DESTINY Breast11

2026 ESMO BREAST CANCER

Annual Congress

Residual cancer burden (RCB) following neoadjuvant treatment with trastuzumab deruxtecan (T-DXd) followed by paclitaxel + trastuzumab + pertuzumab (THP) vs dose-dense doxorubicin + cyclophosphamide followed by THP in high-risk, HER2+ early-stage breast cancer

Lajos Pusztai,[1] Nadia Harbeck,[2] Jean-François Boileau,[3] Shanu Modi,[4] Jiong Wu,[5] Shinji Ohno,[6] Jamil Asselah,[7] Santiago Escrivá-de-Romaní,[8] Atsushi Yoshida,[9] Sung Bae Kim,[10] Rubi Li,[11] Zhenzhen Liu,[12] Bogdan Żurawski,[13] Ling-Ming Tseng,[14,15] Giuseppe Curigliano,[16,17] Catherine Kelly,[18] Cuihong Zhang,[19] Shahana Safdar,[20] Fraser Symmans[21]

[1]Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA; [2]Breast Center, Department of OB&GYN, LMU University Hospital and CCC Munich, Munich, Germany; [3]Surgery and Gerald Bronfman Oncology, Segal Cancer Centre, Jewish General Hospital, McGill University, Montreal, QC, Canada; [4]Department of Medicine, Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; [6]Breast Thyroid Surgery, Sagara Hospital, Kagoshima, Japan; [7]Gerald Bronfman Department of Oncology, McGill University Health Centre, Cedars Cancer Center, Montreal, QC, Canada; [8]Medical Oncology Department, Breast Cancer Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9]Department of Breast Surgical Oncology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan; [10]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [11]Section of Medical Oncology, St. Luke's Medical Center, Quezon City, Philippines; [12]Department of Breast Disease, Henan Breast Cancer Centre, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [13]Department of Outpatient Chemotherapy, The F Łukaszczyk Oncology Center, Bydgoszcz, Poland; [14]Comprehensive Breast Health Center, Taipei Veterans General Hospital, Taipei, Taiwan; [15]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [16]European Institute of Oncology, IRCCS, Milan, Italy; [17]Department of Oncology and Hematology-Oncology, University of Milan, Milan, Italy; [18]Department of Medical Oncology, Mater Private Hospital & Cancer Trials Ireland Breast Group, Dublin, Ireland; [19]Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [20]Clinical Development, Late-Stage Oncology, Oncology R&D, AstraZeneca, Toronto, ON, Canada; [21]Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presentation LBA1; May 6, 2026.

Lajos Pusztai

ESMO

Disclosure information

Lajos Pusztai declares

- Consulting fees and honoraria for advisory board participation from AstraZeneca, Pfizer, Merck, Bristol-Myers Squibb, Stemline-Menarini, BeOne, Personalis, Natera, Agendia, Exact Sciences, and Radionetics

- Institutional research funding from Pfizer, AstraZeneca, Merck, Menarini-Stemline, Radionetics, and Exact Sciences

- Stock ownership in Fourion Inc and stock options in Ataraxis

DESTINY-Breast11: study design

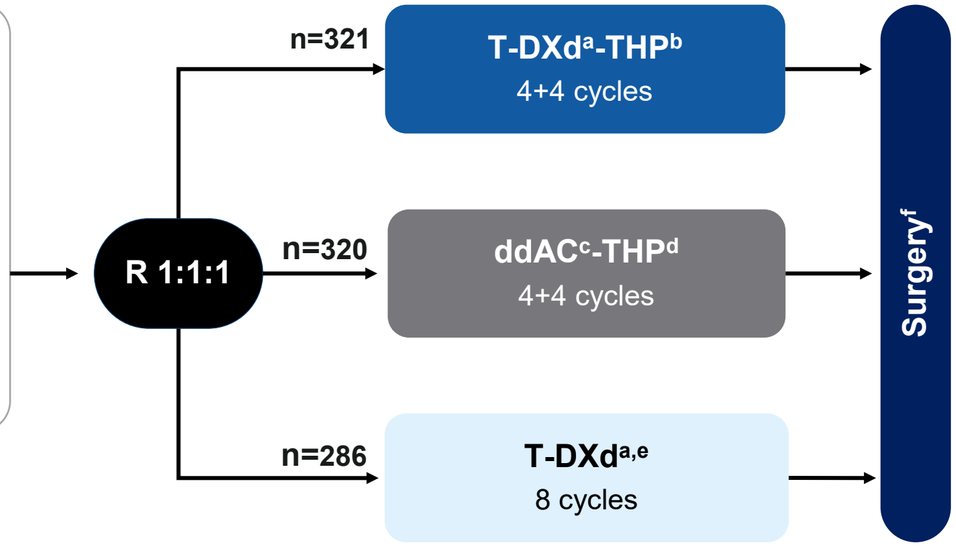
A randomized, global, multicenter, open-label, Phase III study (NCT05113251)[1]

Patient population:

- ≥18 years of age
- Previously untreated HER2-positive eBC
- Confirmed high-risk status, as defined as:
  - ≥cT3 and N0–3 or cT0–4 and N1–3
  - Inflammatory breast cancer

Stratification factors

- HR status: ER and/or PR-positive or -negative
- HER2 status: IHC 3+ or ISH+ in the absence of IHC 3+ status



Recommended post-neoadjuvant treatment per study protocol[g]:

- **pCR:** radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year
- **No pCR:** radiotherapy and T-DM1 for up to 14 cycles
- **HR-positive:** endocrine therapy

Data cut-off: March 12, 2025

Primary endpoint:

- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints:

- pCR (ypT0 ypN0) by blinded central review
- Event-free survival
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional pre-planned analysis:

- **Residual cancer burden (RCB)**

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 the end of treatment to assess left ventricular ejection fraction.

cT, clinical tumor stage; ddAC, dose-dense doxorubicin + cyclophosphamide; eBC, early breast cancer; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, *in situ* hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, nodal stage; pCR, pathological complete response; PR, progesterone receptor; R, randomization; RCB, residual cancer burden; QXW, every X weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab; 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.

[a]5.4 mg/kg Q3W. [b]Paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W). [c]Doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); [d]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). [e]The T-DXd alone arm closed on March 13, 2024, following an Independent Data Monitoring Committee recommendation. The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery. [f]The recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment. [g]Administered as part of the patient's standard of care at the investigator's discretion.

