QUESITO CLINICO B:

Nelle pazienti con carcinoma mammario metastatico HR-positivo/HER2low e HR+/ultralow non pretrattate con chemioterapia, è raccomandabile trastuzumab deruxtecan rispetto alla chemioterapia?

Sintesi delle evidenze e problematiche emerse dal lavoro di gruppo

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Ospedale S. Maria- Terni

- **P**= pazienti con carcinoma mammario metastatico HR+/ HER2 low e HR+/HER2 ultralow
- **I**= trastuzumab deruxtecan
- **C**= chemioterapia
- **O**=PFS, OS, qualità di vita e tossicità

Destiny Breast 06

ORIGINAL ARTICLE

Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer

A. Bardia, X. Hu, R. Dent, K. Yonemori, C.H. Barrios, J.A. O'Shaughnessy, H. Wildiers, J.-Y. Pierga, Q. Zhang, C. Saura, L. Biganzoli, J. Sohn, S.-A. Im, C. Lévy, W. Jacot, N. Begbie, J. Ke, G. Patel, and G. Curigliano, for the DESTINY-Breast06 Trial Investigators*

ABSTRACT

BACKGROUND

Outcomes in patients with hormone receptor–positive metastatic breast cancer worsen after one or more lines of endocrine-based therapy. Trastuzumab deruxtecan has shown efficacy in patients with metastatic breast cancer with low expression of human epidermal growth factor receptor 2 (HER2) after previous chemotherapy.

METHODS

We conducted a phase 3, multicenter, open-label trial involving patients with hormone receptor–positive metastatic breast cancer with low HER2 expression (a score of 1+ or 2+ on immunohistochemical [IHC] analysis and negative results on in situ hybridization) or ultralow HER2 expression (IHC 0 with membrane staining) who had received one or more lines of endocrine-based therapy and no previous chemotherapy for metastatic breast cancer. Patients were randomly assigned in a 1:1 ratio to receive trastuzumab deruxtecan or the physician's choice of chemotherapy. The primary end point was progression-free survival (according to blinded independent central review) among the patients with HER2-low disease. Secondary end points included progression-free survival among all the patients who had undergone randomization, overall survival, and safety.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Bardia can be contacted at abardia@mednet.ucla.edu or at Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA 90404. Dr. Curigliano can be contacted at giuseppe.curigliano@ieo.it or at the European Institute of Oncology, IRCCS, 20141, Department of Oncology and Hematology–Oncology, University of Milan, 20122, Milan, Italy.

*A list of investigators in the DESTINY-Breast06 trial is provided in the Supplementary Appendix, available at NEJM.org.

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DESTINY-Breast06: Phase III Study of T-Dxd in HER2-low/ultralow MBC

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

*History of HER2-low (IHC 1+ or IHC 2+/ISH−) or negative expression (IHC 0) by local test.
HER2-low or HER2-ultralow (IHC 0 with membrane staining) expression as determined by the central laboratory result established on a tissue sample taken in the metastatic setting

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

	n (%)
Capecitabine	257 (59.8)
Nab-paclitaxel	105 (24.4)
Paclitaxel	68 (15.8)

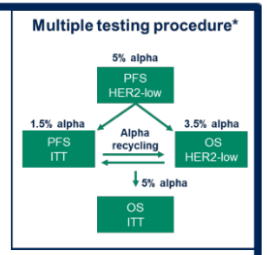
ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)



Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Curigliano G. et al., ASCO 2024; Bardia A. et al., NEJM 2024

Author(s): MC

Question: Trastuzumab deruxtecan compared to chemioterapia in Nelle pazienti con carcinoma mammario metastatico HR- positivo/HER2-low e HR+/HER2-ultralow non pretrattate con chemioterapia

