DESTINY-Breast06

HER2-low and HER2-ultralow status determination in HR+ metastatic breast cancer: DESTINY-Breast06

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On behalf of the DESTINY-Breast06 investigators

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Presenting Author Conflict OF Interest Self－Declaration Form

Presenting Author Name: **Junji Tsurutani**

	Applicability	If applicable, company name, etc.
(1) Position as an officer or advisor	No	
(2) Ownership of stock	No	
(3) Royalties or licensing fees	No	
(4) Honoraria, etc.	**Yes**	**Daiichi Sankyo, Eli Lilly, Kyowa Kirin**
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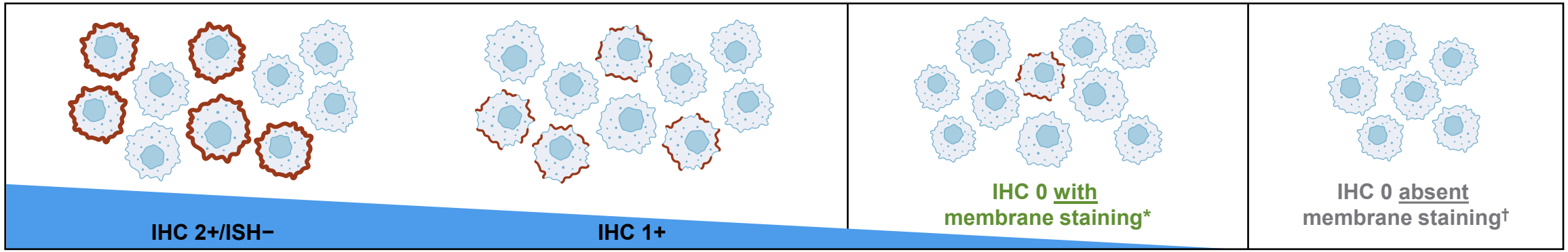
Targeting 'low' and 'ultralow' HER2-expressing tumors in mBC[1]

HER2 IHC categories within HR+, HER2-negative mBC (per ASCO/CAP[2]):

IHC 2+/ISH−	IHC 1+	IHC 0	
		Faint, incomplete membrane staining in ≤10% of tumor cells	Absent membrane staining
Weak-to-moderate complete membrane staining in >10% of tumor cells	Faint, incomplete membrane staining in >10% of tumor cells		



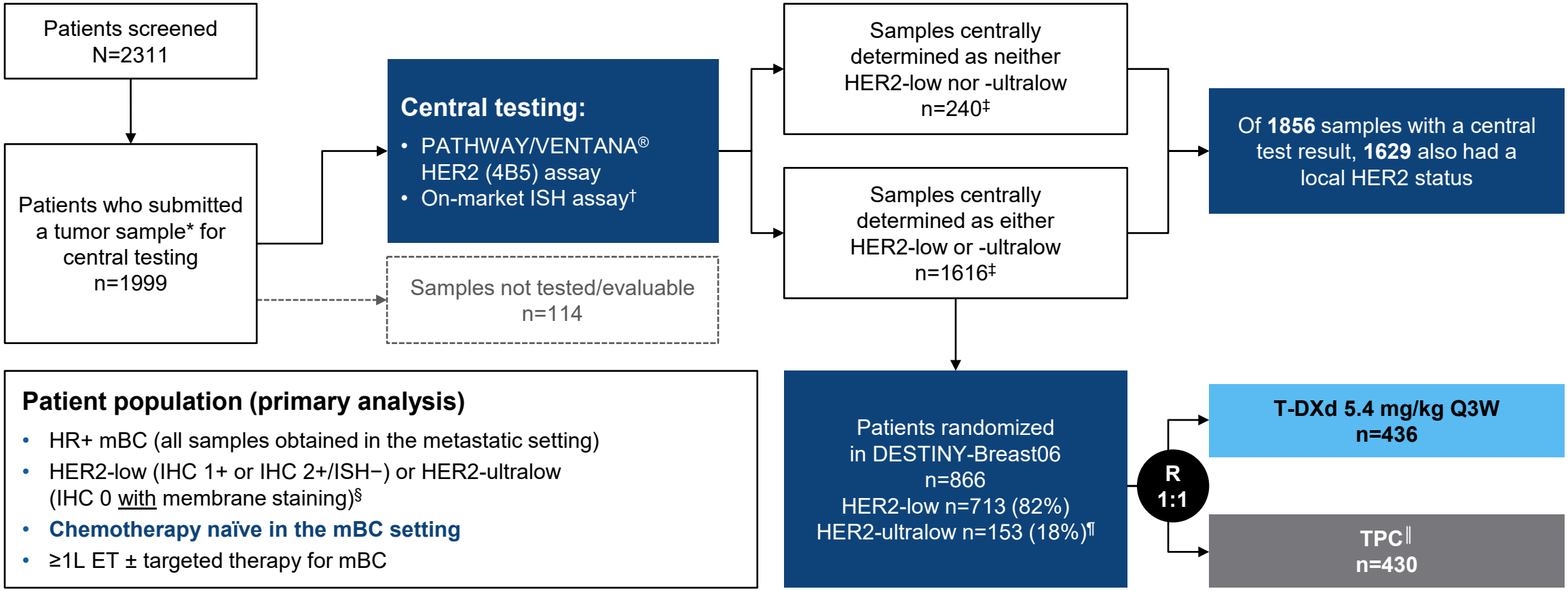
HER2-low ~60–65%[3,4] | **HER2-ultralow* ~20–25%[3–5]**

