# *Moving Beyond the Binary Categorization of HER2 Status: Antibody-Drug Conjugate Therapy in Metastatic Breast Cancer*

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## Disclosures

- **Aditya Bardia, MD,** discloses he has received consulting fees from Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics/Gilead, Sanofi, Daiichi Pharma/ AstraZeneca, Phillips, Eli Lilly, and Foundation Medicine; he has also conducted contracted research for Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics/ Gilead, Daiichi Pharma/AstraZeneca, and Eli Lilly

- During the course of this lecture, the faculty may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications

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## Learning Objectives

- Review the testing for *HER2* levels in patients with breast cancer and potential effects on treatment
- Analyze clinical trial data and treatment guidelines in the metastatic breast cancer population that are categorized as HER2-positive by testing convention
- Describe approaches for recognizing and managing adverse events associated with antibody-drug conjugate (ADC), *HER2*-targeted therapy in advanced or metastatic breast cancer

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## Pre-Read

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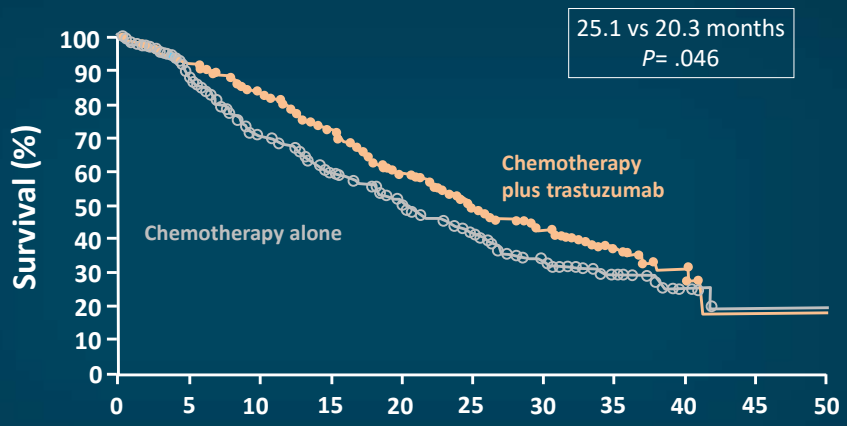
# Trastuzumab Added to Chemotherapy Improves Overall Survival in *HER2*-Positive mBC




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Chemotherapy plus trastuzumab | 235 | 214 | 192 | 165 | 134 | 114 | 96 | 47 | 11 |
| Chemotherapy alone | 234 | 205 | 160 | 136 | 116 | 97 | 76 | 37 | 13 |

mBC = metastatic breast cancer.

Slamon DJ, et al. *N Engl J Med*. 2001;344:783-792.

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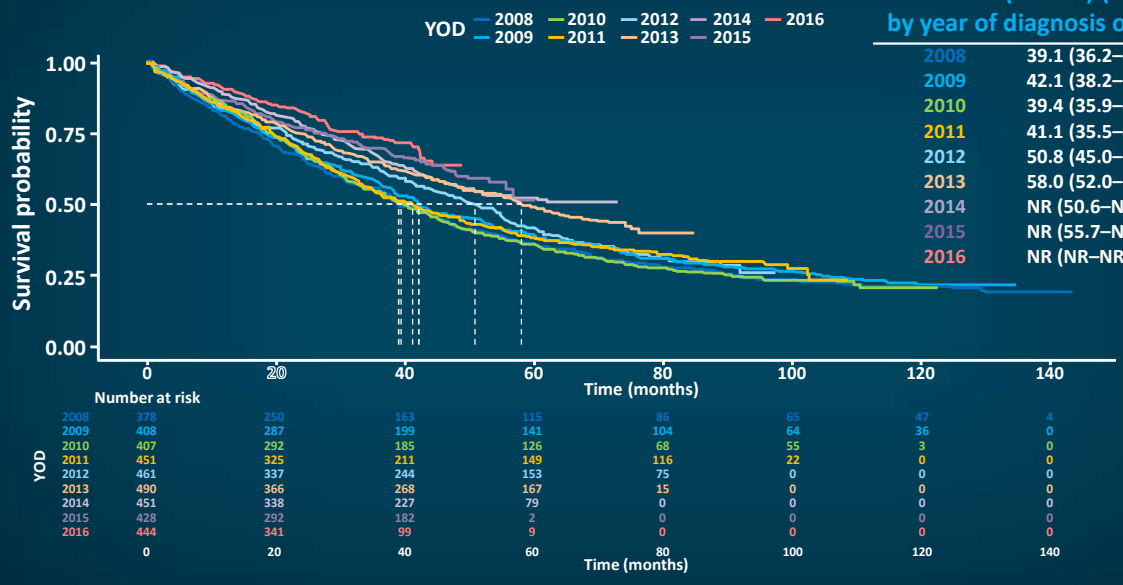
# Overall Survival in *HER2*-Positive mBC by Year of Diagnosis

