors' Conclusions

- Baseline QOL was generally maintained with SG + pembro, with benefits seen in several domains
- TTD in physical functioning was comparable between the groups, with **emotional functioning and pain** favoring SG + pembro vs chemo + pembro
- The sensitivity analyses to evaluate substantial and sustained changes showed that SG + pembro may delay the onset of decline in physical functioning, indicating a benefit in maintaining patients' ability to perform daily activities
- Mean changes from baseline favored SG + pembro for **physical, role, and emotional functioning**, as well as **pain and insomnia**
- There was worsening of symptoms such as **nausea/vomiting and diarrhea**, which are consistent with the safety profile of the SG + pembro group in the study, and can be managed by following established guidelines

SG + pembro maintained overall QOL, patients reported reduced symptom burden and improved functioning in multiple domains; these data complement the clinically meaningful improvement in PFS and support this treatment regimen as a potential new standard of care for patients with PD-L1+ mTNBC

de Azambuja E et al. ESMO 2025;Abstract LBA22.

Dr Sharma: Case Presentation #4

- 52-year-old African American female with left cT2N+ (3.8 cm mass on imaging and 3 abnormal level 1 lymph nodes) TNBC who receives neoadjuvant therapy with KN-522 regimen. Germline testing is negative for BRCA1/2 mutation. At time of surgery (mastectomy with SLNB) there is residual TNBC in breast measuring 1.2 cm and one of four sentinel lymph nodes with metastatic focus measuring 5 mm. She receives adjuvant capecitabine for 6 cycles along with adjuvant pembrolizumab and chest wall and regional nodal radiation.
- Two months after completion of adjuvant pembrolizumab she is noted to have left chest wall lesions. Biopsy of skin lesions confirms metastatic TNBC, PD-L1 CPS < 10. CT scans show three liver lesions. She is started on treatment with first-line sacituzumab govitecan. Scans after three cycles show decrease in liver lesions and improvement in chest wall disease.

TROPION-Breast02

- Dent RA et al. **First-line (1L) datopotamab deruxtecan (Dato-DXd)** vs chemotherapy in patients **with locally recurrent inoperable or metastatic triple-negative breast cancer (mTNBC)** for whom immunotherapy was not an option: **Primary results** from the randomised, **phase 3 TROPION-Breast02 trial**. ESMO 2025;Abstract LBA21.

Abstract LBA21

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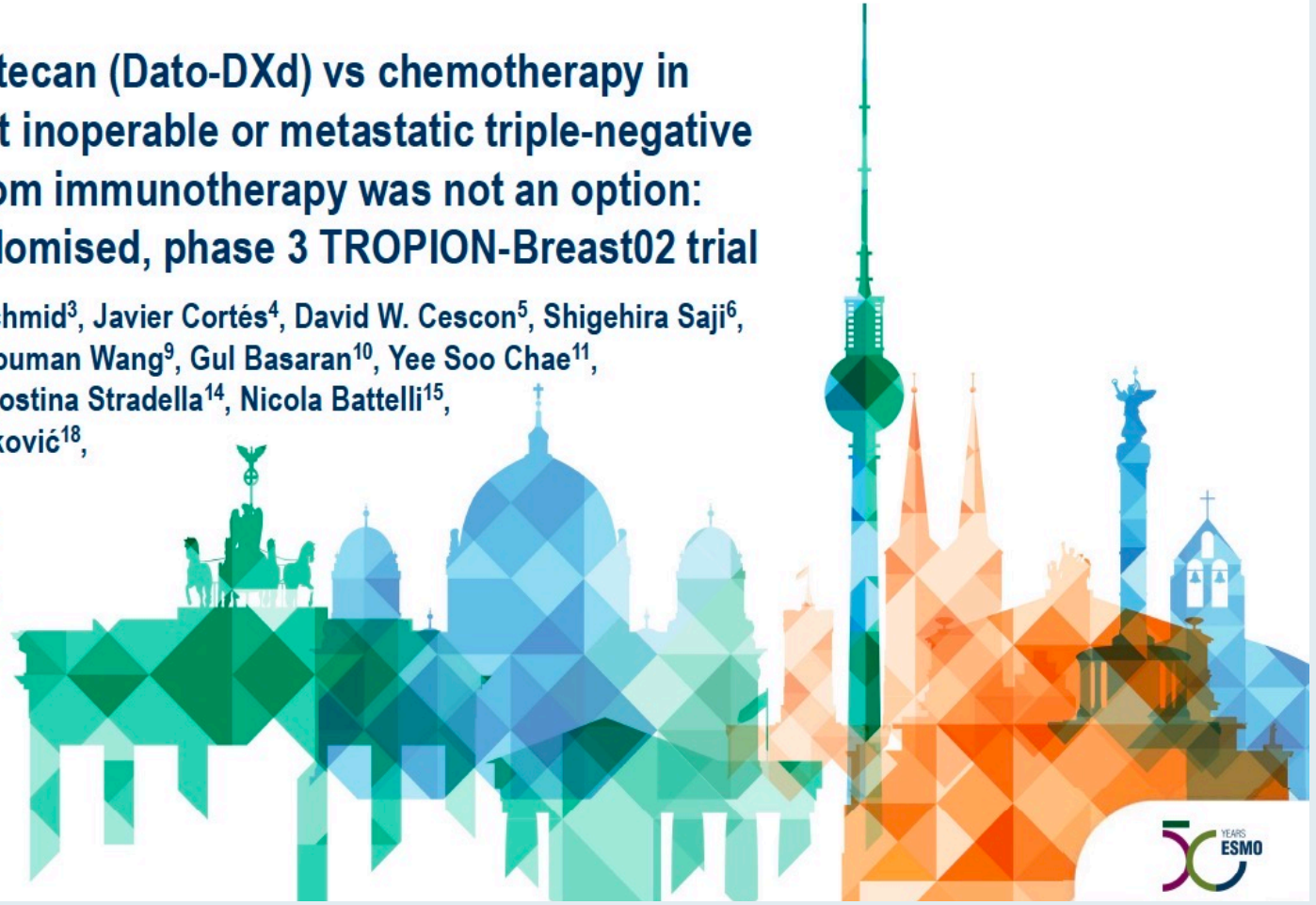
First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Primary results from the randomised, phase 3 TROPION-Breast02 trial

