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Post-T-DXd treatment in patients with HER2-positive metastatic breast cancer: A multicenter cohort study (EN-SEMBLE)

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Conflict of interest disclosure slide for representative speakers or investigators

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Background

- Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate that comprises an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody linked by a tetrapeptide-based cleavable linker to a novel cytotoxic topoisomerase I inhibitor payload.

- Based on the results of DESTINY-Breast02 (NCT03523585), T-DXd has been approved for adults with unresectable or metastatic HER2-positive breast cancer who have previously received at least one prior anti-HER2-based regimen approved in multiple countries.

- T-DXd is the preferred 2nd-line treatment regimen for HER2-positive metastatic breast cancer in the ESMO and NCCN guidelines; however, there are unexplored unmet medical needs in post-T-DXd therapy.

- Determining optimal treatment regimens after discontinuation of T-DXd due to adverse events such as interstitial lung disease (ILD) or progressive disease (PD) is an important clinical issue.

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

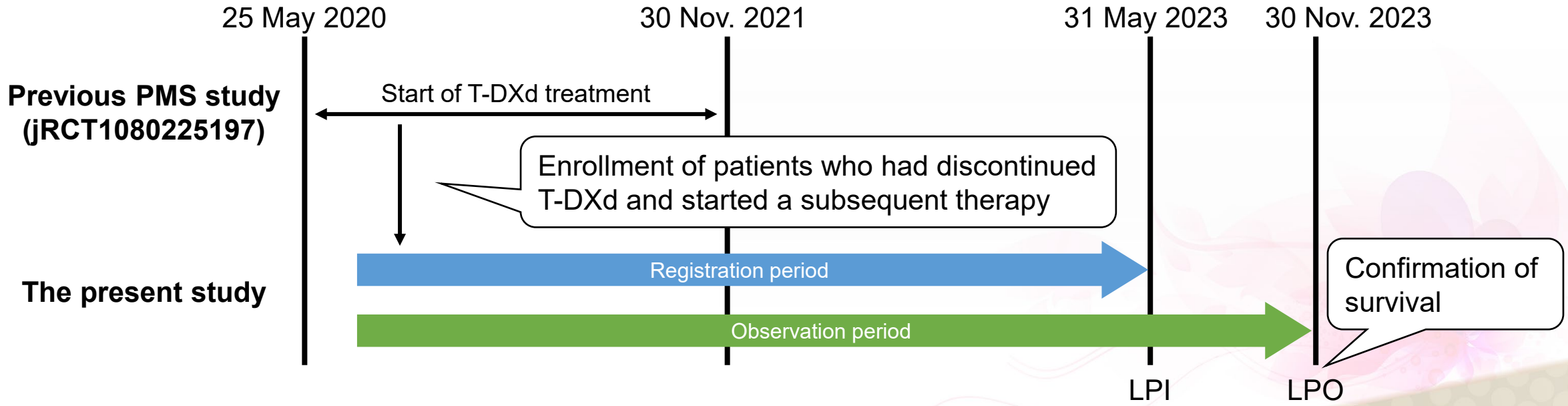
Objective

The EN-SEMBLE study was designed to investigate the treatment regimens undergone after discontinuation of T-DXd, and their effectiveness and safety.

Today, as an interim analysis, we present data on the distribution of post-T-DXd treatment regimens.

Summary of the EN-SEMBLE Study

- **Study design**: Multicenter cohort study (jRCT1030220506).
- **Study period**: 25 May 2020 to 30 Nov. 2023.
- **Study subjects**:
  - All patients who received T-DXd between 25 May 2020 and 30 Nov. 2021 in the previous post-marketing surveillance (PMS) study (jRCT1080225197).
  - Patients who discontinued T-DXd by 31 May 2023 and subsequently received anti-tumor therapy for breast cancer.
- **Data cut-off:** 31 May 2023.
- **Followed up**: until 30 Nov. 2023.