1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

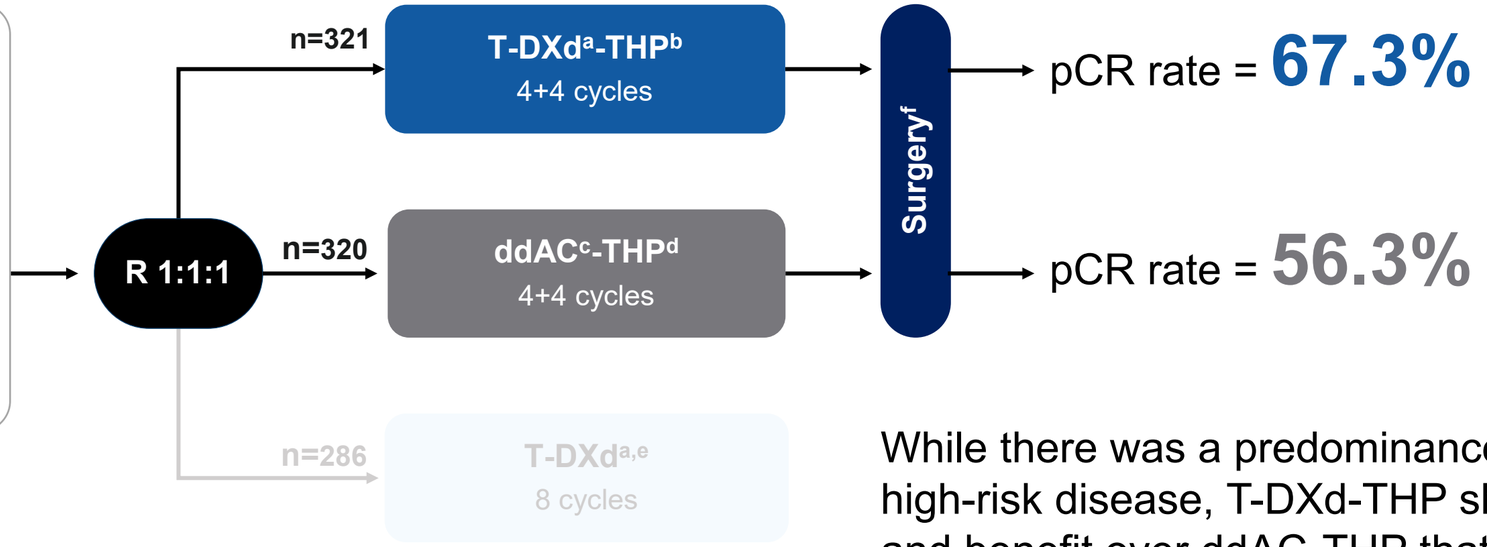
DESTINY-Breast11: primary endpoint[1]

Patient population:

- ≥18 years of age
- Previously untreated HER2-positive eBC
- Confirmed high-risk status, as defined as:
  - ≥cT3 and N0–3 or cT0–4 and N1–3
  - Inflammatory breast cancer

Stratification factors

- HR status: ER and/or PR-positive or -negative
- HER2 status: IHC 3+ or ISH+ in the absence of IHC 3+ status



Δ11.2%[g]

While there was a predominance of HR-positive and high-risk disease, T-DXd-THP showed a high pCR rate, and benefit over ddAC-THP that was independent of HR status and disease stage

T-DXd-THP had a favorable safety profile and showed a statistically significant and clinically meaningful improvement in pCR rate versus ddAC-THP[1]

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 the end of treatment to assess left ventricular ejection fraction.

[a]5.4 mg/kg Q3W. [b]Paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W). [c]Doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); [d]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). [e]The T-DXd alone arm closed on March 13, 2024, following the Independent Data Monitoring Committee recommendation. The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery. [f]The recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment. [g]Difference in pCR rates (%) calculated from stratified Miettinen and Nurminen's method.

1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

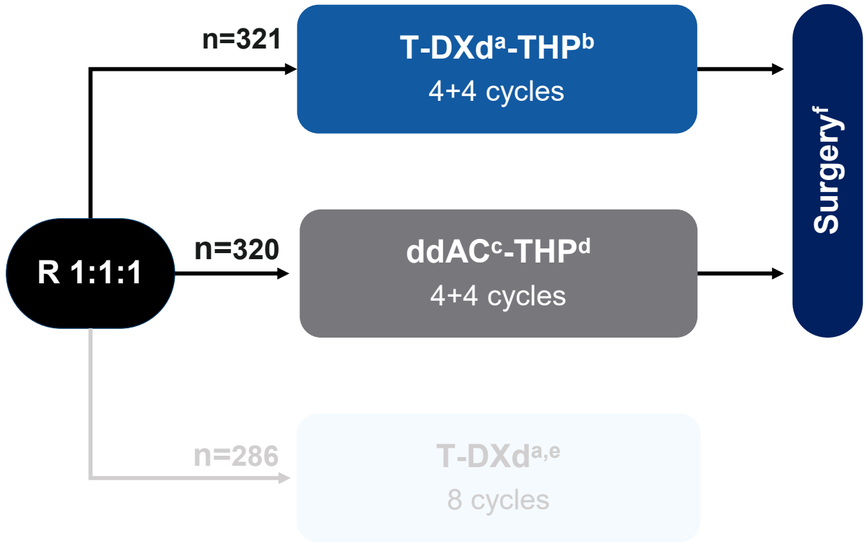
DESTINY-Breast11: additional pre-planned analysis

Patient population:

- ≥18 years of age
- Previously untreated HER2-positive eBC
- Confirmed high-risk status, as defined as:
  - ≥cT3 and N0–3 or cT0–4 and N1–3
  - Inflammatory breast cancer

Stratification factors

- HR status: ER and/or PR-positive or -negative
- HER2 status: IHC 3+ or ISH+ in the absence of IHC 3+ status



Residual cancer burden (RCB)

Data cut-off: March 12, 2025

Primary endpoint:

- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints:

- pCR (ypT0 ypN0) by blinded central review
- Event-free survival
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional pre-planned analysis:

- **Residual cancer burden (RCB)**

We now report additional RCB analyses from DESTINY-Breast11

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 the end of treatment to assess left ventricular ejection fraction.