DESTINY-Breast06 patient population: ~85% of HR+, HER2-negative mBC

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/
*HER2-ultralow – ie HER2 IHC 0 with membrane staining of any intensity in ≤10% of tumor cells – was referred to as HER2 IHC >0 to <1+ in the DESTINY-Breast06 protocol; †no membrane staining is observed
ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; mBC, metastatic breast cancer

1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 3. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161;
4. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 5. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):e13156 (Abstract)

Study design



Patient population (primary analysis)

- HR+ mBC (all samples obtained in the metastatic setting)
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)§
- **Chemotherapy naïve in the mBC setting**
- ≥1L ET ± targeted therapy for mBC

Central testing was performed at Labcorp Geneva, Switzerland; Labcorp Los Angeles, CA, US; and Labcorp Shanghai, China
*In DESTINY-Breast06, the primary tumor samples were breast or regional lymph node samples obtained from patients who had confirmed metastatic disease (ie in the metastatic setting); †Ventana on-market ISH assay at central laboratory; ‡samples not evaluable by ISH excluded; §study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as membrane staining in ≤10% of tumor cells (also known as IHC >0 to <1+). The ITT population comprised HER2-low and HER2-ultralow; ¶HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‖options were capecitabine, nab-paclitaxel, paclitaxel
1L, first line; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Tumor sample characteristics

Sample location

Primary (breast):
sample obtained in the metastatic setting from the primary tumor

Metastatic:
sample obtained from site of metastasis

Characteristics, n (%)	Total screened patients (N=2311)	Randomized patients (n=866)
Region		
America	145 (6.3)	44 (5.1)
Europe	962 (41.6)	440 (50.8)
Asia (excluding China)	409 (17.7)	198 (22.9)
China	242 (10.5)	98 (11.3)
Rest of the world	241 (10.4)	86 (9.9)
Missing	312 (13.5)	0
Tumor location*		
Primary	462 (20.0)	192 (22.2)
Metastatic	**1537 (66.5)**	674 (77.8)
Missing	312 (13.5)	0
Specimen collection type		
Biopsy	1759 (76.1)	764 (88.2)
Excision/resection	240 (10.4)	102 (11.8)
Missing	312 (13.5)	0
Local HER2 IHC test type†		
PATHWAY/VENTANA® HER2 (4B5) assay (Roche Diagnostics)	543 (23.5)	228 (26.3)
HercepTest™ (Agilent)	322 (13.9)	149 (17.2)
Bond Oracle HER2 IHC system (Leica Biosystems)	27 (1.2)	13 (1.5)
Other	62 (2.7)	25 (2.9)
Laboratory-developed test	20 (0.9)	12 (1.4)
Unknown	**1039 (45.0)**	417 (48.2)
Missing	298 (12.9)	22 (2.5)
Sample age		
Up to 6 months	957 (41.4)	451 (52.1)
6 months to 1 year	231 (10.0)	92 (10.6)
1 to 3 years	543 (23.5)	224 (25.9)
>3 years	268 (11.6)	99 (11.4)
Missing	312 (13.5)	0