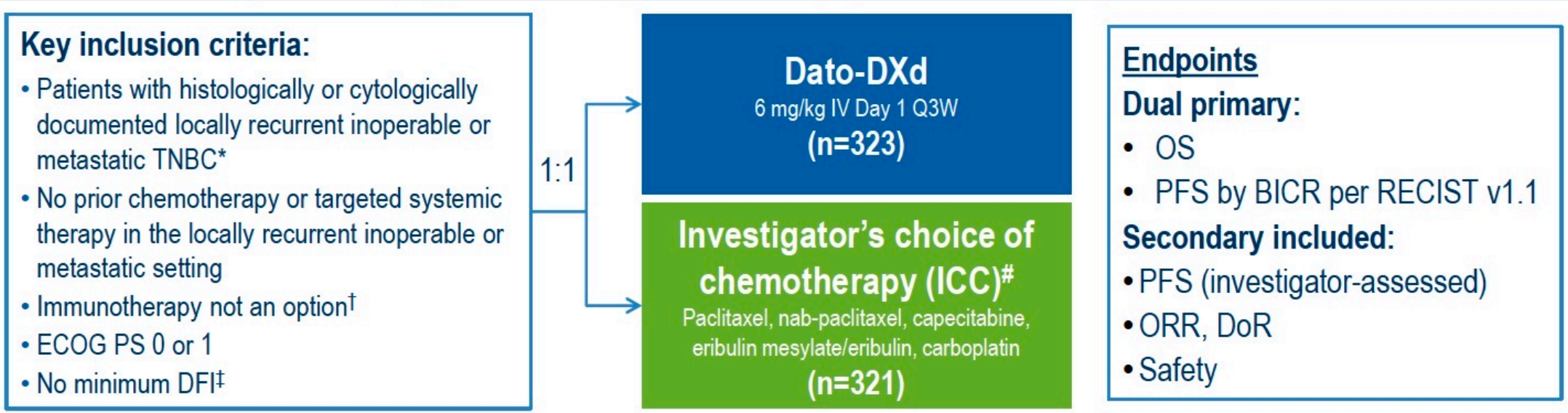
Rebecca A. Dent[1], Zhimin Shao[2], Peter Schmid[3], Javier Cortés[4], David W. Cescon[5], Shigehira Saji[6], Kyung Hae Jung[7], Thomas Bachelot[8], Shouman Wang[9], Gul Basaran[10], Yee Soo Chae[11], Rofhiwa Mathiba[12], Shin-Cheh Chen[13], Agostina Stradella[14], Nicola Battelli[15], Naoki Niikura[16], Kechen Zhao[17], Petra Vuković[18], Micah J. Maxwell[19], Tiffany A. Traina[20]

[1]National Cancer Center Singapore, Singapore; [2]Fudan University Shanghai Cancer Center, Fudan, China; [3]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [4]International Breast Cancer Center (IBCC), Pangaea Oncology, Barcelona, Spain; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Fukushima Medical University, Fukushima, Japan; [7]Asan Medical Center – University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Centre Léon Bérard, Lyon, France; [9]Xiangya Hospital of Central South University, Changsha, China; [10]MAA Acibadem University, School of Medicine, Medical Oncology Department, Istanbul, Türkiye; [11]Kyungpook National University Chilgok Hospital, Kyungpook National University School of Medicine, Kyungpook, Republic of Korea; [12]Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [13]Chang Gung Medical Foundation – Taipei Chang Gung Memorial Hospital, Taipei City, Taiwan; [14]Institut Catala d'Oncologia - Hospital Duran i Reynals (ICO L'Hospitalet), Barcelona, Spain; [15]Ospedale Generale Provinciale Macerata, Macerata, Italy; [16]Tokai University School of Medicine, Kanagawa, Japan; [17]Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Wilmington, DE, USA; [18]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Cambridge, UK; [19]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [20]Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA



RTP RESEARCH TO PRACTICE

Phase III TROPION-Breast02 Study Design

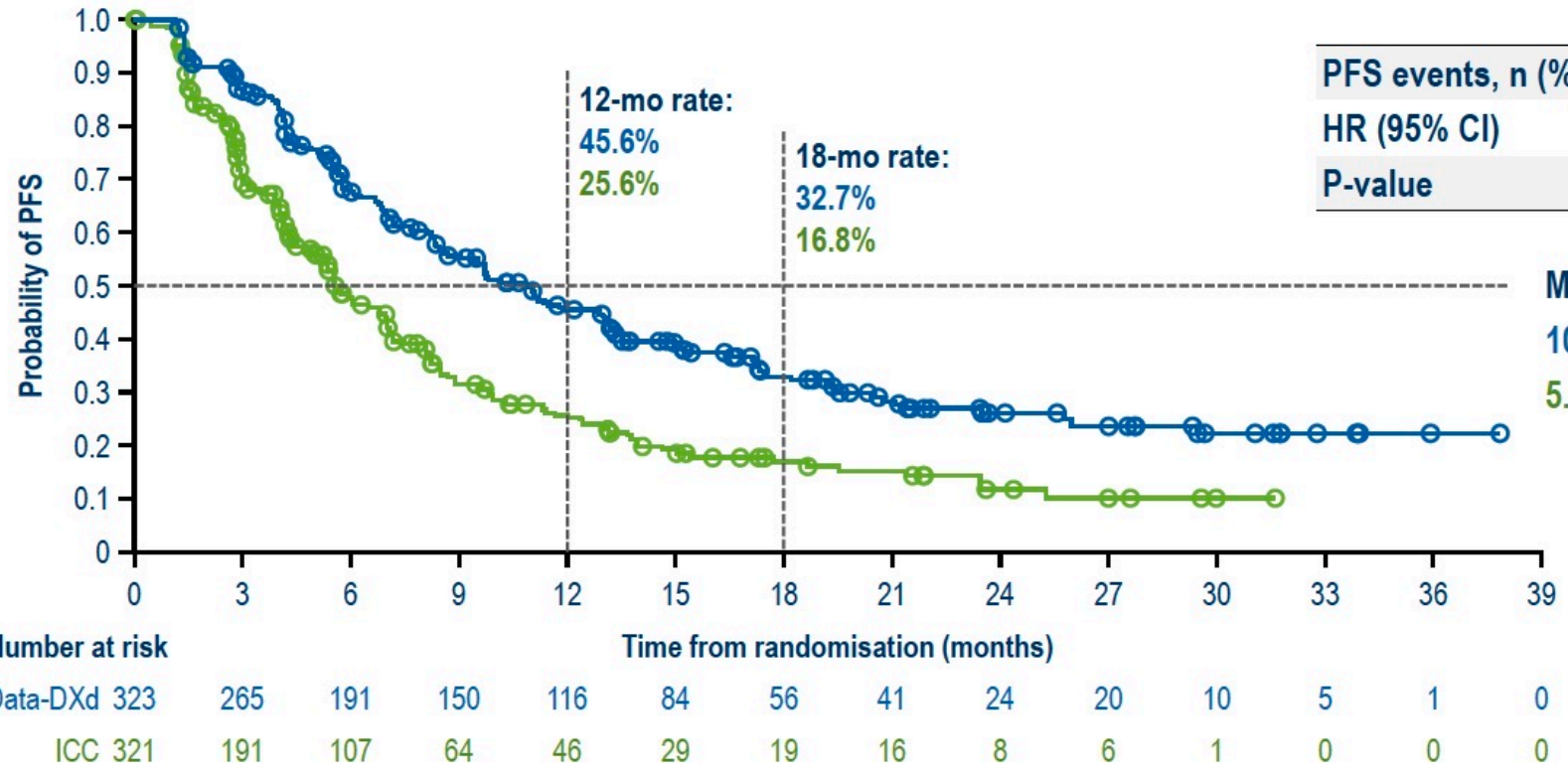


*According to ASCO/CAP criteria. †Including patients with PD-L1-low tumours, or patients with PD-L1-high tumours with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer, (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy. ‡DFI defined as time between date of completion of treatment with curative intent and date of first documented local or distant disease recurrence. §Recruitment of patients with PD-L1-high tumours who would otherwise be eligible for pembrolizumab if regulatory access was available was capped at ~10% of randomised patients. ¶Recruitment of patients with DFI 0–12 months was capped at ~20% of randomised patients. #If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m² IV, D1, 8, 15, Q3W, or nab-paclitaxel 100 mg/m² IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m² orally twice daily, D1–14, Q3W (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m² / eribulin 1.23 mg/m² IV, Day 1, 8, Q3W, or carboplatin AUC6 IV, D1, Q3W. ‖In the Dato-DXd vs ICC arm, 65% vs 72% of patients received any subsequent therapy in any treatment line; 14% vs 30% received a subsequent ADC (sacituzumab govitecan, sacituzumab tirumotecan, trastuzumab deruxtecan).

Dato-DXd = datopotamab deruxtecan

Dent RA et al. ESMO 2025;Abstract LBA21.

Phase III TROPION-Breast02: PFS by BICR



	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

Median PFS (95% CI)

10.8 mo (8.6–13.0)

5.6 mo (5.0–7.0)

Δ 5.3 mo*

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with ICC, reducing the risk of progression or death by 43%

Dent RA et al. ESMO 2025;Abstract LBA21.

Phase III TROPION-Breast02: OS

	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

Median OS (95% CI)

23.7 mo (19.8–25.6)

18.7 mo (16.0–21.8)

Δ 5.0 mo

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with ICC, reducing the risk of death by 21%

Dent RA et al. ESMO 2025;Abstract LBA21.

RTP RESEARCH TO PRACTICE

Phase III TROPION-Breast02: AEs of Special Interest for Dato-DXd

AESI category, n (%) Preferred term*	Dato-DXd (n=319)			ICC (n=309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis†	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events‡§	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis¶	1 (<1)	7 (2)	1 (<1)#	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 11 (3%), 36 (11%), and 0 patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 103/114 patients (90%) at data cutoff

Treatment-related ocular surface events:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 18 (6%), 14 (4%), and 3 (<1%) patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 49/73 patients (67%) at data cutoff

*Details for preferred terms included if reported in ≥20 patients in either arm. †Comprising the preferred terms of aphthous ulcer, mouth ulceration, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis. ‡Comprising the preferred terms of acquired corneal dystrophy, blepharitis, conjunctivitis, corneal disorder, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal lesion, corneal toxicity, dellen, dry eye, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, and xerophthalmia. §In the Dato-DXd arm only, ophthalmologic assessments were required every 3 cycles while on therapy; this was not required in the ICC arm. For all patients in both arms, ophthalmologic assessments were required at baseline, as clinically indicated, and at end of therapy. ¶Comprising the preferred terms of interstitial lung disease and pneumonitis. #Grade 5 – this event was characterised by the investigator as grade 3 pneumonitis, with death assessed as related to breast cancer.

Dent RA et al. ESMO 2025;Abstract LBA21.

Phase III TROPION-Breast02: Authors' Conclusions

- TROPION-Breast02 **met both dual primary endpoints**: first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvement in **OS and PFS** over ICC
  - OS HR 0.79 (95% CI 0.64–0.98); P=0.0291
  - PFS by BICR HR 0.57 (95% CI 0.47–0.69); P<0.0001
  - ≥5-month improvement in both median OS and PFS

TROPION-Breast02 enrolled patients who are **representative of the real-world** TNBC population, including those **often excluded from clinical trials** (e.g. 15% had DFI 0–6 months)

- The Dato-DXd **safety profile was manageable** and generally **consistent** with the known profile
  - Despite more than double the median duration of treatment, rates of grade ≥3 and serious TRAEs were similar, and discontinuations were lower, with Dato-DXd vs ICC

TROPION-Breast02 results support Dato-DXd as the new first-line standard of care for patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option