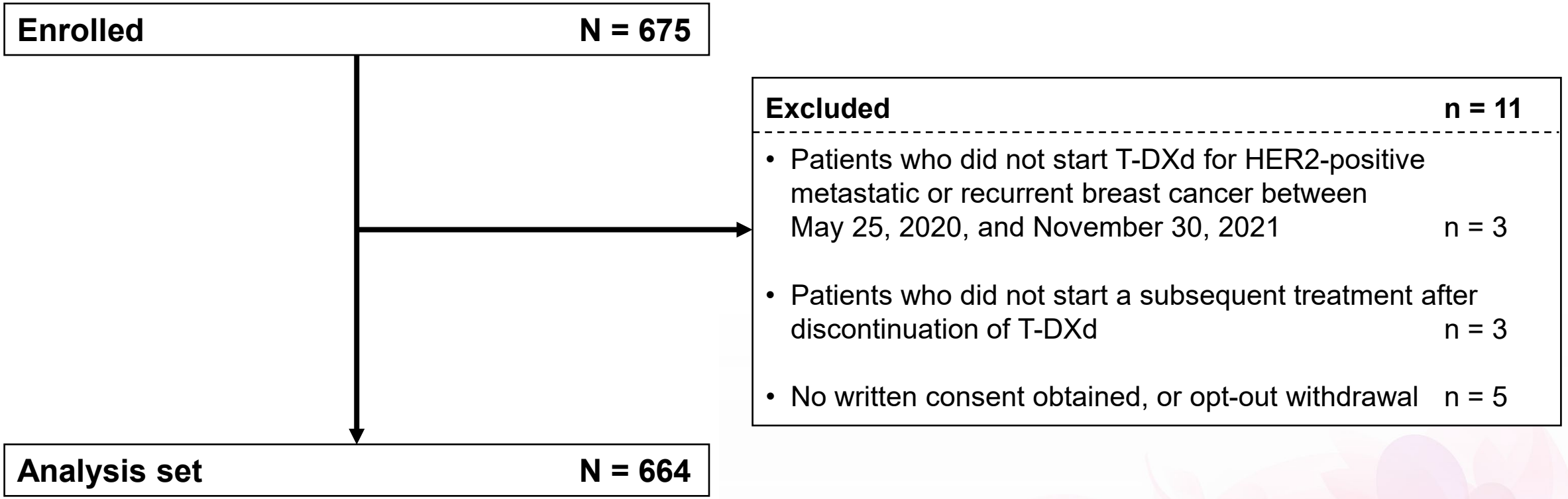


Study Endpoints

- **Distribution of post-T-DXd treatment regimens**

- Effectiveness and safety of post-T-DXd treatment regimens:
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Time to next treatment
  - Overall survival
  - Overall response rate
  - PFS2
  - TTF2
  - Incidence of ILD.
- These endpoints will be evaluated according to reason for discontinuation of T-DXd, such as ILD or PD.