*In DESTINY-Breast06, the primary tumor samples were breast or regional lymph node samples obtained from patients who had confirmed metastatic disease (ie in the metastatic setting); †local test results were not used for selection or stratification but were captured because patients were required to have a history of HER2-negative status for inclusion in the study
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry

Central HER2 IHC score prevalence consistent across key variables in the population locally scored as HER2-negative

Variable, n (%)	IHC 0 absent membrane staining*	HER2-ultralow (IHC 0 with membrane staining)†	IHC 1+	IHC 2+/ISH−	IHC 2+/ISH+	IHC 3+	Total
Overall	**225 (12)**	**402 (22)**	**829 (45)**	**385 (21)**	**11 (<1)**	**4 (<1)**	**1856**
Sample type							
Biopsy	202 (12)	344 (21)	729 (45)	338 (21)	8 (<1)	4 (<1)	1625
Resection	23 (10)	58 (25)	100 (43)	47 (20)	3 (1)	0	231
Sample age							
<3 months	83 (11)	133 (18)	362 (48)	168 (22)	3 (<1)	1 (<1)	750
3 to ≤6 months	14 (10)	31 (22)	59 (42)	35 (25)	3 (2)	0	142
>6 months to ≤12 months	23 (10)	44 (20)	100 (45)	50 (23)	1 (<1)	2 (<1)	220
>1 to ≤3 years	62 (13)	126 (26)	208 (42)	95 (18)	2 (<1)	1 (<1)	494
>3 years	43 (17)	68 (27)	100 (40)	37 (15)	2 (1)	0	250

No difference in prevalence observed between

- **Primary vs metastatic sample site**‡
- **Region** (America, Europe, Asia [excluding China], China)

*No membrane staining is observed; †staining of the membrane in ≤10% of the cancer cells; ‡primary tumor samples were breast or regional lymph node samples obtained from patients who had confirmed metastatic disease (ie in the metastatic setting)
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization

Concordance between central and local results

Results from central scoring

- Of samples scored as HER2-low locally, **94%** met DESTINY-Breast06 inclusion criteria (were either **HER2-low** or **HER2-ultralow** by central testing)
- **Overall percent agreement** was **77.8%** for HER2-low*
- Of samples scored as IHC 0 locally, central testing found
  - 35% were IHC 0 absent membrane staining
  - **40%** were **HER2-ultralow**
  - **24%** were **HER2-low**

64% with membrane staining

Central vs local HER2 scores in patients screened for DESTINY-Breast06†

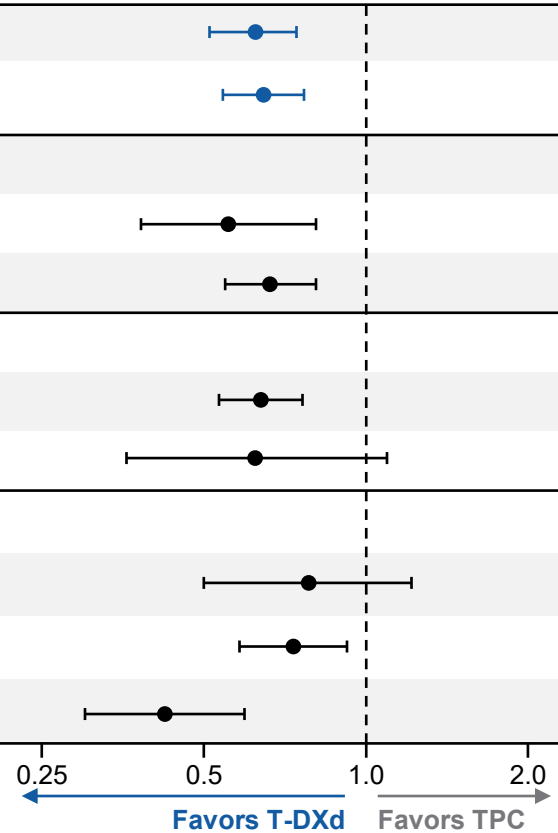
HER2 status by central testing, n		HER2 status by local result, n				
		IHC 0†	HER2-low	IHC 2+/ISH+	IHC 3+	Total
IHC 0†	Absent membrane staining‡	123	65	0	1	189
	With membrane staining (HER2-ultralow)§	140	196	2	1	339
HER2-low		85	999	6	0	1090
IHC 2+/ISH+		1	7	0	0	8
IHC 3+		0	3	0	0	3
Total		349	1270	8	2	1629

