

LBA18
Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC): Additional analyses of DESTINY-Breast09 in key subgroups of interest

S. Loibl¹, Z. Jiang², R. Barroso-Sousa³, Y.H. Park⁴, C. Saura Manich⁵, M. Rimawi⁶, A. Schneeweiss⁷, M. Toi⁸, S-A. Im⁹, Z. Tong¹⁰, U. Demirci¹¹, C.M. Villarreal Garza¹², C-S. Huang¹³, T. Takano¹⁴, V. Guarneri¹⁵, S. Mondal¹⁶, D. Huang¹⁷, A. Zeng¹⁸, S.M. Tolaney¹⁹

¹ Medicine and Research Department, GBG Forschungs GmbH, Neu-Isenburg, Germany, ² Department of Breast Oncology, Fifth Medical Center of PLA General Hospital, Beijing, China, ³ Hospital Brasilia, Rede Américas, Brasilia, Brazil, ⁴ Department of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ⁵ Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, ⁶ Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, United States of America, ⁷ National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany, ⁸ Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan, ⁹ Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, ¹⁰ Department of Breast Cancer Pathology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, ¹¹ Department of Medical Oncology, Ankara Memorial Hospital, Ankara, Türkiye, ¹² Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnológico de Monterrey, Nuevo Leon, Mexico, ¹³ Department of Surgery, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan, ¹⁴ Department of Breast Medical Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan, ¹⁵ Department of Surgery, Oncology and Gastroenterology, University of Padua, and Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy, ¹⁶ Oncology Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Wilmington, United States of America, ¹⁷ Global Medicines Development, Oncology R&D, AstraZeneca, Mississauga, Canada, ¹⁸ Late Development Oncology, Clinical Development, Oncology R&D, AstraZeneca, Gaithersburg, United States of America ¹⁹ Department of Medical Oncology, Dana Farber Cancer Institute, Boston, United States of America

Background

In the DESTINY-Breast09 (NCT04784715) interim analysis, first-line treatment with T-DXd + P significantly improved progression-free survival (PFS) vs THP for pts with HER2+ a/mBC, with no new safety signals identified. Here, we report outcomes in key subgroups, focusing on stratification factors.

Methods

Pts had HER2+ (IHC 3+ or ISH+) a/mBC with no prior systemic therapy and ≤1 line of endocrine therapy for a/mBC. Pts had to have a disease-free interval of >6 months between (neo)adjuvant therapy and a/mBC. Pts with hormone receptor (HR)+ disease could receive endocrine therapy after taxane discontinuation or six cycles of T-DXd. Randomization (1:1:1) to T-DXd + placebo, T-DXd + P, or THP was stratified by de-novo/recurrent disease, HR+/- status, and *PIK3CA* mutation (m) detected/undetected status. The primary endpoint was PFS by blinded independent central review (BICR). Confirmed objective response rate (ORR) by BICR, duration of response (DOR) by BICR, and safety were secondary endpoints.

Results

Of pts assigned to T-DXd + P (n=383) or THP (n=387), 52% had de-novo a/mBC, 54% had HR+ status, and 31% had detected *PIK3CA*m. Baseline characteristics were balanced across treatments. Use of concurrent endocrine therapy occurred in 13.5% (T-DXd + P) vs 38.3% (THP) of pts with HR+ disease. At data cutoff (Feb 26, 2025), PFS was longer with T-DXd + P than THP in all subgroups per strata. T-DXd + P also consistently improved confirmed ORR and DOR vs THP (Table). Safety outcomes in subgroups were in line with the overall population.

