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First-line (1L) trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-mutant (HER2m) NSCLC: Patient-reported outcomes (PROs) from DESTINY-Lung04 (DL-04)

S. Novello[1], J.K. Rotow[2], K. Tanaka[3], K. Goto[4], M-J. Ahn[5], P.K. Cheema[6], J. Mazieres[7], A. Passaro[8], Y. Zhang[9], E. Nadal[10], H-W. Ko[11], N.S. Menon[12], E. Bria[13], S. Padda[14], W. Nassib William Junior[15], S. Mannix[16], L. Jung[17], E. Schreffler[18], B.T. Li[19], Y-L. Wu[20]

[1] Department of Oncology, Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Orbassano, University of Turin, Turin, Italy, [2] Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, United States of America, [3] Department of Respiratory Medicine, Kyushu University Hospital, Fukuoka, Japan, [4] Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [5] Section of Hematology-Oncology, Department of Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea, [6] Division of Medical Oncology, University of Toronto, William Osler Health System, Brampton, Canada, [7] Department of Pulmonology, CHU de Toulouse, Université de Toulouse, Toulouse, France, [8] Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milan, Italy, [9] Department of Medical Oncology, Lung Cancer and Gastrointestinal Unit, Hunan Cancer Hospital, Changsha, Hunan, China, [10] Department of Medical Oncology, Institut Català d'Oncologia (ICO), L'Hospitalet de Llobregat, Barcelona, Spain, [11] Division of Pulmonary Oncology, Department of Chest Medicine, Linkou Chang Gung Memorial Hospital, Department of Medicine, College of Medicine, Chang Gung University, Taoyuan City, Taiwan, [12] Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India, [13] Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy, [14] Department of Hematology/Oncology, Fox Chase Cancer Center, Temple Health, Philadelphia, United States of America, [15] Department of Thoracic Oncology, Groupo Oncoclínicas, São Paulo, Brazil, [16] Clinical Outcomes Assessment Measurement Science, Evinova, AstraZeneca Group, Gaithersburg, United States of America, [17] Oncology Biometrics, Oncology R&D, AstraZeneca, Gaithersburg, United States of America, [18] Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, United States of America, [19] Global Medical Affairs, Oncology Business Unit, AstraZeneca, Gaithersburg, United States of America[20] Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China

Background

In DL-04, 1L T-DXd significantly improved PFS vs pembrolizumab (P) + chemotherapy (C) in pts with advanced/metastatic HER2m NSCLC. Safety was generally consistent with the known profiles of each drug. Here, we report PROs from DL-04, focusing on pulmonary symptoms and pt-reported tolerability while on treatment (Tx).

Methods

DL-04 (NCT05048797) is a global, open-label, phase 3 study of pts with Tx-naïve HER2m (exon 19/20) NSCLC randomized 1:1 to T-DXd 5.4 mg/kg or P 200 mg + C (cisplatin 75 mg/m^2 or carboplatin AUC 5 + pemetrexed 500 mg/m^2), all IV Q3W. Secondary PRO endpoints were time to deterioration (TTD) in pulmonary symptoms while on Tx (cough, dyspnea, chest pain) via NSCLC-SAQ and pt-reported tolerability on Tx (including physical function [PF] via EORTC QLQ-C30 PF subscale, overall side-effect bother via Patient Global Impression of Treatment Tolerability [PGI-TT], and symptomatic AEs via EORTC and PRO-CTCAE item libraries). High side-effect bother (score of 4 or 5 via PGI-TT, first 12 weeks only) was exploratory.

Results

As of June 9, 2026, 454 pts were randomized. Median (range) Tx duration was 12.3 (0.7–44.8) months [mo] with T-DXd vs 7.1 (0.7–49.1) mo with P+C. T-DXd vs P+C delayed median (95% CI) TTD in cough (26.2 [17.1, NC] vs 11.0 [7.4, NC] mo; HR [95% CI] 0.66 [0.44, 0.99]), with favorable trends in dyspnea (10.1 [6.5, NC] vs 5.1 [3.2, 11.0] mo; HR 0.77 [0.54, 1.09]) and chest pain (NC [11.5, NC] vs 14.3 [8.3, NC] mo; HR 0.80 [0.54, 1.18]). The proportion of pts with maintained/improved PF was similar across arms until Week 18 and generally higher with T-DXd from Week 20, including at end of Tx (EOT, 66.7% T-DXd vs 57.7% P+C). Overall side-effect bother was similar across arms for most timepoints. The proportion of pt-weeks with high side-effect bother was 13.4% in each arm. Symptomatic AEs will be reported at the congress.