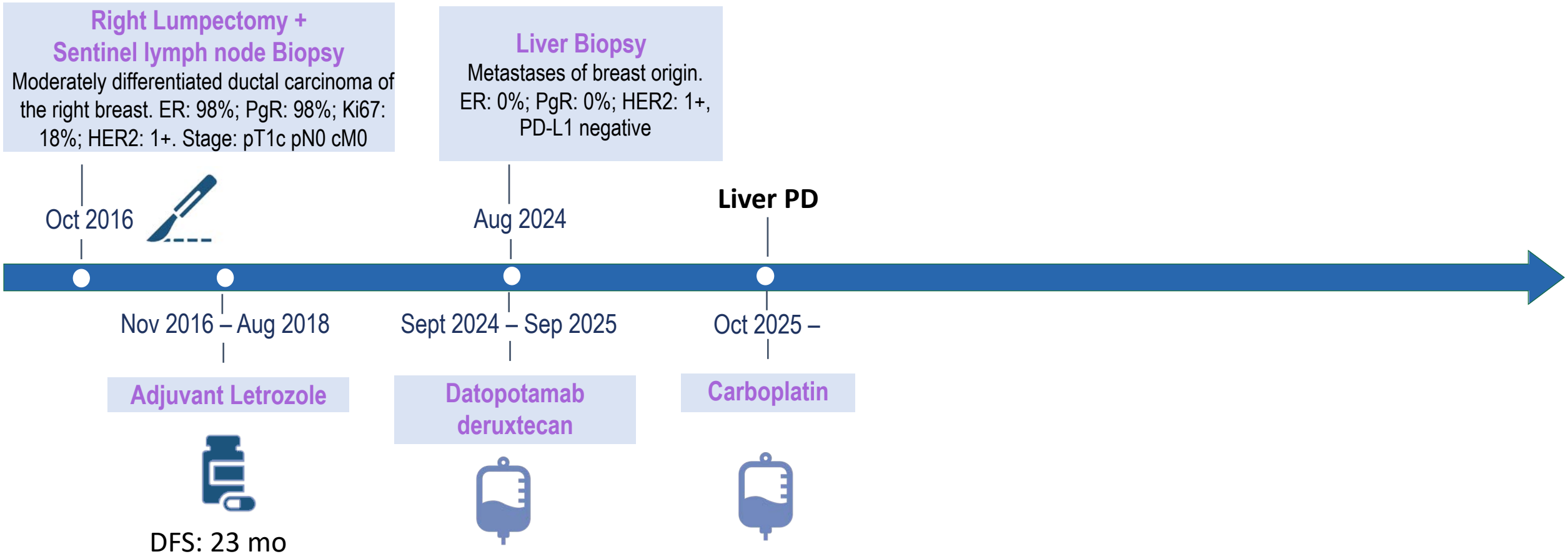
Dent RA et al. ESMO 2025;Abstract LBA21.

RTP RESEARCH TO PRACTICE

Prof Curigliano: Case Presentation #4

Clinical case

- 58 –year-old woman, Caucasian ethnicity
- BMI: 23, non-smoker, drinks socially, cephalosporins allergy, thalassemia minor
- Family history of cancer: mother with ovarian cancer

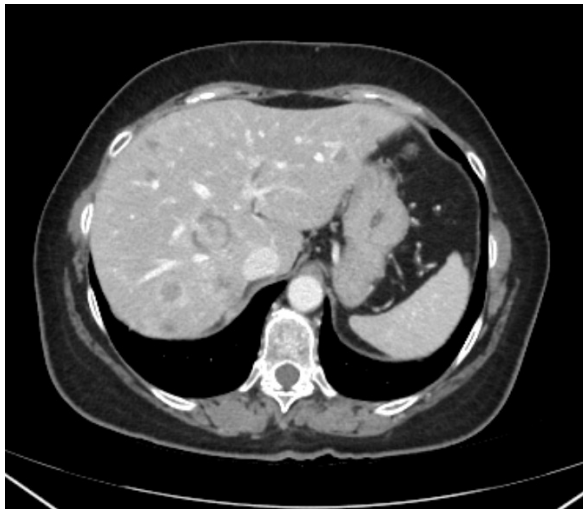


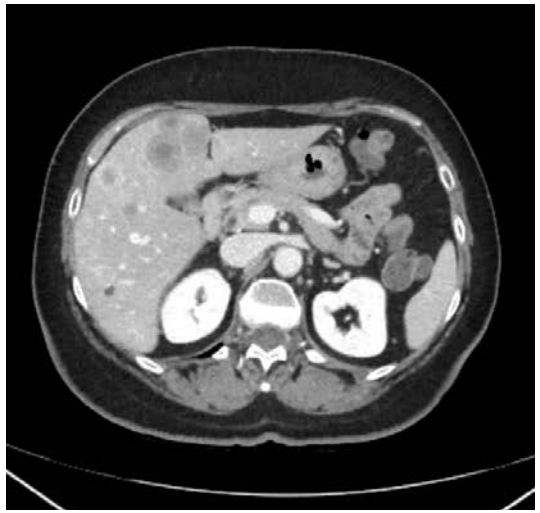
Prof Curigliano: Case Presentation #4 (Continued)