## ESME-mBC Registry




| Median OS (95% CI) (months) by year of diagnosis of mBC | |
|---|---|
| 2008 | 39.1 (36.2–46.5) |
| 2009 | 42.1 (38.2–50.8) |
| 2010 | 39.4 (35.9–45.4) |
| 2011 | 41.1 (35.5–48.3) |
| 2012 | 50.8 (45.0–55.5) |
| 2013 | 58.0 (52.0–68.4) |
| 2014 | NR (50.6–NR) |
| 2015 | NR (55.7–NR) |
| 2016 | NR (NR–NR) |

| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| YOD | 0 | 20 | 40 | 60 | 80 | 100 | 120 | 140 | |
| 2008 | 378 | 250 | 163 | 115 | 86 | 65 | 47 | 4 | Time (months) |
| 2009 | 408 | 287 | 199 | 141 | 104 | 64 | 36 | 0 | |
| 2010 | 407 | 292 | 185 | 126 | 68 | 55 | 3 | 0 | |
| 2011 | 451 | 325 | 211 | 149 | 116 | 22 | 0 | 0 | |
| 2012 | 461 | 337 | 244 | 153 | 75 | 0 | 0 | 0 | |
| 2013 | 490 | 366 | 268 | 167 | 15 | 0 | 0 | 0 | |
| 2014 | 451 | 338 | 227 | 79 | 0 | 0 | 0 | 0 | |
| 2015 | 428 | 292 | 182 | 2 | 0 | 0 | 0 | 0 | |
| 2016 | 444 | 341 | 99 | 9 | 0 | 0 | 0 | 0 | |

CI = confidence interval; ESME = Epidemiological Strategy and Medical Economics; NR = not reached; OS = overall survival; YOD = year of diagnosis.

Grinda T, et al. *European Society for Medical Oncology (ESMO) Open*. 2021;6:100114.