Conclusions

T-DXd + P demonstrated a clinically meaningful efficacy benefit vs THP regardless of disease history, or HR or *PIK3CA*m status, with no new safety signals. Results were consistent with the overall population and support T-DXd + P as a new first-line treatment option across all pts with HER2+ a/mBC. Table: LBA18

<i>De novo</i>		Recurrent		HR+		HR-		<i>PIK3CA</i> m		No <i>PIK3CA</i> m	
T-DXd + P THP		T-DXd + P THP		T-DXd + P THP		T-DXd + P THP		T-DXd + P THP		T-DXd + P THP	
(n=200)	(n=200)	(n=183)	(n=187)	(n=207)	(n=209)	(n=176)	(n=178)	(n=116)*	(n=121)	(n=266)	(n=266)

	<i>De novo</i> T-DXd + P THP (n=200) (n=200)		Recurrent T-DXd + P THP (n=183) (n=187)		HR+ T-DXd + P THP (n=207) (n=209)		HR- T-DXd + P THP (n=176) (n=178)		<i>PIK3CA</i> m T-DXd + P THP (n=116)* (n=121)		No <i>PIK3CA</i> m T-DXd + P THP (n=266) (n=266)	
Confirmed ORR, % (95% CI)†	90.5 (85.6, 94.2)	82.0 (76.0, 87.1)	79.2 (72.6, 84.9)	74.9 (68.0, 80.9)	81.2 (75.2, 86.2)	77.0 (70.7, 82.6)	89.8 (84.3, 93.8)	80.3 (73.7, 85.9)	81.0 (72.7, 87.7)	73.6 (64.8, 81.2)	87.2 (82.6, 91.0)	80.8 (75.6, 85.4)
Median DOR, mo (95% CI)†	39.2 (35.1, NC)	31.3 (24.5, NC)	35.3 (27.3, NC)	21.9 (18.4, NC)	35.3 (34.8, NC)	26.4 (22.3, NC)	39.2 (39.2, NC)	26.3 (20.2, NC)	34.8 (34.8, NC)	18.4 (13.2, 26.1)	39.2 (35.3, NC)	NC (25.6, NC)

*n=1 missing status; †BICR NC, not calculable.

Clinical trial identification

NCT04784715.

Editorial acknowledgement

Under the guidance of authors, medical writing support was provided by Conor O'Boyle, PhD, of Helios Medical Communications, part of Helios Global Group, and was funded by AstraZeneca in accordance with Good Publication Practice (GPP) guidelines.

Legal entity responsible for the study

AstraZeneca.

Funding

This study is sponsored 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).