Setting: inpatients

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	trastuzumab deruxtecan	chemioterapia	Relative (95% CI)	Absolute (95% CI)		
Overall survival, ITT population (follow-up: median 18.6 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	436 participants	430 participants	**HR 0.81** (0.66 to 1.01) [death for any cause]	**8 more per 100** (from 0 fewer to 15 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
							-	38.0%		**8 more per 100** (from 0 fewer to 15 more)		
Progression free survival (follow-up: median 18.6 months; assessed with: BICR)												
1	randomised trials	not serious[a]	not serious	not serious	not serious[a]	none	436 participants	430 participants	**HR 0.64** (0.54 to 0.76) [progression or death for any cause]	**12 more per 100** (from 8 more to 16 more)	⨁⨁⨁⨁ High[a]	CRITICAL
							-	61.0%		**12 more per 100** (from 8 more to 16 more)		
Best Objective Response (follow-up: median 18.6 months; assessed with: BICR)												
1	randomised trials	not serious[a]	not serious	not serious	not serious[a]	none	250/436 (57.3%)	134/430 (31.2%)	**RR 1.84** (1.56 to 2.16)	**26 more per 100** (from 17 more to 36 more)	⨁⨁⨁⨁ High[a]	IMPORTANT
Time to deterioration (follow-up: median 18.6 months; assessed with: EORTC QOLQ-30 Global Health Status)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	trastuzumab deruxtecan	chemioterapia	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[e]	not serious	not serious	serious[f]	none	436 participants	430 participants	**HR 0.93** (0.73 to 1.17) [Time to deterioration 1]	**3 fewer per 100** (from 11 fewer to 6 more)	⨁⨁◯◯ Low[e,f]	CRITICAL
							-	62.0%		**3 fewer per 100** (from 11 fewer to 6 more)		

Time to deterioration (follow-up: median 18.6 months; assessed with: EORTC QOLQ-C30 Physical Functioning)

1	randomised trials	serious[e]	not serious	not serious	serious[g]	none	436 participants	430 participants	**HR 0.71** (0.55 to 0.91) [Time to deterioration]	**12 fewer per 100** (from 21 fewer to 3 fewer)	⨁⨁◯◯ Low[e,g]	CRITICAL
							-	63.0%		**12 fewer per 100** (from 21 fewer to 3 fewer)		

Time to deterioration (follow-up: median 18.6 months; assessed with: EORTC-QOLQ-C30 fatigue)

1	randomised trials	serious[e]	not serious	not serious	serious[g]	none	436 participants	430 participants	**HR 0.77** (0.63 to 0.95) [Time to deterioration]	**9 fewer per 100** (from 16 fewer to 2 fewer)	⨁⨁◯◯ Low[e,g]	CRITICAL
							-	81.0%		**9 fewer per 100** (from 16 fewer to 2 fewer)		

Time to deterioration (follow-up: median 18.6 months; assessed with: EORTC QOLQ-C30 Pain)

1	randomised trials	serious[e]	not serious	not serious	not serious[d]	none	436 participants	430 participants	**HR 0.51** (0.39 to 0.65) [Time to deterioration]	**24 fewer per 100** (from 33 fewer to 16 fewer)	⨁⨁⨁◯ Moderate[d,e]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	trastuzumab deruxtecan	chemioterapia	Relative (95% CI)	Absolute (95% CI)		
							-	75.0%		**24 fewer per 100** (from 33 fewer to 16 fewer)		

Any AEs grade 3 or higher, related to treatment (follow-up: median 18.6 months; assessed with: CTCAE)

1	randomised trials	serious[e]	not serious	not serious	serious[b]	none	176/434 (40.6%)	131/417 (31.4%)	**RR 1.29** (1.08 to 1.55)	**9 more per 100** (from 3 more to 17 more)	⨁⨁◯◯ Low[e,h]	CRITICAL

Any AEs leading to discontinuation (follow-up: median 18.6 months)

1	randomised trials	serious[e]	not serious	not serious	serious[b]	none	56/434 (12.9%)	33/417 (7.9%)	**RR 1.63** (1.08 to 2.45)	**5 more per 100** (from 1 more to 11 more)	⨁⨁◯◯ Low[e,h]	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95%CLs of absolute effect consistent with both greater and comparable efficacy