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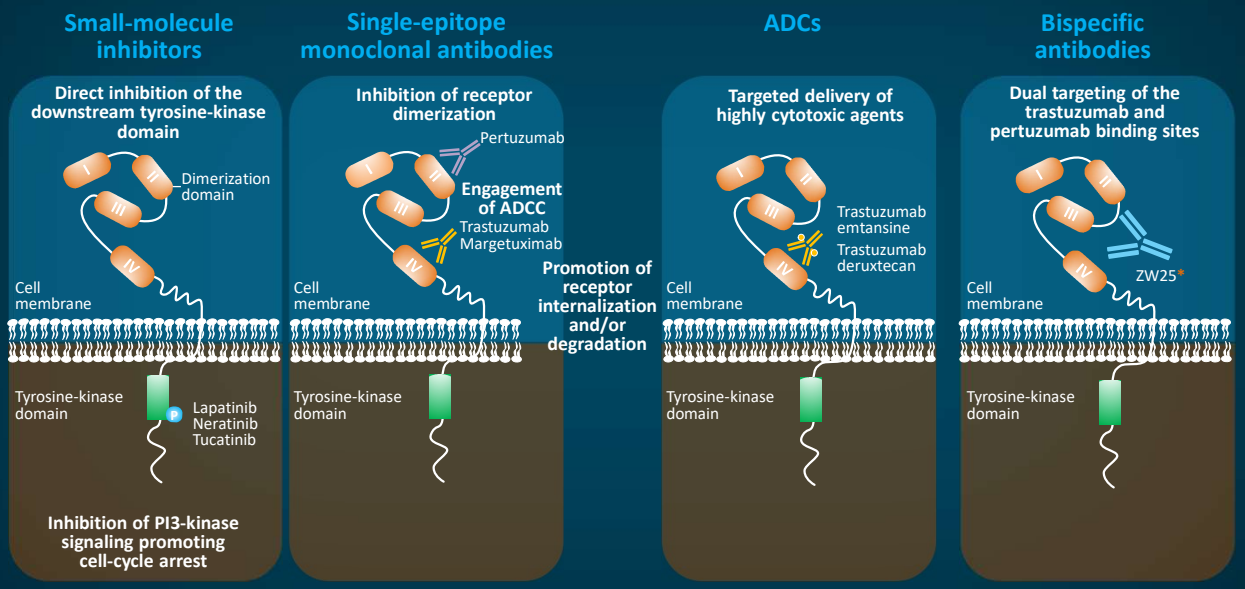
# Mechanisms of Action of *HER2*-Targeted Therapies




ADCC = antibody-dependent cellular toxicity.

Oh DY, Bany Y-J. *Nat Rev Clin Oncol*. 2020;17(1):33-48.

**ZW25 is an investigational agent.*

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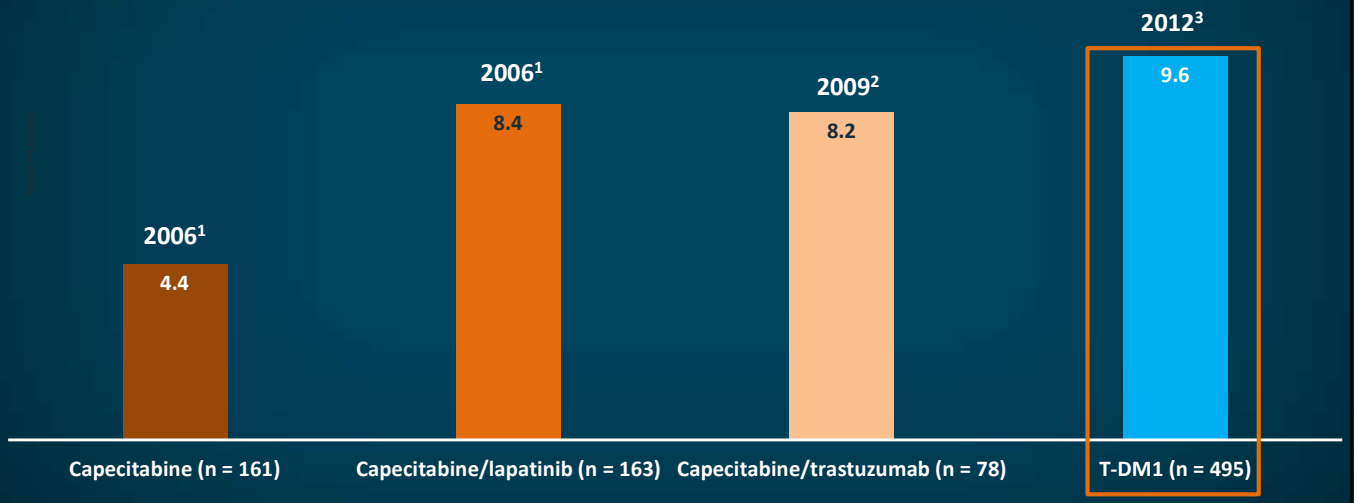
# Evolution of PFS After Trastuzumab/Taxane




PFS = progression-free survival; T-DM1 = trastuzumab emtansine.