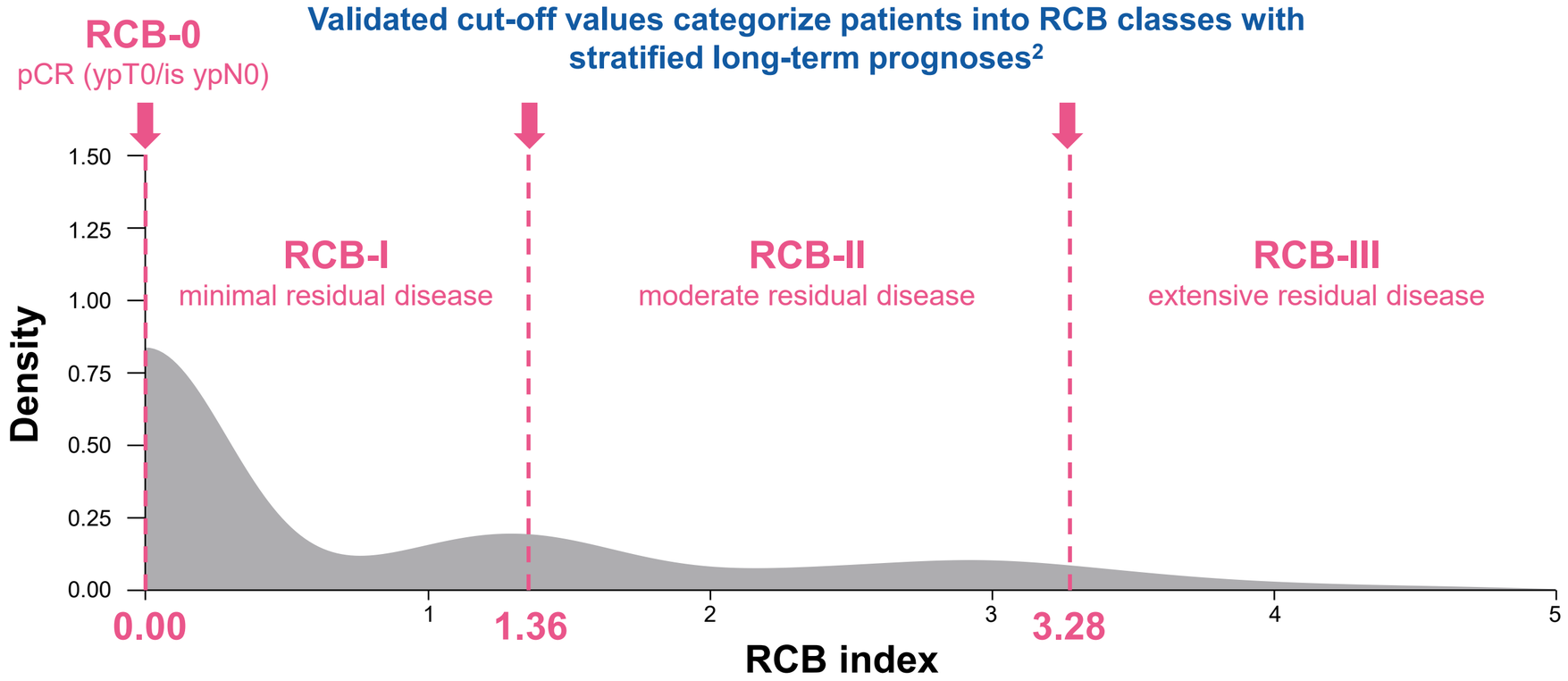
[a]5.4 mg/kg Q3W. [b]Paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W). [c]Doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); [d]Paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W). [e]The T-DXd alone arm closed on March 13, 2024, following the Independent Data Monitoring Committee recommendation. The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery. [f]The recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment.

1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

Residual cancer burden (RCB)[1]

- The RCB index provides a continuous, quantitative measure of residual invasive disease in the breast and axillary nodes after neoadjuvant chemotherapy[1–5]
- Categorization of patients by RCB class provides important prognostic information about patients with residual disease that is complementary to pCR assessment[1–3]



1. Symmans WF, et al. *J Clin Oncol* 2007;25:4414–4422. 2. Symmans WF, et al. *J Clin Oncol* 2017;35:1049–1060. 3. Yau C, et al. *Lancet Oncol* 2022;23:149–160. 4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2026. 5. College of American Pathologists. Protocol for the examination of resection specimens from patients with invasive carcinoma of the breast (2024). Available from https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates.

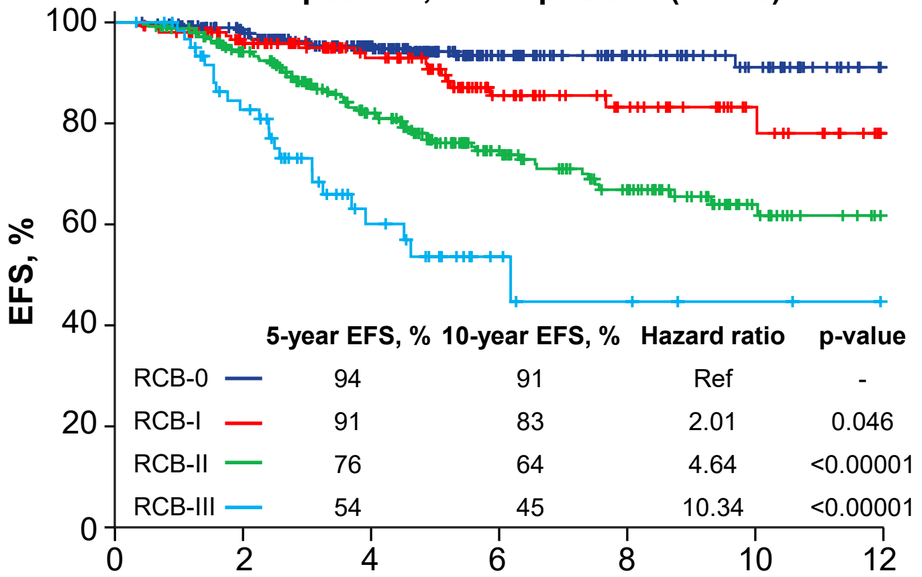
Lajos Pusztai

Lower RCB can predict improved long-term benefit

- Both RCB-0 and RCB-I are associated with meaningful EFS in HR-positive/HER2-positive and HR-positive/HER2-positive cancers[1–3]