b. not a serious risk of detection bias for a blinded, independent, assessment

c. MID for benefit HR=0.55

d. 95%CI of absolute effect consistent with a unique clinical interpretation

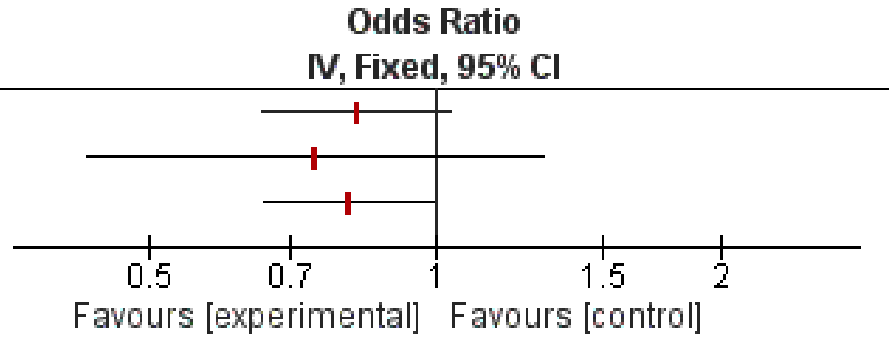
e. serious risk of performance/detection bias (unblinded referral/assessment by participants/investigators)

f. 95% CI of absolute effect consistent with opposite clinical interpretation

g. 95% CI of absolute effect consistent with both better and comparable QoL

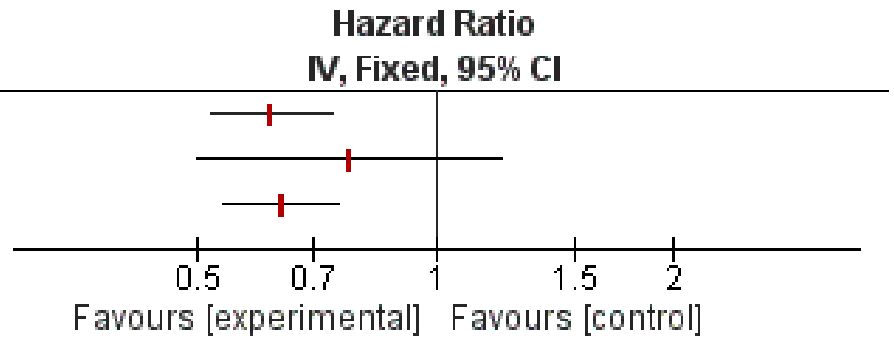
h. 95% CI of absolute effect consistent with both better and comparable toxicity

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
HER2_low	-0.19	0.1169	0.83 [0.66, 1.04]
HER2-ultralow	-0.29	0.2838	0.75 [0.43, 1.31]
ITT_population	-0.21	0.106	0.81 [0.66, 1.00]



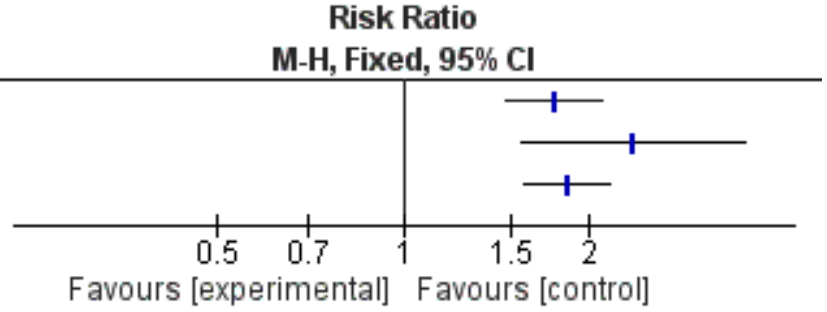
OS

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
HER2_low	-0.48	0.0897	0.62 [0.52, 0.74]
HER2-ultralow	-0.25	0.2269	0.78 [0.50, 1.21]
ITT_population	-0.45	0.0867	0.64 [0.54, 0.76]



PFS

Study or Subgroup	Trast_derux Events	Total	chemotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
HER2_low	203	359	114	354	1.76 [1.47, 2.09]
HER2-ultralow	47	76	20	76	2.35 [1.55, 3.56]
ITT_population	250	436	134	430	1.84 [1.56, 2.16]



OR

- Priorità SI
- Effetto desiderabile GRANDE
- Certezza BASSA (imprecision, rischio di bias, detection)
- Nessuna importante variabilità o incertezza
- Bilancio a favore dell'intervento
- Costi No rimborsabilità
- Equità Ridotta (no indicazione)
- Fattibilità si
- Accettabilità Condizionata a favore