Disclosure

S. Loibl: Financial Interests, Institutional, Advisory Board: Amgen, AstraZeneca, BMS, Celgene, DSI, GSK, Lilly, Pfizer, Pierre Fabre, Roche, SeaGen, Sanofi, Gilead, Merck, Novartis, Bicycle Therapeutics, Jazz Pharmaceuticals, BeiGene, Bayer; Financial Interests, Institutional, Invited Speaker: AstraZeneca, DSI, Novartis, Pfizer, Roche, Gilead, Seagen, Medscape, Stemline-Menarini; Financial Interests, Personal, Full or part-time Employment, CEO: GBG Forschungs GmbH; Financial Interests, Institutional, Advisory Board, Ki67 Quantifier: VMscope GmbH; Financial Interests, Institutional, Research Grant: AstraZeneca, Celgene, Novartis, Immunomedics/Gilead, Pfizer, Roche, Daiichi Sankyo; Financial Interests, Institutional, Funding: AbbVie, Molecular Health, Greenwich Life Sciences; Financial Interests, Institutional, Other, PIPenelope/Padma: Pfizer; Financial Interests, Institutional, Other, SC PALOMA3: Pfizer; Financial Interests, Institutional, Other, SC SOLAR1: Novartis; Financial Interests, Institutional, Other, SC ASCENT: Immunomedics/Gilead; Financial Interests, Institutional, Other, SC HERCLIMB: SeaGen; Financial Interests, Institutional, Other, SC Katherine: Roche; Financial Interests, Institutional, Other, SC Capitello; EC Cambria 1; PI and EC Cambria 2: AstraZeneca; Financial Interests, Institutional, Other, SC Inavo: Roche; Financial Interests, Institutional, Other, SC Destiny B05; SC Destiny B09: Daiichi Sankyo; Non-Financial Interests, Principal Investigator, After publication of primary endpoint: PI Aphinity; Non-Financial Interests, Advisory Role, Group in Germany responsible for breast cancer guidelines: AGO Kommission Mamma; Non-Financial Interests, Member, German Gynaecological Oncology society: AGO; Non-Financial Interests, Member, German Cancer Society: DKG; Non-Financial Interests, Member: ASCO; Non-Financial Interests, Member, Member guideline committee; past chair in ESMO Breast: ESMO; Other, Other, EP14153692.No financial interest, Institutional: Patent; Other, Other, EP21152186.No financial interest, institutional: Patent; Other, Other, EP18209672.No financial interest, Institutional: Patent; Other, Other, EP24210258.No financial interest, institutional: Patent. R. Barroso-Sousa: Financial Interests, Personal, Advisory Role: AstraZeneca/Daiichi Sankyo, Pfizer, Roche, Libbs, MSD, Lilly, AstraZeneca/Merck, AstraZeneca, Novartis; Financial Interests, Personal, Speaker's Bureau: MSD, Lilly, Novartis, AstraZeneca, Daiichi Sankyo/AstraZeneca, Roche, Gilead Sciences, Libbs, Pfizer; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: AstraZeneca/Daiichi Sankyo, MSD, Novartis; Financial Interests, Personal, Research Funding: AstraZeneca/Daiichi Sankyo. Y.H. Park: Financial Interests, Personal, Advisory Board: AstraZeneca, Pfizer, Roche, Novartis, MSD, Daiichi Sankyo, Helsinn, Voronoi, Aimer Blo; Financial Interests, Personal, Invited Speaker: AstraZeneca, Pfizer, Roche, Novartis, MSD, Daiichi Sankyo; Financial Interests, Institutional, Other, Research Grant: AstraZeneca, Pfizer, Roche, MSD; Financial Interests, Personal, Writing Engagement: Lilly; Non-Financial Interests, Principal Investigator: AstraZeneca, Pfizer, Novartis, MSD, Lilly, Roche, Daiichi Sankyo. C. Saura Manich: Financial Interests, Personal, Advisory Board: AstraZeneca, Boehringer Ingelheim, Bristol Meyers Squibb, Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann - La Roche Ltd, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Piere Fabre, PintPharma, Puma, Roche Farma, Sanofi-Aventis, SeaGen, Zymeworks, Genentech, Innoup, Millenium, Pharmalex Spain SLU; Financial Interests, Personal, Other, SC: Byondis B.V., GSK, Macrogenics, Menarini, Merus, Synthon Biopharmaceuticals; Financial Interests, Personal, Invited Speaker: Sociedade Portuguesa de Oncologia.; Financial Interests, Personal, Member of Board of Directors: Cooperative breast cancer group SOLTI; Financial Interests,