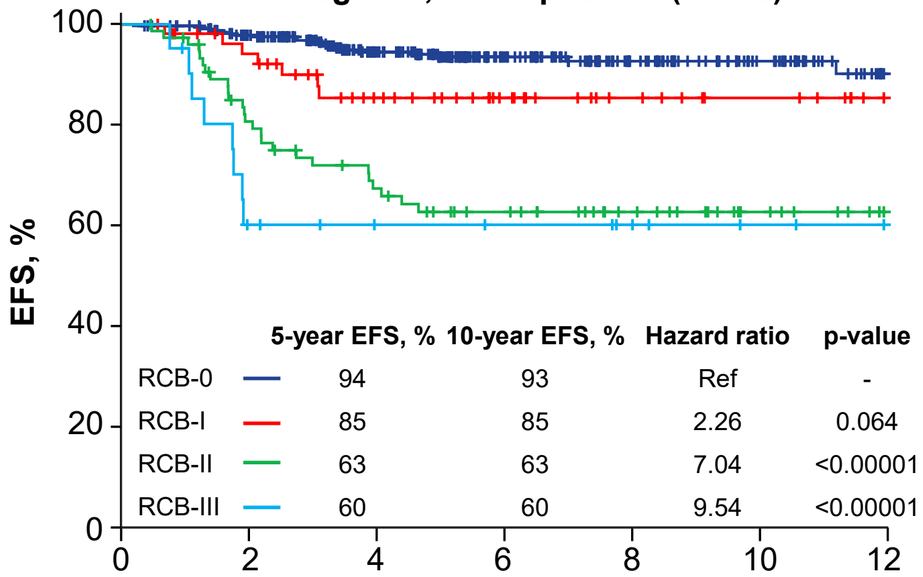
EFS after neoadjuvant HER2-targeted therapy (Yau C, et al. 2022)[3,a]

HR-positive, HER2-positive (n=756)[b]



	5-year EFS, %	10-year EFS, %	Hazard ratio	p-value
RCB-0	94	91	Ref	-
RCB-I	91	83	2.01	0.046
RCB-II	76	64	4.64	<0.00001
RCB-III	54	45	10.34	<0.00001

HR-negative, HER2-positive (n=488)[c]



	5-year EFS, %	10-year EFS, %	Hazard ratio	p-value
RCB-0	94	93	Ref	-
RCB-I	85	85	2.26	0.064
RCB-II	63	63	7.04	<0.00001
RCB-III	60	60	9.54	<0.00001

Time since start of neoadjuvant chemotherapy, years

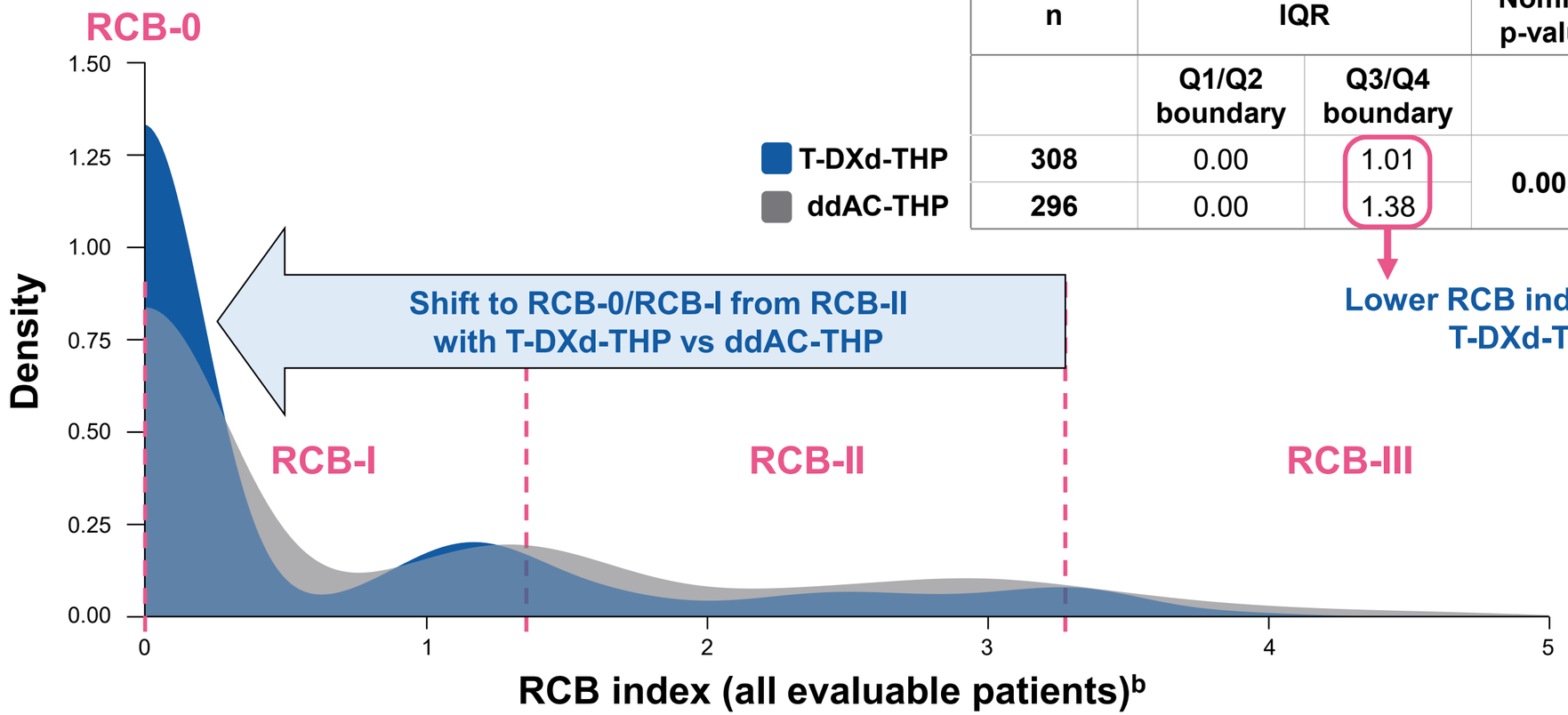
RCB-0/RCB-I status is a predictor of improved long-term outcomes

EFS, event-free survival.
[a]Figures reproduced from Yau C, et al. *Lancet Oncol* 2022;23:149–160, under the terms of the Creative Commons user license BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en). [©]The Authors. Published by Elsevier Ltd. [b]Median follow-up, 61 months. [C]Median follow-up, 65 months.
1. Symmans WF, et al. *J Clin Oncol* 2007;25:4414–4422. 2. Symmans WF, et al. *J Clin Oncol* 2017;35:1049–1060. 3. Yau C, et al. *Lancet Oncol* 2022;23:149–160.