Clinical case

Dato-DXd
5.4 mg/Kg

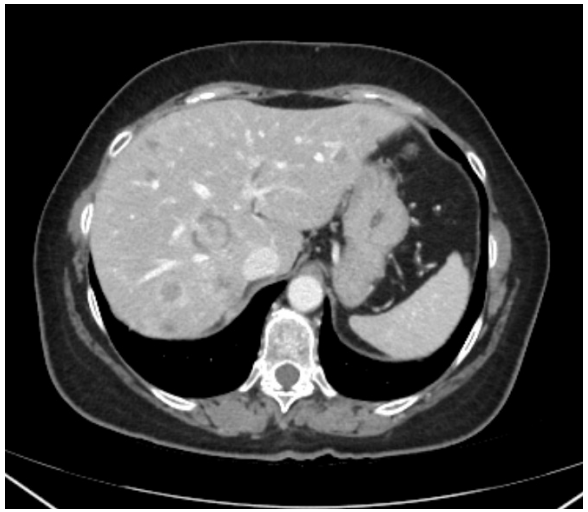
Sept 2024

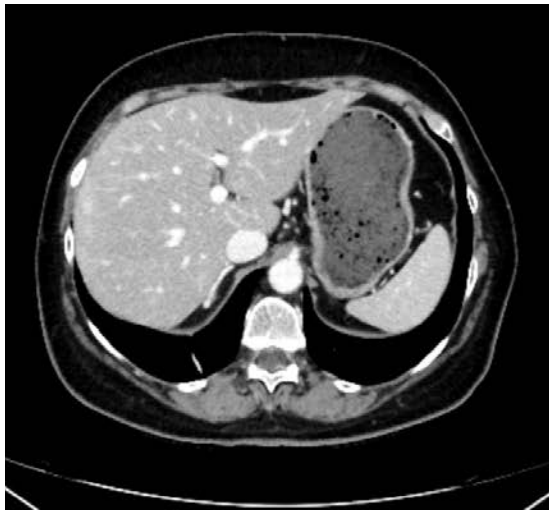


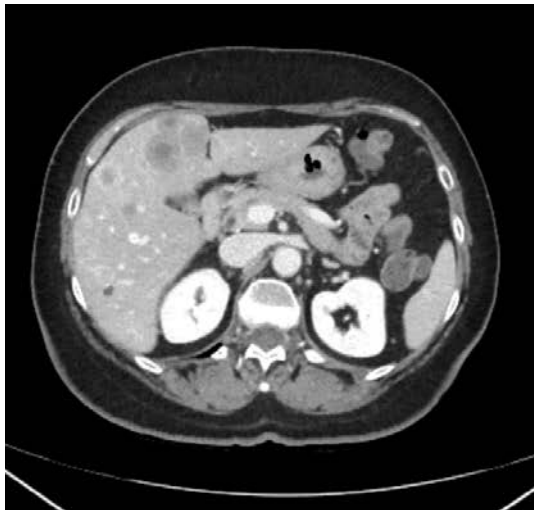


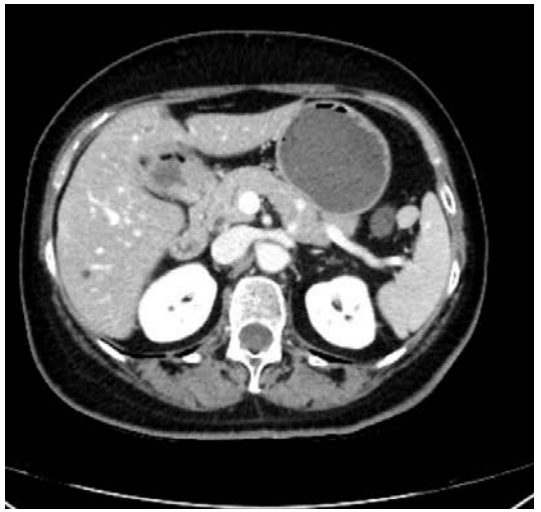
Prof Curigliano: Case Presentation #4 (Continued)

Clinical case



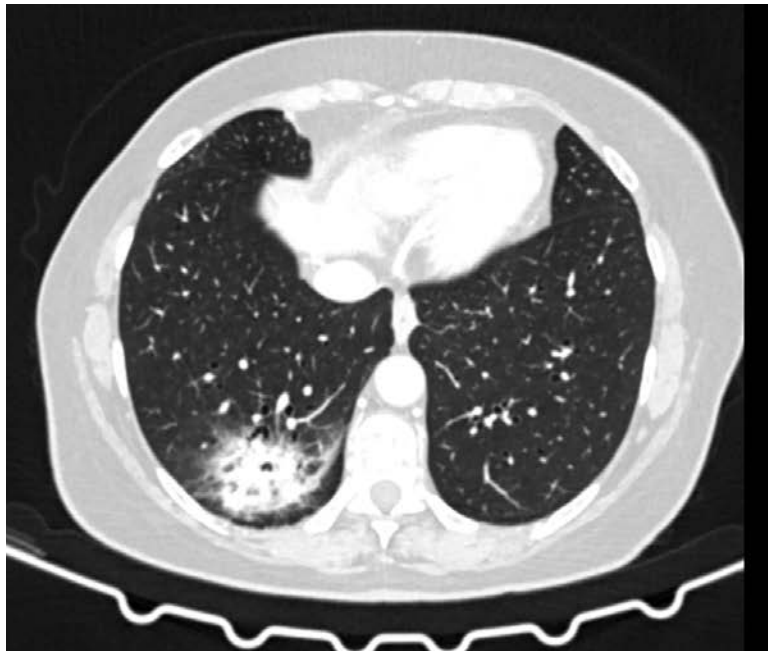






Prof Curigliano: Case Presentation #4 (Continued)

Clinical case

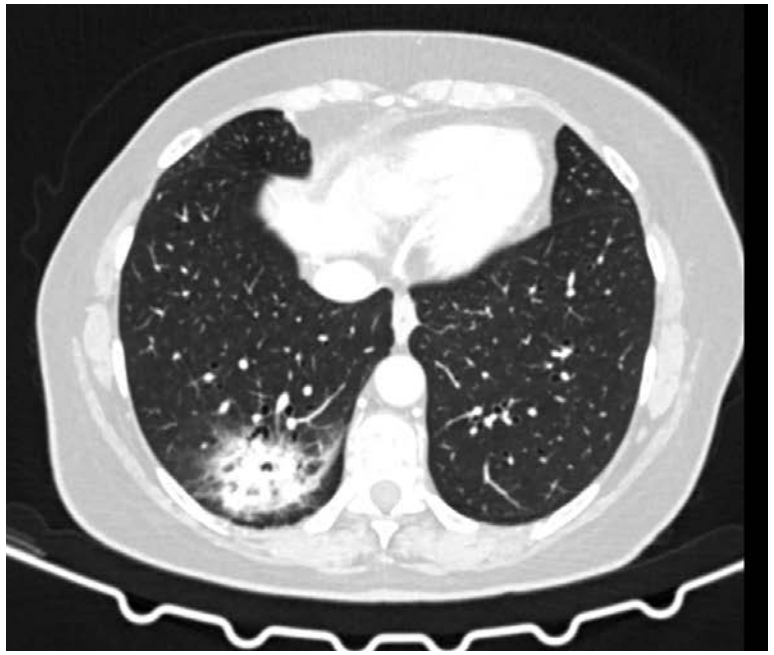


Oct 2024

No symptoms. SpO2: 98%

Prof Curigliano: Case Presentation #4 (Continued)

Clinical case

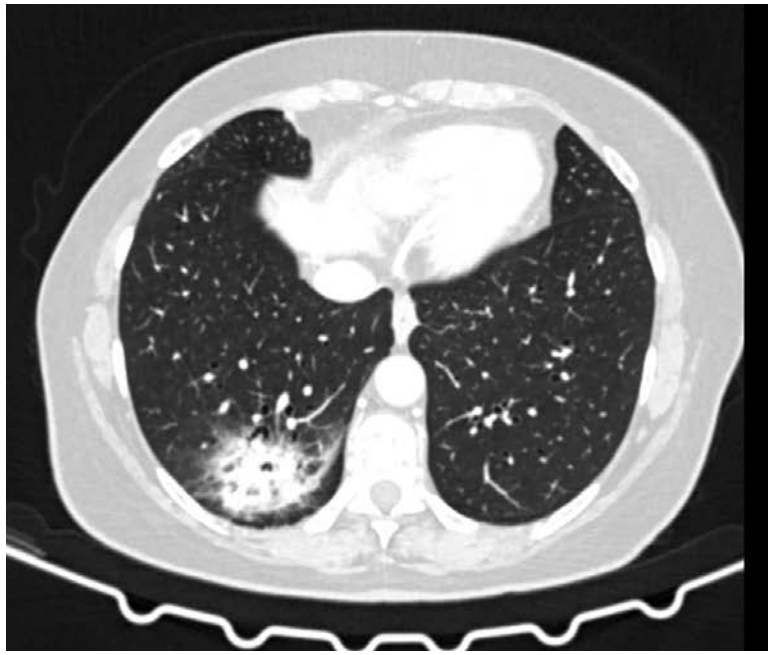


Oct 2022

No symptoms. SpO2: 98%
Dato-DXd interruption
Pulmonary function test in the normal range
Pulmonologist consultation