Institutional, Research Grant: AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Cytomx Therapeutics, Daiichi Sankyo, Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Genentech, GSK, Immunomedics, Innoup Farma, MacroGenics, Menarini Ricerche, Merus, Novartis, Pfizer, Puma, Roche, Sanofi-Aventis, Seattle Genetics; Financial Interests, Institutional, Coordinating PI: Byondis B.V.; Financial Interests, Institutional, Funding, institutional financial interest in form of financial support for clinical trials or contracted research: Amgen, BeiGene, Debiopharm International SA, Janssen-Cilag SA, Merck Health KGAA, Merck Sharp & Dohme, Mirati, Pharma Mar, Servier, Taiho Pharma USA Inc, Spanish Association Against Cancer Scientific Foundation and Cancer Research UK.; Financial Interests, Personal, Research Grant: Cooperative breast cancer group SOLTI.; Financial Interests, Personal, Coordinating PI: BN congress organization S.L. ; Non-Financial Interests, Member: Spanish Society of Medical Oncology (SEOM), American Society for Clinical Oncology (ASCO), Geicam (Spanish Breast Cancer Research Group), European Society for Medical Oncology (ESMO), Sinology Society of the Official College of Physicians of Barcelona (COMB), The European Association for Cancer Research (EACR.), Advisory Board on Cáncer Infertility and Pregnancy. (ABCIP); Non-Financial Interests, Member, Junta Directiva y Comité Científico: SOLTI group (Academic research group in breast cancer); Other, Member of the Consensus Panellist Group: International multidisciplinary consensus on the integration of radiotherapy with new systemic treatments for breast cancer: European Society for Radiotherapy and Oncology (ESTRO)-endorsed recommendations.: Consensus Panellist Group; Other, Associate Editor and Peer reviewer Breast Care Journal: Karger Publishers. M. Rimawi: Financial Interests, Personal, Advisory Board, Consulting: Novartis, AstraZeneca, Pfizer, Sermonix, Gilead, Menarini-Stemline; Financial Interests, Personal, Advisory Board, Advisory Board: Tempus AI; Financial Interests, Personal and Institutional, Coordinating PI: Greenwich Life Sciences. A. Schneeweiss: Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Roche, Pfizer, AstraZeneca, Daiichi Sankyo, Gilead Sciences; Financial Interests, Personal, Other, Honoraria: Amgen, Aurikamed, ClinSol, Connectmedica, Gilead Sciences, GSK, I-MED, Lilly, MCI Deutschland, MSD, Novartis, Onkowissen, Promedicis, Pfizer, Roche, Seagen, Streamedup!, AstraZeneca, Daiichi Sankyo, coma UroGyn, if-kongress, iOMEDICO; Financial Interests, Institutional, Research Funding: Roche Pharma AG. M. Toi: Financial Interests, Personal, Invited Speaker: AstraZeneca, Chugai, Devicore medical Japan, Eisai, Exact Science, MSD, Pfizer, Taiho, Yakult; Financial Interests, Personal, Advisory Board: Bertis, Kansai Medical Net; Financial Interests, Personal, Advisory Board, + Invited speaker: Daiichi Sankyo, Eli Lilly and companies; Financial Interests, Personal, Invited Speaker, + Invited speaker: Kyowa-Kirin; Financial Interests, Institutional, Funding, Funding to translational research of KBCRN assoc studies: The Kyoto Breast Cancer Research Network association; Non-Financial Interests, Member of Board of Directors, No salary: The Kyoto Breast Cancer Research Network association, The Japan Breast Cancer Research group association, Organisation for Oncology and Translational Research; Other, Other, Associate editor: Scientific Reports, Breast Cancer Research and Treatment, Cancer Science; Other, Other, Editorial board member: Asian Journal of Surgery, Asian Journal of Breast Surgery, Translational Breast Cancer Research. S. Im: Financial Interests, Personal, Advisory Board, no payment: AstraZeneca, Novartis, Eisai, Roche, Pfizer, Lilly, MSD, GSK, Daiichi Sankyo; Financial Interests, Institutional, Research Grant: AstraZeneca, Pfizer, Roche, Eisai; Financial Interests, Institutional, Local PI: AstraZeneca; Financial