Lajos Pusztai

Distribution of RCB index in DESTINY-Breast11

	All evaluable patients				Patients who did not achieve pCR (RCB >0)	
	n	IQR		Nominal p-value[a]	n	Median
		Q1/Q2 boundary	Q3/Q4 boundary			
T-DXd-THP	308	0.00	1.01	0.0059	87	1.5
ddAC-THP	296	0.00	1.38		112	1.7



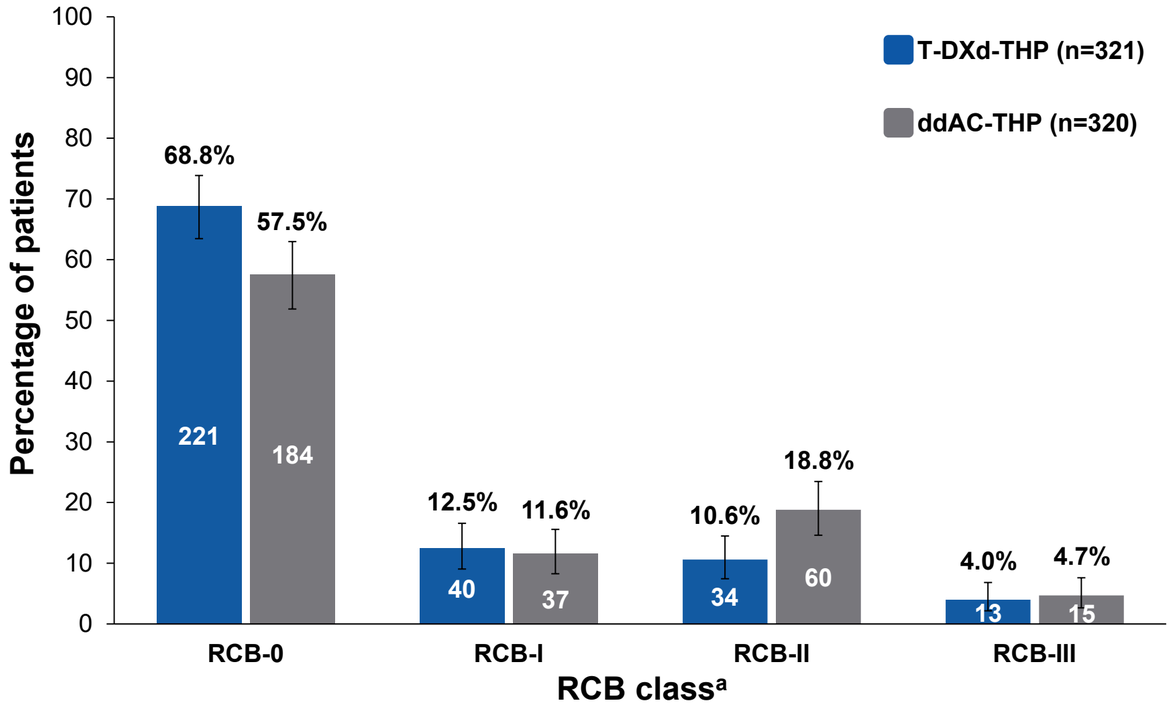
Lower RCB index = less residual disease with T-DXd-THP than with ddAC-THP

Overall, and among patients who did not achieve pCR, the distribution of RCB index indicated less residual disease with T-DXd-THP than with ddAC-THP

IQR, interquartile range; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.
[a]Wilcoxon rank sum test (*post hoc* analysis). [b]Assessed by blinded central review.

Lajos Pusztai

RCB class by treatment arm[1]



RCB class, n (%)[a]	T-DXd-THP (n=321)	ddAC-THP (n=320)	
RCB-0	221 (68.8)	184 (57.5)	
RCB-I	40 (12.5)	37 (11.6)	
RCB-II	34 (10.6)	60 (18.8)	Δ −8.2%[b]
RCB-III	13 (4.0)	15 (4.7)	
Combined RCB-0 and RCB-I	**261 (81.3)**	**221 (69.1)**	**Δ +12.2%[b]**

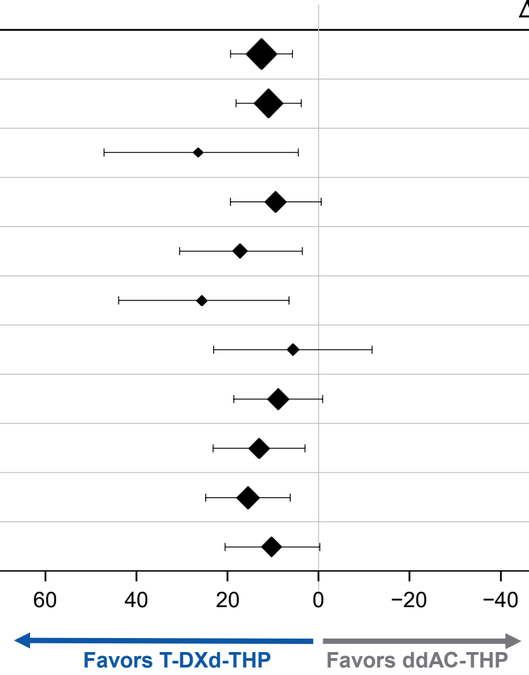
Improvement in the combined RCB-0 and RCB-I rate with T-DXd-THP versus ddAC-THP was primarily due to an increase in patients with RCB-0 and a decrease in patients with RCB-II

[a]Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters or any bridging/off-study neoadjuvant treatment. Hence, there may be differences between pCR rate and RCB=0. Missing RCB values for 13 patients in the T-DXd-THP arm and 24 patients in the ddAC-THP arm.
[b]Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method.
1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

Combined RCB-0 and RCB-I rates by demographics

		T-DXd-THP, n/N (%)	ddAC-THP, n/N (%)	Δ(RCB-0 and RCB-I) (95% CI)[a]
All patients		261/321 (81.3)	221/320 (69.1)	**12.2** (5.6,18.9)
Age at baseline	<65 years	229/282 (81.2)	203/288 (70.5)	**10.7** (3.7, 17.7)
	≥65 years	32/39 (82.1)	18/32 (56.3)	**25.8** (4.3, 45.9)
Geographical region	Asia	121/152 (79.6)	107/152 (70.4)	**9.2** (−0.6, 18.9)
	Western Europe	60/69 (87.0)	54/77 (70.1)	**16.8** (3.5, 29.8)
	North America	37/43 (86.0)	25/41 (61.0)	**25.1** (6.3, 42.8)
	Rest of the world[b]	43/57 (75.4)	35/50 (70.0)	**5.4** (−11.5, 22.5)
Race	Asian	127/160 (79.4)	111/157 (70.7)	**8.7** (−0.9, 18.2)
	White	117/140 (83.6)	97/137 (70.8)	**12.8** (2.9, 22.6)
Menopausal status	Pre-menopausal	152/184 (82.6)	110/163 (67.5)	**15.1** (6.1, 24.2)
	Post-menopausal	100/125 (80.0)	107/153 (69.9)	**10.1** (−0.3, 20.0)