1. Geyer C, et al. *N Engl J Med*. 2006;355:2733-2743. 2. von Minckwitz G, et al. *J Clin Oncol*. 2009;27:1999-2006. 3. Verma S, et al. *N Engl J Med*. 2012;367:1783-1791.

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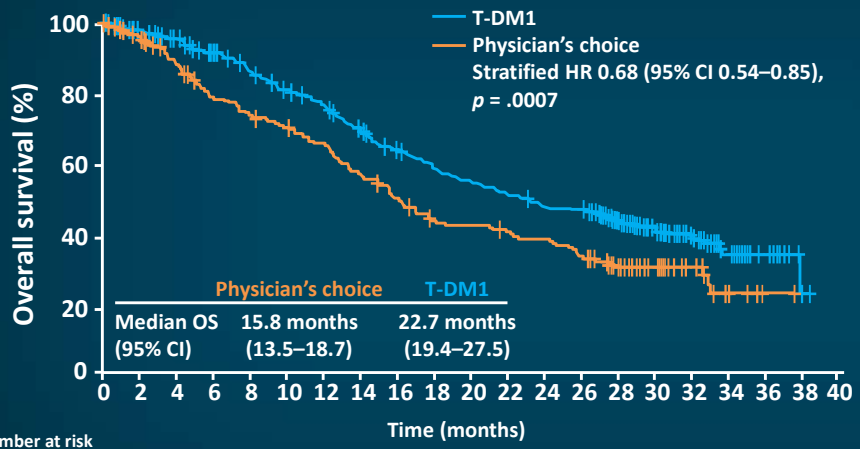
# TH3RESA: T-DM1 vs Physician's Choice Systemic Therapy

## Overall survival (ITT population)




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 | 404 (0) | 368 (17) | 321 (29) | 280 (35) | 226 (43) | 192 (44) | 167 (45) | 132 (66) | 54 (138) | 12 (172) | 0 |
| Physician's Choice | 198 (0) | 150 (28) | 122 (31) | 107 (33) | 80 (34) | 66 (36) | 59 (37) | 39 (45) | 16 (68) | 1 (80) | 0 |

| | Median # of months | # of events |
|---|---|---|
| T-DM1 | 22.7 | 161 |
| Physician's choice | 15.8 | 87 |

**Physician's choice**

- Single-agent chemotherapy
- Single-/dual-agent hormonal or *HER2*-directed therapy
- Combination therapy

ITT = intention-to-treat; T-DM1 = trastuzumab emtansine.

Krop IE, et al. *Lancet Oncol.* 2017;18:743-754.

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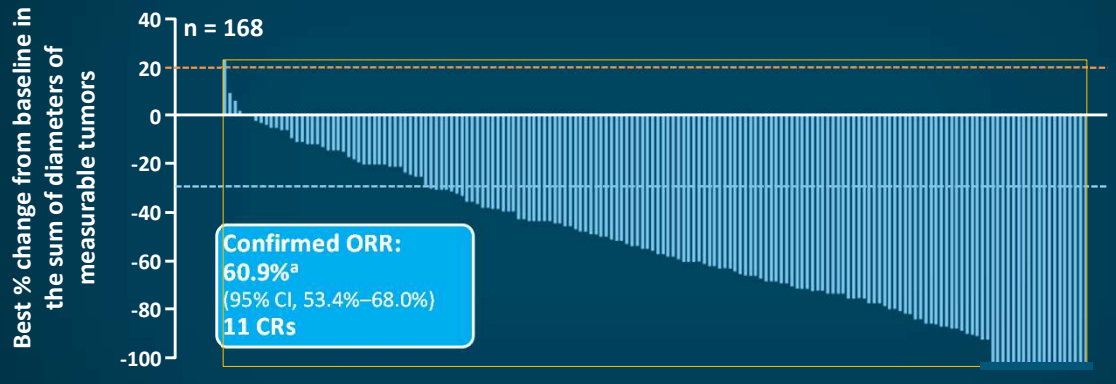
# DESTINY-Breast01: Best Change in Tumor Size




By independent central review. The line at 20% indicates progressive disease; the line at −30% indicates partial response.

[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N = 184).