Patient Disposition

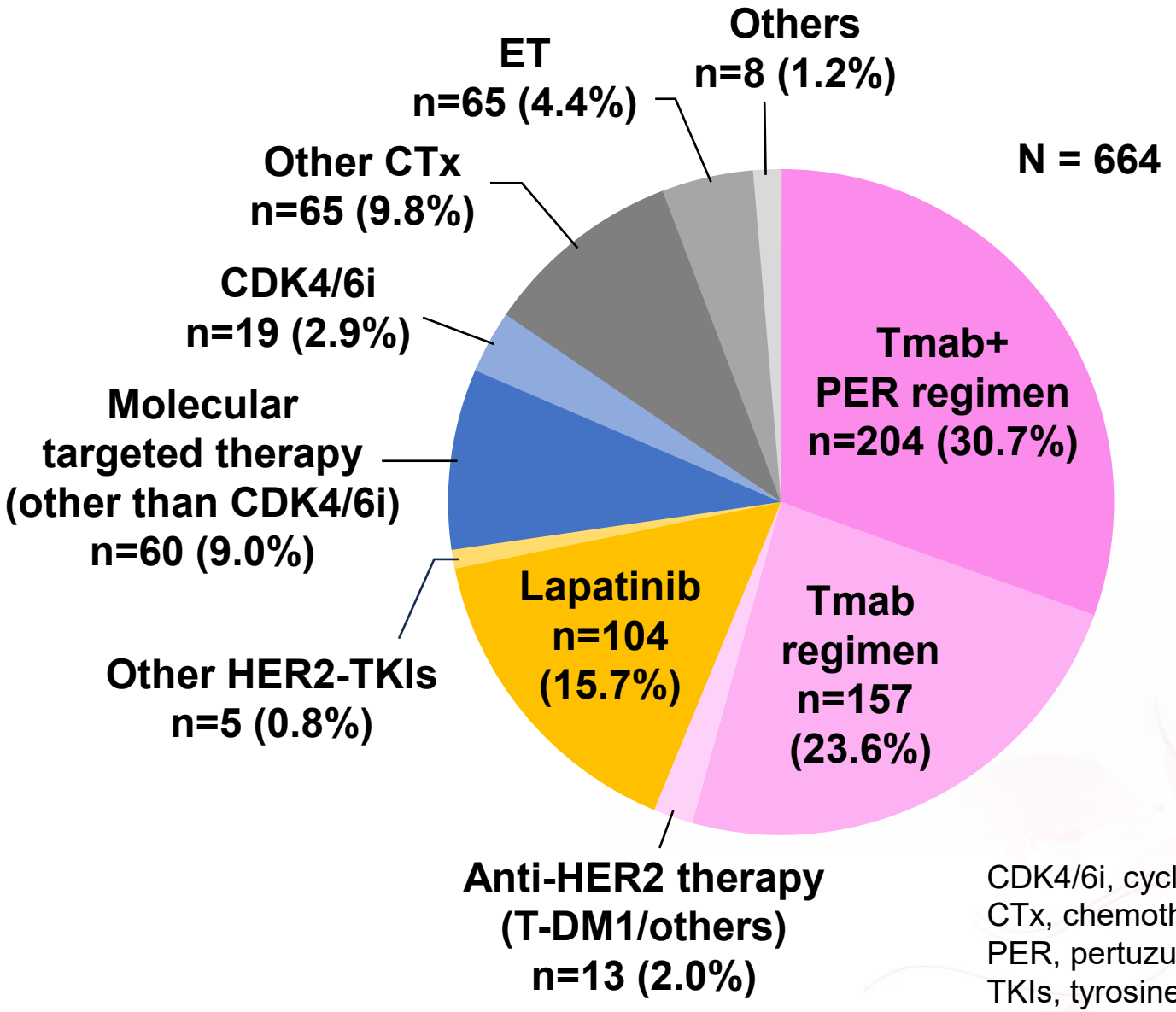


Patient Characteristics

		N = 664
Age, years	<65, n (%)	415 (62.5)
	≥65, n (%)	249 (37.5)
	Mean ± SD	60.0 ± 11.0
	Median (min, max)	60.0 (30, 89)
	25th, 75th percentiles	52.0, 68.0
Sex	Male, n (%)	3 (0.5)
	Female, n (%)	661 (99.5)

Data are for the first day of the first post-T-DXd treatment.

Distribution of Post-T-DXd Treatments



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CTx, chemotherapy; ET, endocrine therapy; PER, pertuzumab; T-DM1, trastuzumab emtansine; TKIs, tyrosine kinase inhibitors; Tmab, trastuzumab.

Trastuzumab and Other Anti-HER2 Therapy

Regimen	N (%)
Trastuzumab regimens	**157 (23.6)**
Trastuzumab + chemotherapy regimens	**111 (16.7)**
Trastuzumab + eribulin	36 (5.4)
Trastuzumab + vinorelbine	25 (3.8)
Trastuzumab + S-1	13 (2.0)
Trastuzumab + gemcitabine	10 (1.5)
Trastuzumab + capecitabine	9 (1.4)
Trastuzumab + paclitaxel	8 (1.2)
Trastuzumab + paclitaxel + carboplatin	4 (0.6)
Trastuzumab + docetaxel + carboplatin	2 (0.3)
Trastuzumab + carboplatin	1 (0.2)
Trastuzumab + cyclophosphamide + capecitabine	1 (0.2)
Trastuzumab + docetaxel	1 (0.2)
Trastuzumab + epirubicin + fluorouracil	1 (0.2)