Prof Curigliano: Case Presentation #4 (Continued)

Clinical case



Oct 2022

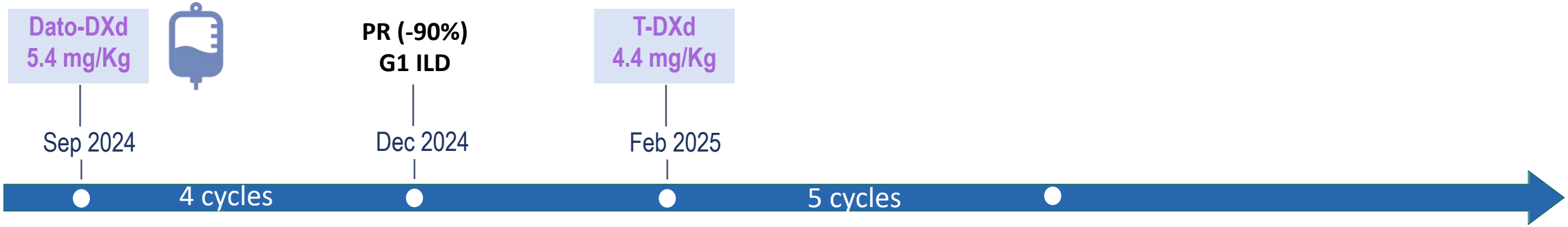
No symptoms. SpO2: 98%
Dato-DXd interruption
Pulmonary function test in the normal range
Pulmonologist consultation

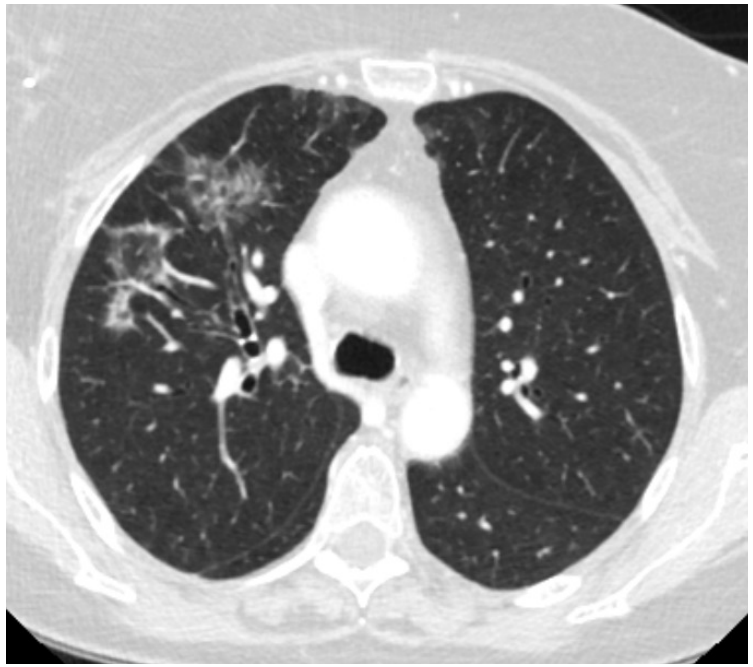
- Dexamethasone 4.5 mg/die for 10 days followed by tapering
- Levofloxacin 750 mg/die for 10 days

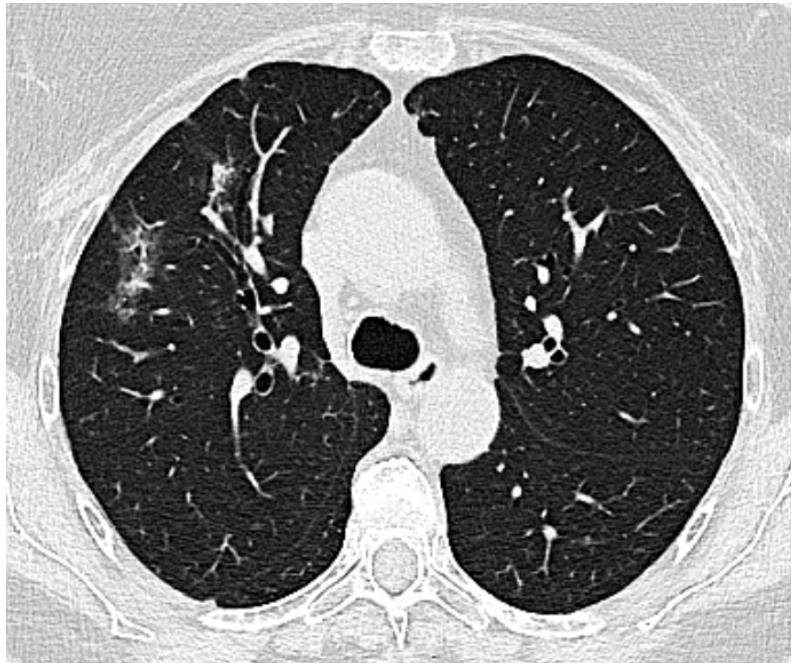
Chest HRCT follow-up after 10 days, and every month

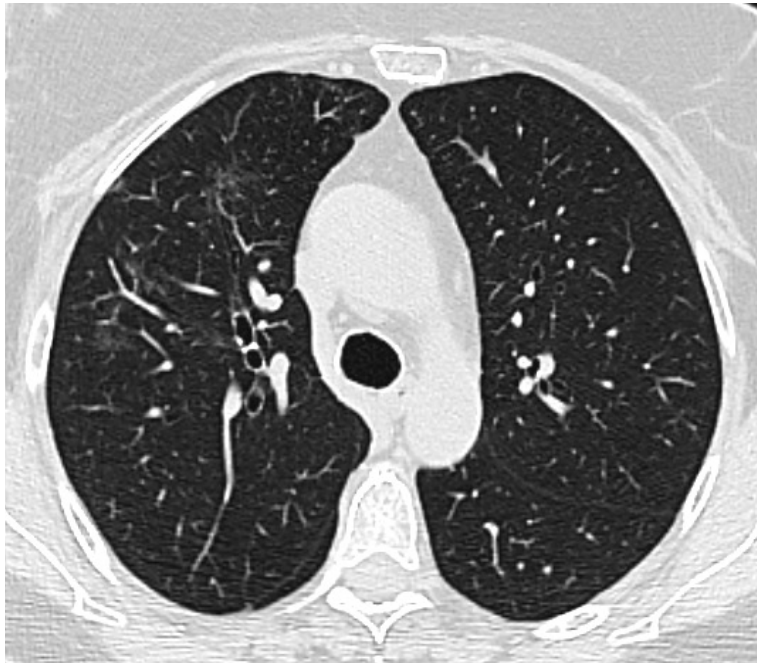
Prof Curigliano: Case Presentation #4 (Continued)