CI = confidence interval; CR = complete response; ORR = overall response rate.

Krop IE, et al. San Antonio Breast Cancer Symposium (SABCS) 2019; Abstract GS1-03. Modi S, et al. *N Engl J Med.* 2020;382:610-621.

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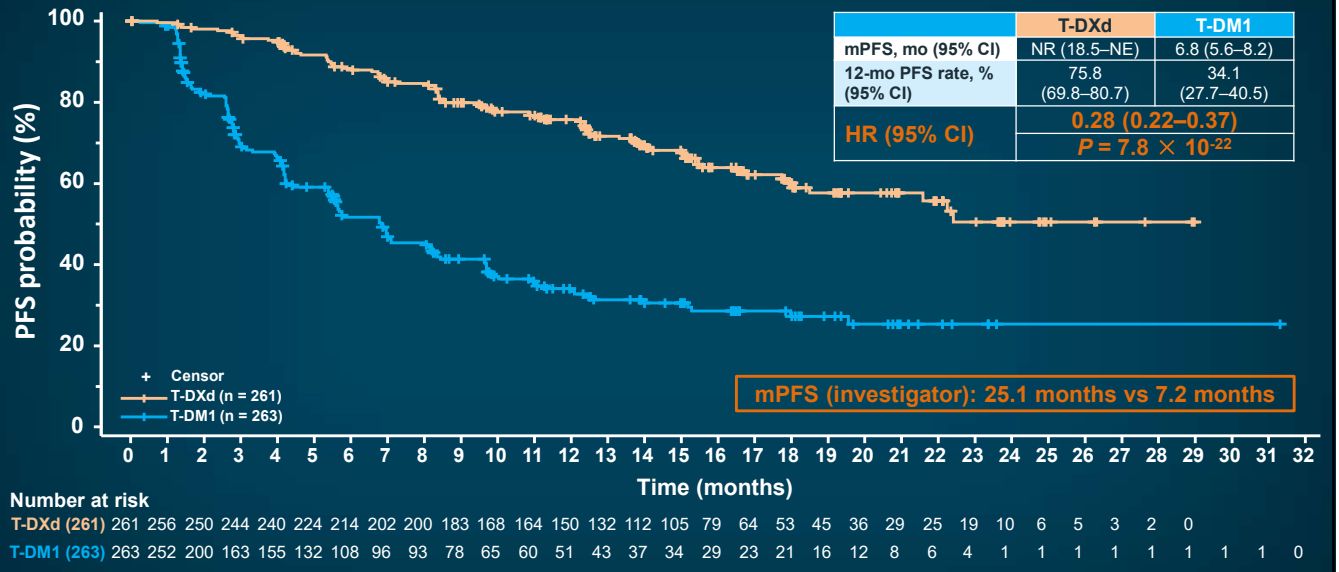
# DESTINY-Breast03 Primary Endpoint: PFS by BICR




| | T-DXd | T-DM1 |
|---|---|---|
| mPFS, mo (95% CI) | NR (18.5–NE) | 6.8 (5.6–8.2) |
| 12-mo PFS rate, % (95% CI) | 75.8 (69.8–80.7) | 34.1 (27.7–40.5) |
| HR (95% CI) | 0.28 (0.22–0.37) | |
| | $P = 7.8 \times 10^{-22}$ | |

**Number at risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (261) | 261 | 256 | 250 | 244 | 240 | 224 | 214 | 202 | 200 | 183 | 168 | 164 | 150 | 132 | 112 | 105 | 79 | 64 | 53 | 45 | 36 | 29 | 25 | 19 | 10 | 6 | 5 | 3 | 2 | 0 |
| T-DM1 (263) | 263 | 252 | 200 | 163 | 155 | 132 | 108 | 96 | 93 | 78 | 65 | 60 | 51 | 43 | 37 | 34 | 29 | 23 | 21 | 16 | 12 | 8 | 6 | 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

BICR = blinded independent central review; HR = hazard ratio; INV = investigator; mo = month; NE = not estimable; NR = not reached.