Regimen	N (%)
Trastuzumab + endocrine therapy regimens	**18 (2.7)**
Trastuzumab + fulvestrant	6 (0.9)
Trastuzumab + anastrozole	5 (0.8)
Trastuzumab + tamoxifen	3 (0.5)
Trastuzumab + exemestane	2 (0.3)
Trastuzumab + endocrine therapy (other)	1 (0.2)
Trastuzumab + letrozole	1 (0.2)
Trastuzumab-alone regimens	**28 (4.2)**
Trastuzumab	28 (4.2)

Regimen	N (%)
Trastuzumab emtansine regimens	**12 (1.8)**
Trastuzumab emtansine	12 (1.8)
Anti-HER2 therapy (other) regimens	**1 (0.2)**
Anti-HER2 therapy (other)	1 (0.2)

Trastuzumab + Pertuzumab Regimens

Regimen	N (%)
Trastuzumab + pertuzumab regimens	**204 (30.7)**
Trastuzumab + pertuzumab + chemotherapy regimens	**153 (23.0)**
Trastuzumab + pertuzumab + eribulin	77 (11.6)
Trastuzumab + pertuzumab + vinorelbine	18 (2.7)
Trastuzumab + pertuzumab + docetaxel	13 (2.0)
Trastuzumab + pertuzumab + paclitaxel	13 (2.0)
Trastuzumab + pertuzumab + capecitabine	10 (1.5)
Trastuzumab + pertuzumab + S-1	8 (1.2)
Trastuzumab + pertuzumab + gemcitabine	6 (0.9)
Trastuzumab + pertuzumab + capecitabine + exemestane	1 (0.2)
Trastuzumab + pertuzumab + chemotherapy (other)	1 (0.2)
Trastuzumab + pertuzumab + docetaxel + endocrine therapy (other)	1 (0.2)
Trastuzumab + pertuzumab + eribulin + letrozole	1 (0.2)
Trastuzumab + pertuzumab + eribulin + others	1 (0.2)
Trastuzumab + pertuzumab + irinotecan	1 (0.2)
Trastuzumab + pertuzumab + paclitaxel + LH-RH analog + tamoxifen	1 (0.2)
Trastuzumab + pertuzumab + S-1 + LH-RH analog	1 (0.2)

Regimen	N (%)
Trastuzumab + pertuzumab + endocrine therapy regimens	**18 (2.7)**
Trastuzumab + pertuzumab + fulvestrant	6 (0.9)
Trastuzumab + pertuzumab + letrozole	6 (0.9)
Trastuzumab + pertuzumab + anastrozole	3 (0.5)
Trastuzumab + pertuzumab + tamoxifen	2 (0.3)
Trastuzumab + pertuzumab + exemestane	1 (0.2)
Trastuzumab + pertuzumab only regimens	**31 (4.7)**
Trastuzumab + pertuzumab	31 (4.7)
Trastuzumab + pertuzumab other regimens	**2 (0.3)**
Trastuzumab + pertuzumab + everolimus	1 (0.2)
Trastuzumab + pertuzumab + other	1 (0.2)

LH-RH, luteinizing hormone-releasing hormone

HER2-Tyrosine Kinase Inhibitors

Regimen	N (%)
HER2-TKIs regimens	**109 (16.4)**
Lapatinib regimens	**104 (15.7)**
Lapatinib + capecitabine	90 (13.6)
Lapatinib + letrozole	4 (0.6)
Lapatinib + anastrozole	3 (0.5)
Lapatinib	2 (0.3)
Lapatinib + capecitabine + LH-RH analog	1 (0.2)
Lapatinib + capecitabine + other	1 (0.2)
Lapatinib + chemotherapy (other)	1 (0.2)
Lapatinib + exemestane	1 (0.2)
Lapatinib + trastuzumab + letrozole	1 (0.2)
Other HER2-TKIs regimens	**5 (0.8)**
Other HER2-TKIs + trastuzumab + capecitabine	5 (0.8)