Clinical case









ER-Negative, HER2 (0 or low), PD-L1-positive mBC: Sequencing of Systemic Therapies

ER-negative, HER2-low, PD-L1-positive (immunotherapy)

- T-DXd versus TROP2-targeted ADC (sacituzumab govitecan, datopotamab deruxtecan)
- Capecitabine
- Other chemotherapy

ER-negative, HER2-negative, PD-L1-positive (immunotherapy)

- Sacituzumab govitecan versus datopotamab deruxtecan
- Capecitabine
- Other chemotherapy

Clinical factors:

- PS, comorbidities
- Tumor-related symptoms
- Visceral, CNS disease
- Prior systemic treatment

ER-Negative, HER2 (0 or low), PD-L1-negative mBC: Sequencing of Systemic Therapies

ER-negative, HER2-low, PD-L1-negative

- T-DXd versus TROP2-targeted ADC (sacituzumab govitecan, datopotamab deruxtecan)
- Capecitabine
- Other chemotherapy

ER-negative, HER2-negative, PD-L1-negative

- Sacituzumab govitecan versus datopotamab deruxtecan
- Capecitabine
- Other chemotherapy

Clinical factors:

- PS, comorbidities
- Tumor-related symptoms
- Visceral, CNS disease
- Prior systemic treatment

ILD Grading per CTCAE v.5

- **Grade 1**: asymptomatic
- **Grade 2**: symptomatic
- **Grade 3-4**: severe symptoms, O2 indicated

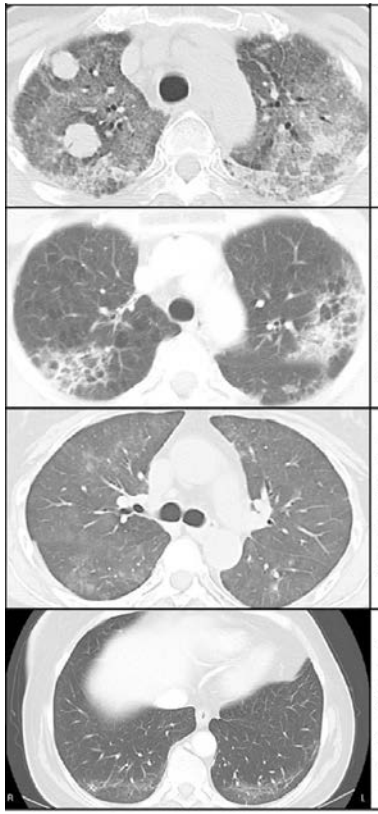
ILD: CT patterns

- The most common radiologic findings include widespread patchy consolidations and/or ground-glass opacities, with or without intralobular reticular opacity and septal thickening.

Imaging pattern	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Total	55 (42.3)	45 (34.6)	17 (13.1)	2 (1.5)	11 (8.5)	130 (100.0)
OP	43 (78.2)	28 (62.2)	7 (41.2)	1 (50.0)	3 (27.3)[a]	82 (63.1)
HP	9 (16.4)	12 (26.7)	1 (5.9)	0 (0.0)	0 (0.0)	22 (16.9)
DAD	0 (0.0)	1 (2.2)	9 (52.9)	1 (50.0)	8 (72.7)	19 (14.6)
NSIP	2 (3.6)	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.1)
Other[b]	1 (1.8)	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)

Data are shown as *n* (%)

DAD diffuse alveolar damage, *HP* hypersensitivity pneumonitis, *ILD/pneumonitis* interstitial lung disease or pneumonitis, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia



DAD pattern
A female patient in her 70s with unresectable breast cancer. Pulmonary metastases were visible at the right upper lobe (a). Widespread ground glass opacities with consolidation, subtle reticular shadows, and traction bronchiectasis were visible in the whole lung on the CT scan 6 days after onset (b).

OP pattern
A female patient in her 40s with unresectable breast cancer. No abnormal findings in the lung at baseline CT scan (a). Patchy ground glass opacities/consolidation were visible in the peripheral zone of the upper lobe of the bilateral lung (b).

HP pattern
A female patient in her 50s with unresectable breast cancer. No abnormal findings in the lung at baseline CT scan (a). Widespread and inhomogeneous ground glass opacities without traction bronchiectasis were visible in the CT scan at onset (b).

NSIP pattern
A female patient in her 60s with unresectable breast cancer. No abnormal findings in the lung at baseline CT scan (a). Ground glass opacities with traction bronchiectasis in bilateral peripheral area were visible in a basal predominant distribution on the CT scan 84 days after onset. (b).

Baba, IJCO 2023

ILD risk factors

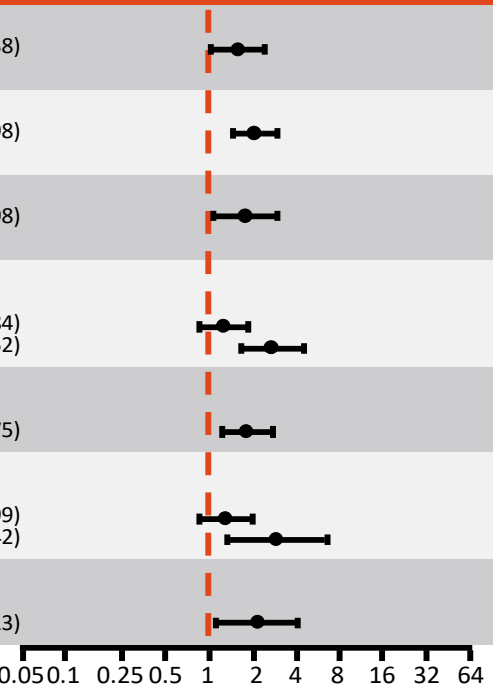
- **T-DXd associated risk factors**: age, enrollment in Japan, T-DXd dose, SpO2, moderate/severe renal impairment, presence of lung comorbidities (not including lung cancer), time since initial diagnosis