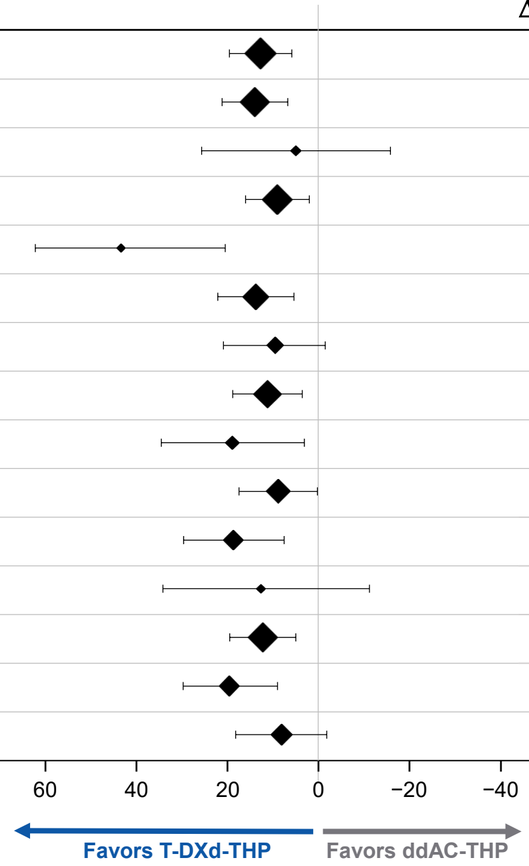
Consistent improvement in combined RCB-0 and RCB-I rates with T-DXd-THP versus ddAC-THP across all pre-specified subgroups

CI, confidence interval.
[a]Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters or any bridging/off-study neoadjuvant treatment. Hence, there may be differences between pCR rate and RCB=0. Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method. The size of the marker corresponds to the total subgroup size. [b]Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia.

Lajos Pusztai

Combined RCB-0 and RCB-I rates by clinical characteristics

		T-DXd-THP, n/N (%)	ddAC-THP, n/N (%)	Δ(RCB-0 and RCB-I) (95% CI)[a]
All patients		261/321 (81.3)	221/320 (69.1)	**12.2** (5.6,18.9)
ECOG PS score	0	231/278 (83.1)	195/280 (69.6)	**13.5** (6.5, 20.4)
	1	30/43 (69.8)	26/40 (65.0)	**4.8** (−15.4, 24.8)
HER2 status	IHC 3+	232/280 (82.9)	210/283 (74.2)	**8.7** (1.9, 15.4)
	Other[b]	29/40 (72.5)	11/36 (30.6)	**41.9** (19.7, 60.1)
HR status[1]	Positive	184/236 (78.0)	152/235 (64.7)	**13.3** (5.1, 21.3)
	Negative	75/83 (90.4)	69/85 (81.2)	**9.2** (−1.5, 20.1)
AJCC clinical stage	II–IIIA	202/248 (81.5)	183/259 (70.7)	**10.8** (3.4, 18.1)
	IIIB–IIIC	58/72 (80.6)	38/61 (62.3)	**18.3** (2.9, 33.3)
Clinical tumor stage	cT0–2	147/176 (83.5)	141/188 (75.0)	**8.5** (0.2, 16.8)
	cT3–4	114/145 (78.6)	80/132 (60.6)	**18.0** (7.2, 28.6)
Nodal status	N0	21/26 (80.8)	24/35 (68.6)	**12.2** (−10.9, 33.0)
	N+	234/287 (81.5)	196/281 (69.8)	**11.8** (4.8, 18.8)
Tumor grade	G1–2	110/134 (82.1)	98/155 (63.2)	**18.9** (8.6, 28.7)
	G3–4	126/153 (82.4)	97/130 (74.6)	**7.7** (−1.8, 17.5)