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1–16.6) and for T-DM1 was 13.9 months (range, 11.8–15.1).

Cortes J, et al. ESMO 2021 Annual Meeting; Abstract LBA-1.

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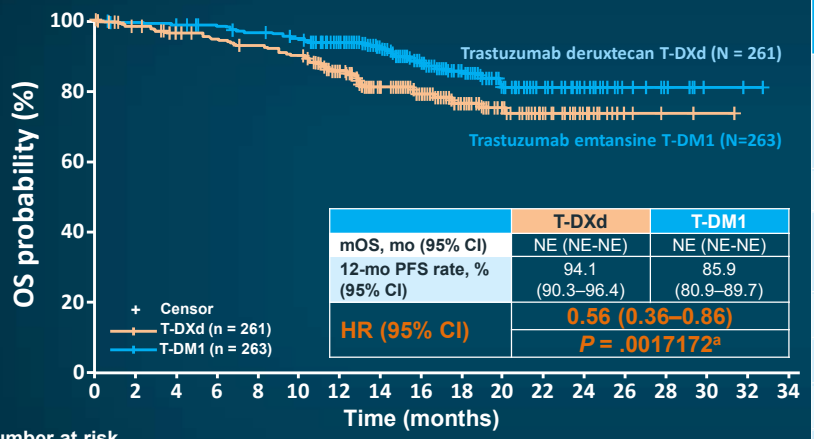
# DESTINY-Breast03 Secondary Endpoints: Overall Survival and Response Rate[1]




| | T-DXd | T-DM1 |
|---|---|---|
| mOS, mo (95% CI) | NE (NE-NE) | NE (NE-NE) |
| 12-mo PFS rate, % (95% CI) | 94.1 (90.3–96.4) | 85.9 (80.9–89.7) |
| HR (95% CI) | 0.56 (0.36–0.86) | |
| | $P = .0017172$[a] | |

**Number at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (261) | 261 | 254 | 243 | 218 | 133 | 56 | 24 | 7 | 2 | 1 | 0 |
| T-DM1 (263) | 263 | 243 | 231 | 188 | 120 | 52 | 18 | 3 | 1 | 0 | 0 |

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm).

[a]$P = .007172$ but does not cross pre-specified boundary of $P < .000265$.

| | T-DXd (n = 261) | T-DM1 (n = 263) |
|---|---|---|
| **Confirmed ORR** [95% CI] n (%)[b] | 208 **(79.7)** [74.3–84.4] | 90 **(34.2)** [28.5–40.3] |
| | $P < .0001$ | |
| **Complete response (CR)** | 42 **(16.1)** | 23 **(8.7)** |
| **Partial response (PR)** | 166 **(63.6)** | 67 **(25.5)** |
| Stable disease (SD) | 44 (16.9) | 112 (42.6) |
| Progressive disease (PD) | 3 (1.1) | 46 (17.5) |
| Not evaluable | 6 (2.3) | 15 (5.7) |
| CR + PR + SD (disease control rate [DCR]) | 252 (96.6) | 202 (76.8) |

1. Cortés J, et al. ESMO 2021; Abstract LBA-1. 2. Baselga J, et al. *N Engl J Med.* 2012;366:109-119.

CLEOPATRA: ORR = 80%, CR = 5.5%[2]

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# Interstitial Lung Disease/Pneumonitis in Different Regions

| Adjudicated as drug-related ILD/pneumonitis,[a] n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade |
| Overall | T-DXd (n = 257) | 7 (2.7) | 18 (7.0) | 2 (0.8) | 0 | 0 | 27 (10.5) |
| | T-DM1 (n = 261) | 4 (1.5) | 1 (0.4) | 0 | 0 | 0 | 5 (1.9) |
| Asia subgroup | T-DXd (n = 147) | 5 (3.4) | 10 (6.8) | 1 (0.7) | 0 | 0 | 16 (10.9) |
| | T-DM1 (n = 159) | 3 (1.9) | 1 (0.6) | 0 | 0 | 0 | 4 (2.5) |
| Non-Asia subgroup | T-DXd (n = 110) | 2 (1.8) | 8 (7.3) | 1 (0.9) | 0 | 0 | 11 (10.0) |
| | T-DM1 (n = 102) | 1 (1.0) | 0 | 0 | 0 | 0 | 1 (1.0) |