Note: The sample used for central testing may not have been the same as that used for the local test result

*Agreement was assessed between central and local laboratories determining if samples were 'HER2-low' or 'not HER2-low' and overall percent agreement was calculated as the total number of samples that agreed divided by the total number of tests. Agreement was not calculated for HER2-ultralow because separating IHC 0 into 'absent membrane staining' and 'with membrane staining' at local sites was not part of standard practice; †per American Society of Clinical Oncology / College of American Pathologists 2018 guidelines; ‡no membrane staining is observed; §staining of the membrane in ≤10% of the cancer cells
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH+, in situ hybridization–positive

PFS (BICR) in ITT by tumor sample characteristics and IHC score

Subgroup	Number of events / patients (%)		Median, months (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
HER2-low (primary endpoint)	225/359 (62.7)	232/354 (65.5)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)	0.62 (0.51, 0.74)
ITT (ie HER2-low and HER2-ultralow) (secondary endpoint)	269/436 (61.7)	271/430 (63.0)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)	0.63 (0.53, 0.75)
Tumor location*					
Primary	55/93 (59.1)	63/99 (63.6)	14.9 (9.8, 19.4)	7.9 (5.8, 9.7)	0.55 (0.38, 0.80)
Metastatic	214/343 (62.4)	208/331 (62.8)	13.2 (12.0, 15.2)	8.1 (7.0, 9.5)	0.66 (0.55, 0.80)
Specimen collection type					
Biopsy	232/375 (61.9)	249/389 (64.0)	13.1 (11.3, 15.2)	8.1 (6.9, 9.3)	0.63 (0.53, 0.76)
Excision/resection	37/61 (60.7)	22/41 (53.7)	16.4 (9.7, 19.5)	8.3 (6.9, 18.1)	0.62 (0.36, 1.08)
HER2 IHC expression					
IHC 0 with membrane staining	44/76 (57.9)	39/76 (51.3)	13.2 (9.8, 17.3)	8.3 (5.8, 15.2)	0.78 (0.50, 1.21)
IHC 1+	157/239 (65.7)	150/234 (64.1)	13.1 (11.0, 15.2)	8.2 (7.1, 9.8)	0.73 (0.59, 0.92)
IHC 2+/ISH−	65/117 (55.6)	80/118 (67.8)	15.2 (12.2, 21.4)	7.0 (6.2, 8.4)	0.43 (0.31, 0.60)



*Primary tumor samples were breast or regional lymph node samples obtained from patients who had confirmed metastatic disease (ie in the metastatic setting)
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; ITT, intent-to-treat; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Conclusions and future directions

- Patients with HR+, HER2-low or HER2-ultralow mBC derived clinically meaningful benefit from T-DXd vs TPC
- Patients likely to benefit from T-DXd could be identified regardless of sample type or location
- Overall percent agreement for HER2-low between local and central results was **78%**
  - Almost all (**94%**) of patients with a local HER2-low score were centrally scored as either HER2-low or HER2-ultralow and hence were eligible to participate in DESTINY-Breast06
- A majority (**64%**) of patients with a local HER2 IHC 0 score were centrally scored as HER2-low (**24%**) or HER2-ultralow (**40%**)
  - It may be advisable for patients with HR+ mBC scored as HER2 IHC 0 to be reassessed to determine if they may be eligible for treatment with T-DXd
- Increased awareness of low HER2 expression levels is desirable

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

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ORIGINAL ARTICLE

Analytical and clinical validation of PATHWAY HER2 (4B5) assay for assessment of HER2-low/HER2-ultralow status and eligibility for trastuzumab deruxtecan in DESTINY-Breast06

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