Interests, Institutional, Coordinating PI, Clinical Trial Budget: Eisai; Financial Interests, Institutional, Local PI, Clinical Trial Budget: Novartis, Roche, Pfizer, Daiichi Sankyo, MSD, Lilly; Financial Interests, Institutional, Research Grant, Clinical Trial Budget: Boryung Pharm. C.M. Villarreal Garza: Financial Interests, Personal, Invited Speaker: MSD Oncology, Novartis, Pfizer, Lilly; Financial Interests, Personal, Advisory Board: MSD Oncology, Lilly, Amplity Health, Novartis; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: MSD Oncology, Pfizer; Financial Interests, Personal, Research Grant: Pfizer; Non-Financial Interests, Member of Board of Directors: MILC - Medicos e Investigadores en la Lucha contra el Cancer. C. Huang: Non-Financial Interests, Personal and Institutional, Advisory Board, Grants to the institution: Daiichi Sankyo, Novartis, AstraZeneca, Eli Lilly, Pfizer, Roche; Non-Financial Interests, Personal and Institutional, Research Grant, Grants to the institution: Daiichi Sankyo, Novartis, AstraZeneca, EirGenix, Eli Lilly, Pfizer; Non-Financial Interests, Personal and Institutional, Speaker's Bureau, Grants to the institution: Daiichi Sankyo, Novartis, AstraZeneca, Eli Lilly, Pfizer, Roche; Non-Financial Interests, Institutional, Research Grant, Grants to the institution: MSD, Roche; Non-Financial Interests, Institutional, Advisory Board, Grants to the institution: MSD; Financial Interests, Institutional, Research Grant, Grants to the institution: OBI Pharma, Seagen, Aston Sci; Financial Interests, Personal and Institutional, Advisory Board, Grants to the institution: Gilead; Financial Interests, Personal and Institutional, Research Grant, Grants to the institution: Gilead; Financial Interests, Personal and Institutional, Sponsor/Funding, Grants to the institution: Gilead. T. Takano: Financial Interests, Personal, Invited Speaker: Daiichi Sankyo, Chugai, Eli Lilly, Gilead Sciences. V. Guarneri: Financial Interests, Personal, Advisory Board: Eli Lilly, Novartis, MSD, Gilead, Exact Sciences, Olema Oncology, AstraZeneca, Daiichi Sankyo, Pfizer, Roche, Pierre Fabre, Menarini Stemline, Eli Lilly; Financial Interests, Personal, Invited Speaker: Eli Lilly, Novartis, GSK, AstraZeneca, Gilead, Exact Sciences, zentiva, Menarini Stemline, Daiichi Sankyo, Roche; Financial Interests, Personal, Writing Engagement: Gilead; Financial Interests, Institutional, Local PI: Eli Lilly, Roche, BMS, Novartis, AstraZeneca, MSD, Synton Biopharmaceuticals, Merck, GSK, Daiichi Sankyo, Nerviano, Pfizer; Non-Financial Interests, Member: ASCO. S. Mondal: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks or ownership: AstraZeneca. D. Huang: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. A. Zeng: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks or ownership: AstraZeneca. S.M. Tolaney: Financial Interests, Personal, Advisory Role: Novartis, Pfizer, Merck, Lilly, AstraZeneca, Genentech, Eisai, Sanofi, Bristol Myers Squibb, Seagen, CytomX Therapeutics, Daiichi Sankyo, Immunomedics/Gilead, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, Umoja Biopharma, Menarini Group, AADi, Artios, Incyte, Bayer, Jazz Pharmaceuticals, Natera, Tango Therapeutics, Systimmune, eFFECTOR Therapeutics, Hengrui Pharmaceutica, Sumitovant Biopharma, Cullinan Oncology, Circle Pharma, Arvinas, BioNTech, Johnson & Johnson, Ambrx, Launch Therapeutics, Zuellig Pharma, Bicycle Therapeutics, BeiGene, Mersana, Summit Therapeutics; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Lilly, Sanofi, Gilead Sciences, Jazz Pharmaceuticals, Pfizer, Arvinas; Financial Interests, Institutional, Research Funding: Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Bristol Myers Squibb, Eisai, AstraZeneca, NanoString Technologies, Seagen, OncoPep, Gilead Sciences, Jazz Pharmaceuticals, Menarini/Stemlin; Non-Financial Interests, Personal, Other, Uncompensated relationship: AstraZeneca, Gilead Sciences. All other authors have declared no conflicts of interest.