HER2-TKIs, HER2-tyrosine kinase inhibitors; LH-RH, luteinizig hormone-releasing hormone

Eribulin Regimens

Regimen	N (%)
Eribulin regimens	**130 (19.6)**
Eribulin + anti-HER2 antibody (trastuzumab, pertuzumab) regimens	**115 (17.3)**
Eribulin + trastuzumab + pertuzumab	77 (11.6)
Eribulin + trastuzumab	36 (5.4)
Eribulin + trastuzumab + pertuzumab + letrozole	1 (0.2)
Eribulin + trastuzumab + pertuzumab + other	1 (0.2)
Eribulin-alone regimens	**14 (2.1)**
Eribulin	14 (2.1)
Eribulin other regimens	**1 (0.2)**
Eribulin + docetaxel	1 (0.2)

Bevacizumab Regimens

Regimen	N (%)
Bevacizumab regimens	**53 (8.0)**
Bevacizumab + paclitaxel	52 (7.8)
Bevacizumab + nab-paclitaxel	1 (0.2)

CDK4/6 Inhibitor Regimens

Regimen	N (%)
CDK4/6 inhibitor regimens	**19 (2.9)**
Abemaciclib + fulvestrant	8 (1.2)
Abemaciclib + anastrozole	3 (0.5)
Abemaciclib + exemestane	1 (0.2)
Abemaciclib + letrozole	1 (0.2)
Abemaciclib + LH-RH analog + fulvestrant	1 (0.2)
Abemaciclib + paclitaxel	1 (0.2)
Palbociclib + letrozole	3 (0.5)
Palbociclib + fulvestrant	1 (0.2)

CDK, cyclin-dependent kinase; LH-RH, luteinizig hormone-releasing hormone

Chemotherapy-free/based Regimens

Regimen	N (%)
Chemotherapy-free regimens	**180 (27.1)**
Anti-HER2 therapy	74 (11.1)
Anti-HER2 therapy + endocrine therapy	45 (6.8)
Endocrine therapy	28 (4.2)
Molecular targeted therapy (other than anti-HER2 therapy) + endocrine therapy	20 (3.0)
Molecular targeted therapy (other than anti-HER2 therapy)	3 (0.5)
Anti-HER2 therapy + molecular targeted therapy (other than anti-HER2 therapy)	1 (0.2)
Anti-HER2 therapy + other	1 (0.2)
Endocrine therapy + other	1 (0.2)
Immune checkpoint inhibitor	1 (0.2)
Other	6 (0.9)
Chemotherapy-based regimens	**484 (72.9)**
Anti-HER2 therapy + chemotherapy	354 (53.3)
Chemotherapy	65 (9.8)
Molecular targeted therapy (other than anti-HER2 therapy) + chemotherapy	54 (8.1)
Anti-HER2 therapy + chemotherapy + endocrine therapy	6 (0.9)
Anti-HER2 therapy + chemotherapy + other	2 (0.3)
Anti-HER2 therapy + molecular targeted therapy (other than anti-HER2 therapy) + chemotherapy	2 (0.3)
Immune checkpoint inhibitor + chemotherapy	1 (0.2)

Conclusions

- In this interim analysis, the actual treatment regimens used in post-T-DXd treatment for breast cancer were ascertained in clinical settings in Japan.

- Over half of the patients continued anti-HER2 therapy, and the main subsequent regimens after discontinuation of T-DXd treatment were as follows:
  Trastuzumab + pertuzumab regimen (30.7%)
  Trastuzumab regimen (23.6%)
  Lapatinib (15.7%), alone or in combination.

- In the final analysis, the EN-SEMBLE study will investigate the effectiveness and safety of the post-T-DXd regimens.

- The results of the EN-SEMBLE study will provide insights into the optimization of post-T-DXd treatment, which is an unmet medical need.

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