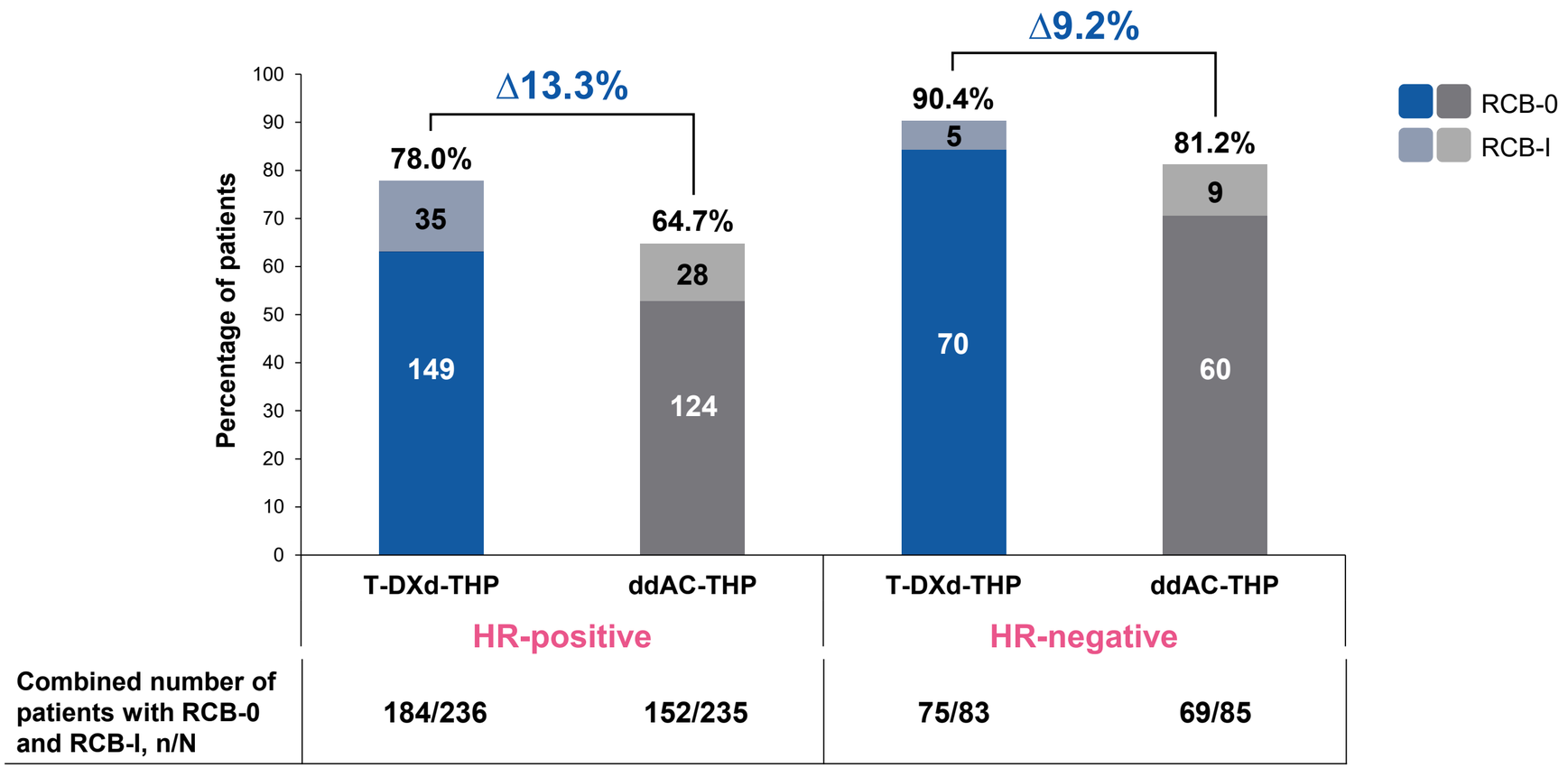


Consistent improvement in combined RCB-0 and RCB-I rates with T-DXd-THP versus ddAC-THP across all pre-specified subgroups

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade.
[a]Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters or any bridging/off-study neoadjuvant treatment. Hence, there may be differences between pCR rate and RCB=0. Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method. The size of the marker corresponds to the total subgroup size. [b]ISH+ in the absence of IHC 3+ status. 1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

Combined RCB-0 and RCB-I rates by HR status[a]



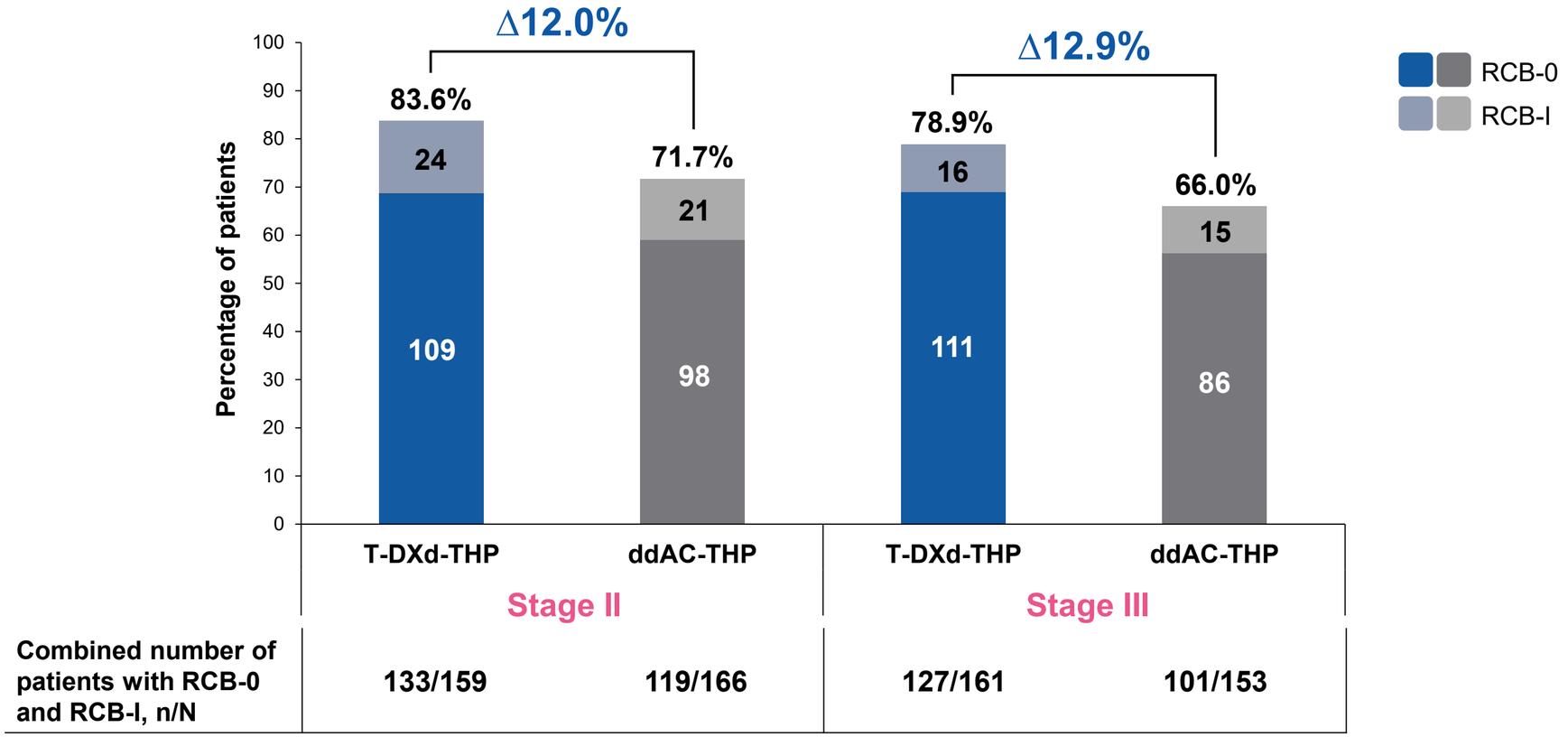
Combined RCB-0 and RCB-I rates were higher with T-DXd-THP than with ddAC-THP in patients with HR-positive and HR-negative disease

[a]Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters or any bridging/off-study neoadjuvant treatment. Hence, there may be differences between pCR rate and RCB=0. Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method.

1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179.