- Patients with severe lung comorbidities were not included in DESTINY trials

- **Screen lung diseases** (e.g., ILD, pneumonitis, pulmonary fibrosis, severe radiation pneumonitis, preexisting chronic lung condition requiring the use of corticosteroids within the past 6 months)
  - If the forced vital capacity or DLCO is ≤70% predicted and/or the HRCT findings are indicative of chronic lung conditions, the multidisciplinary team should be consulted

Subgroup Analysis

Potential risk factor	Patients, *n* (N=1150)	Hazard ratio* (95% CI)
Age Group		
<65 years	754	1.56 (1.02-2.38)
≥65 years	396	Ref
Country		
Japan	506	2.08 (1.45-2.98)
Non-Japan	644	Ref
Lung comorbidities†		
Yes	81	1.75 (1.03-2.98)
No	1069	Ref
Baseline renal function‡,§		
Normal	470	Ref
Mild Decrease	458	1.24 (0.83-1.84)
Moderate/Severe Decrease	196	2.73 (1.65-4.52)
Time since disease diagnosis‡		
0 to ≤4 years	624	Ref
>4 years	403	1.82 (1.20-2.75)
Dose		
5.4 mg/kg q3w	315	Ref
6.4 mg/kg q3w	808	1.30 (0.85-1.99)
>6.4 mg/kg q3w	27	2.92 (1.32-6.42)
Baseline SpO_2‡		
≥95%	1080	Ref
<95%	57	2.14 (1.11-4.13)



Powell, ESMO Open 2022

Risk factors

- There was an apparent association between moderate renal impairment at baseline and higher rates of ILD/pneumonitis and earlier onset (**Table 4**)

Table 4. Adjudicated Drug-Related ILD/pneumonitis in the T-DXd Pooled Safety Group According to Renal Status at Baseline

Renal Function Status	Pooled T-DXd (N = 1216)[a]		
	Normal[b] (n = 665)	Mild[c] (n = 417)	Moderate[d,e] (n = 128)
Adjudicated highest CTCAE grade, n (%)			
Any grade	75 (11.3)	48 (11.5)	31 (24.2)
Grade 1	21 (3.2)	13 (3.1)	6 (4.7)
Grade 2	42 (6.3)	30 (7.2)	20 (15.6)
Grade 3	8 (1.2)	2 (0.5)	1 (0.8)
Grade 4	0	0	0
Grade 5	4 (0.6)	3 (0.7)	4 (3.1)
Time to first adjudicated drug-related ILD/pneumonitis onset, median (range), days	250.0 (26-960)	165.5 (41-630)	126.0 (33-632)
Adjudicated drug-related ILD/pneumonitis associated with drug discontinuation, n (%)	54 (8.1)	36 (8.6)	24 (18.8)

[a]In DESTINY-Breast04, a protocol deviation and an error concerning laboratory migration resulted in data from 6 patients not being included in the subgroup analysis by renal impairment at baseline.
[b]CrCl, >90 mL/min.
[c]CrCl, 60-89 mL/min.
[d]CrCl, 30-59 mL/min in accordance with guidelines.[7,8]

Park, ESMO Breast 2024

Diagnosis

- No finding is pathognomonic for ILD, which makes it a **diagnosis of exclusion**
- **HRCT**
- **Pulse Oximetry**
- **Lab test**: CBC, liver and kidney function, electrolytes, CRP, ESR, PCT, LDH, additional infective analysis based on suspect (blood culture, expectorated sputum, urinary antigens, β-D glucan), tumor markers and autoimmune antibodies
- **Pulmonologist consultation**
- **Additional tests**:
  - ***Arterial blood gases***
  - ***Bronchoalveolar lavage***: lymphocytosis, eosinophilia, and/or neutrophilia, with the most frequent finding being lymphocytic alveolitis with the predominance of CD8+ cells.
  - ***Blood culture***
  - ***Pulmonary function testing*****:** restrictive pattern, with decreased total lung capacity, residual volume, vital capacity, and impaired diffusing capacity, based on the damage of the alveolar-capillary interface

Box. Other Causes of ILD Beyond Treatment With Anti-ERBB2 ADC

Progression of the underlying oncologic disease

Infective pneumonia (ie, bacterial, mycotic, and viral, including SARS-CoV-2)

Radiotherapy-induced pneumonitis

Other drug-induced lung toxic effect (ie, cancer drug or concomitant medication)

Smoking-related ILD

Cardiogenic pulmonary edema

Connective tissue disorders (eg, scleroderma, lupus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis/polymyositis, ankylosing spondylitis, and mixed connective tissue disease)

Occupational/environmental (eg, pneumoconiosis, anthracosis, asbestosis, silicosis, and hypersensitivity pneumonitis)

Vasculitis

Sarcoidosis

Pulmonary hemorrhage syndromes

Idiopathic interstitial fibrosis

Alveolar proteinosis

Amyloidosis

Bronchiolitis obliterans

Chronic eosinophilic pneumonia

Lymphocytic infiltrative lung disease

Tarantino, JAMA Oncology 2021

Grade 1 ILD management

- The administration of T-DXd must be interrupted
- Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks
- Monitor and weekly follow-up for onset of clinical symptoms and pulse oximetry
- Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
- T-DXd can be restarted in case of complete resolution of the event (ILD recovery period for T-DXd retreatment is 18 weeks in recent studies, if no progression of disease)
  - Same dose if resolved in ≤ 28 days from day of onset
  - -1 level if resolved in >28 days

Grade 2-4 ILD management

- Permanent discontinuation of T-DXd

G2	G3-4
• Prednisolone or equivalent (1 mg/kg/die) for at least 2 weeks, followed by gradual taper over at least 4 weeks • In case of worsening or no improvement observed in 3 to 5 days, increase the dose (2 mg/kg/d) and/or switch to IV methylprednisolone (2 mg/kg/d)	• Hospitalization • Methylprednisolone or equivalent (0.5-1 g/die) for 3 days, followed by prednisolone (1 mg/kg/die), for at least 2 weeks, followed by gradual taper over at least 4 weeks

- Oxygen supplementation according to SpO2
- Broad-spectrum antibiotics when an underlying infection cannot be ruled out
- In, corticosteroid-refractory cases, consider alternative etiologies or additional immunosuppressive agents (infliximab, mycophenolate mofetil, intravenous immunoglobulin, or cyclophosphamide)
- Re-image as clinically indicated

Practical Perspectives: Clinical Investigators Review Actual Cases of Patients with Advanced Gastroesophageal Cancers

A CME/MOC-Accredited Live Webinar

Tuesday, November 18, 2025
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Moderator

Neil Love, MD

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