- No grade 4 or 5 adjudicated drug-related ILD/pneumonitis events were observed with T-DXd
- ILD/pneumonitis rates were similar between the overall population and the Asia subgroup and between the Asia and the non-Asia subgroups

ILD = interstitial lung disease; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
Asia subgroup defined as patients enrolled in China, Hong Kong, Japan, Republic of Korea, and Taiwan.
[a]Patients with history of ILD/pneumonitis necessitating steroids were excluded.
Hurvitz S, et al. San Antonio Breast Cancer Symposium (SABCS) 2021 Annual Meeting; Abstract GS3-01.

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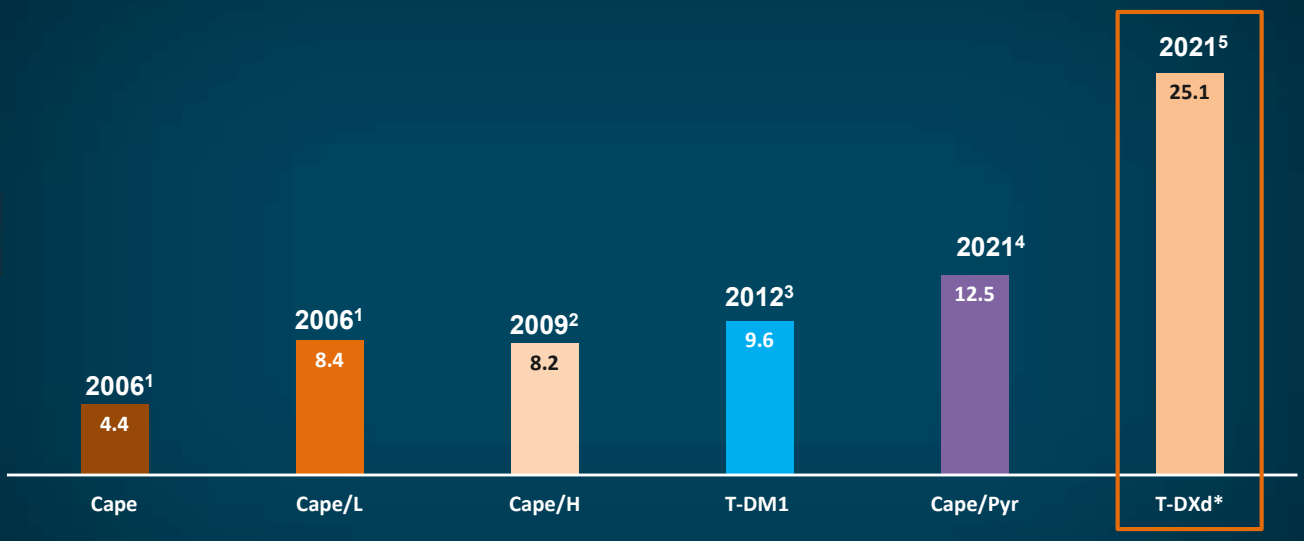
# Evolution of PFS After Trastuzumab/Taxane




Cape = capecitabine; DCO = data cut-off; H = trastuzumab; L = lapatinib; (m)PFS = (median) progression-free survival; Pyr = pyrotinib; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
*BICR assessed mPFS was NR at DCO, therefore investigator assessed mPFS has been included pending further follow-up.
1. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 2. von Minckwitz G, et al. *J Clin Oncol.* 2009;27:1999-2006. 3. Verma S, et al. *N Engl J Med.* 2012;367:1783-1791. 4. Xu B, et al. *Lancet Oncol.* 2021;22:351-360. 5. Cortes J, et al. ESMO 2021 Annual Meeting; Abstract LBA-1.
**Pyrotinib is an investigational agent.*

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