Lajos Pusztai

Combined RCB-0 and RCB-I rates by disease stage[a]

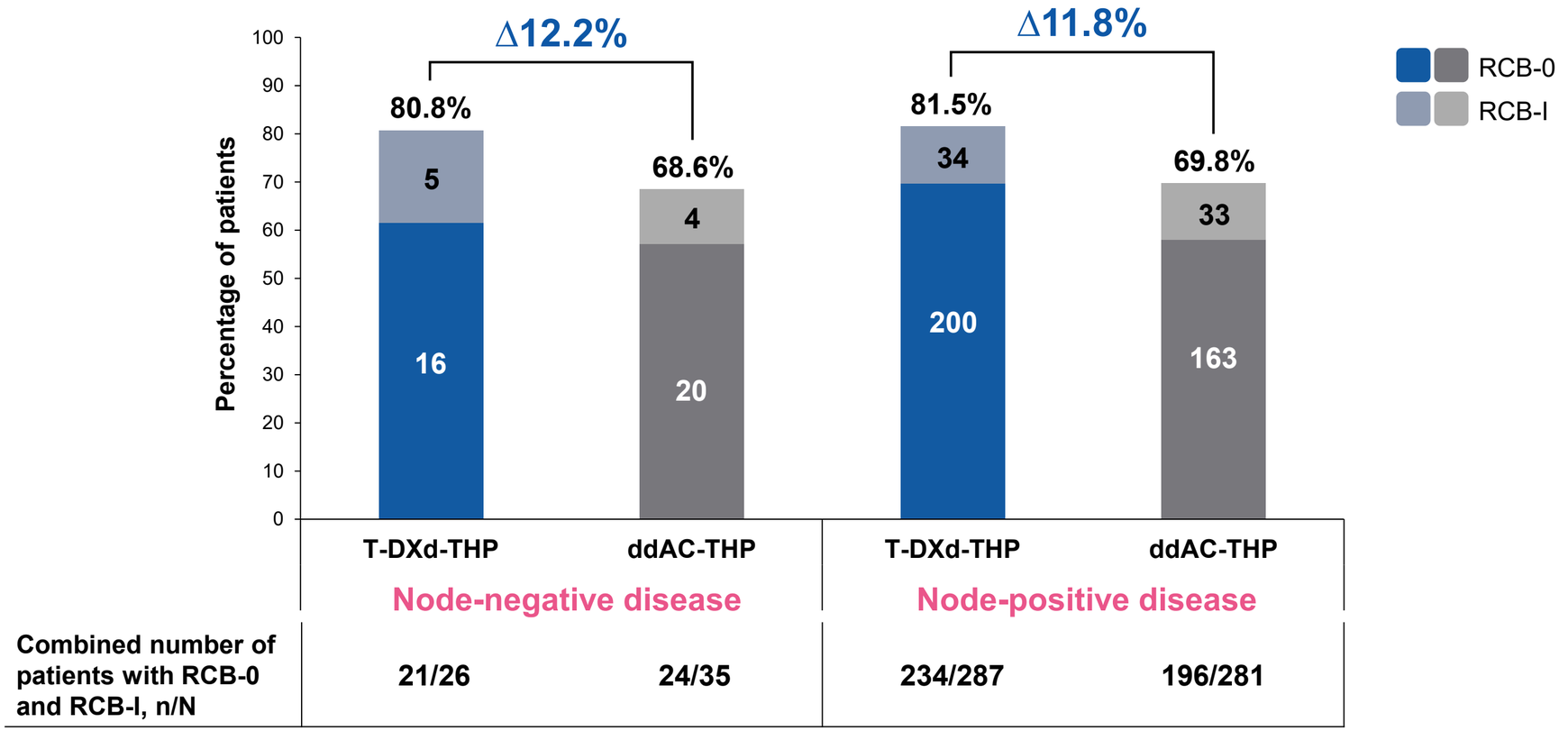


Combined RCB-0 and RCB-I rates were higher with T-DXd-THP than with ddAC-THP in patients with stage II and III disease

[a]*Post hoc* subgroup analysis. Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters or any bridging/off-study neoadjuvant treatment. Hence, there may be differences between pCR rate and RCB=0. Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method. Patients with T2/N0 status were not included in the stage II subgroup.

Lajos Pusztai

Combined RCB-0 and RCB-I rates by nodal stage[a]



Combined RCB-0 and RCB-I rates were higher with T-DXd-THP than with ddAC-THP in patients with node-positive and node-negative disease

[a]Unlike pCR results, RCB analysis is based on raw data and is not corrected for non-starters, or any bridging/off study neoadjuvant treatment. Hence there may be differences between pCR rate and RCB=0. Differences in rates (%) were calculated from unstratified Miettinen and Nurminen's method. Patients with T2/N0 status were not included in the stage II subgroup.

Lajos Pusztai

Conclusions

- In **DESTINY-Breast11**, an improved pCR rate and a favorable safety profile were demonstrated with neoadjuvant T-DXd-THP versus ddAC-THP[1]
- Analysis of the RCB index showed that the extent of residual disease was also reduced with T-DXd-THP versus ddAC-THP in patients who did not achieve pCR
    - Improvements were driven by an increase in patients with favorable RCB-0 and RCB-I classes, due to a shift from the RCB-II class
- The combined RCB-0 and RCB-I rate, a validated predictor of favorable long-term survival[2–4] that is complementary to pCR, was higher with T-DXd-THP versus ddAC-THP overall (81.3% vs 69.1%) and across all subgroups, irrespective of HR status, tumor size, nodal status, or disease stage
- These results reinforce the primary pCR analysis and demonstrate that T-DXd-THP is more effective than ddAC-THP for the neoadjuvant treatment of high-risk HER2-positive eBC[1]

Across all subgroups, residual disease was reduced with T-DXd-THP versus ddAC-THP, expanding the benefit to patients without pCR and supporting T-DXd-THP as neoadjuvant treatment for eligible patients with HER2-positive eBC

1. Harbeck N, et al. *Ann Oncol* 2026;37:166–179. 2. Symmans WF, et al. *J Clin Oncol* 2007;25:4414–4422. 3. Symmans WF, et al. *J Clin Oncol* 2017;35:1049–1060. 4. Yau C, et al. *Lancet Oncol* 2022;23:149–160.

Lajos Pusztai

Acknowledgments

Thank you

- Patients and their families for their participation
- Study-site staff for their contributions
- Members of the Independent Data Monitoring Committee and the Interstitial Lung Disease Adjudication Committee
- Labcorp Central Laboratory Services for pathology support

This study was sponsored by AstraZeneca and designed by AstraZeneca in collaboration with Daiichi Sankyo.

In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
Medical writing support was provided by Victoria Simms, PhD, from BOLDSCIENCE, Ltd., funded by AstraZeneca.

Scan the Quick Response (QR) code for a copy of this presentation