Conclusions

TTD in pt-reported pulmonary symptoms favored T-DXd vs P+C. Tx tolerability (PF and overall/high side-effect bother) was generally comparable between arms, with PF generally higher with T-DXd from Week 20 and at EOT. These results, alongside efficacy and safety data from the primary analysis, support T-DXd as a new 1L Tx option for HER2m NSCLC.

Clinical trial identification

NCT05048797.

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Legal entity responsible for the study

AstraZeneca.

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Disclosure

S. Novello: Financial Interests, Personal, Invited Speaker: AZ, MSD, Eli Lilly, Novartis, BeiGene, Amgen, Thermo Fisher, Accord, BeOne; Financial Interests, Personal, Advisory Board: BI, BMS, Pfizer, Takeda, Roche, Sanofi, Amgen, J&J, Pierre Fabre, PharmaMar; Financial Interests, Institutional, Coordinating PI, IIT: MSD, BI; Financial Interests, Institutional, Coordinating PI: AZ, AMG, Eli Lilly, Sanofi, J&J, Roche; Financial Interests, Institutional, Funding: PharmaMar; Non-Financial Interests, Leadership Role, president of this european advocacy: WALCE; Non-Financial Interests, Member: IASLC, AIOM, ASCO. J.K. Rotow: Financial Interests, Personal, Other, Consulting: AbbVie, Amgen, AstraZeneca, BMS, BioAtla, Boehringer Ingelheim, Catalyst, Daiichi Sankyo, EMD Serono, G1 Therapeutics, Genentech, Gilead, Jazz, Johnson and Johnson, Merus, Novocure, Nuvalent, Nuvation Bio, Pfizer, Regeneron, Summit, Takeda, Ottimo Pharma, Blossom Hill; Financial Interests, Personal, Invited Speaker: AstraZeneca, Daiichi Sankyo, Pfizer, Johnson and Johnson; Financial Interests, Institutional, Local PI: AbbVie, Bicycle Therapeutics, BioAtla, Blueprint Medicines, Daiichi Sankyo, Enliven, EpimAb, Lilly, ORIC, RedCloud, Summit, Black Diamond, Synthekine, ImmunityBio, Blossom Hill, Altor Bioscience, BioNTech; Financial Interests, Institutional, Coordinating PI: AstraZeneca; Financial Interests, Personal, Local PI: Regeneron. K. Goto: Financial Interests, Personal, Invited Speaker: Amgen K.K., AstraZeneca K.K., Boehringer Ingelheim Taiwan, Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Nippon Boehringer Ingelheim Co., Ltd., Nippon Kayaku Co.,Ltd., Novartis Pharma K.K., Regeneron Pharmaceuticals, Inc, Sysmex Corporation., Taiho Pharmaceutical Co., Ltd., Amoy Diagnosties Co.,Ltd., ArriVent Biopharma, Inc., Bayer HealthCare Pharmaceuticals Inc., Eisai Co., Ltd., Merck Biopharma Co., Ltd., Ono Pharmaceutical CO., LTD., Takeda Pharmaceutical Co., Ltd., Amgen K.K.; Financial Interests, Personal, Advisory Board: Amgen K.K., ArriVent Biopharma, Inc., Astellas Pharma Inc., Bayer HealthCare Pharmaceuticals Inc., Bayer Yakuhin, Ltd., Boehringer Ingelheim Taiwan, Bristol-Myers Squibb K.K., Daiichi Sankyo Co., Ltd., Foresight Diagnostics, Guardant Health Japan Corp., Nippon Boehringer Ingelheim Co., Ltd., Taiho Pharmaceutical Co., Ltd., Amgen Inc., Eli Lilly Japan K.K., Haihe Biopharma Co., Ltd., iTeos Therapeutics Inc., Novartis Pharma K.K., Pharma Mar, S.A.; Financial Interests, Personal, Other, consultant: Amplity, Inc., Boehringer Ingelheim International GmbH, GSK AG, Nippon Boehringer Ingelheim Co., Ltd., Pfizer Inc., GSK K.K.; Financial Interests, Personal and Institutional, Funding: AMCO INC., AbbVie Inc., AccuraGen Inc., Amgen K.K., AnHeart Therapeutics Inc., ArriVent Biopharma, Inc., AstraZeneca K.K., Bayer Yakuhin, Ltd., Belgian Volition SRL, BillionToOne, Inc., Blueprint Medicines Corporation., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Craif Inc., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Haihe Biopharma Co., Ltd., Ignyta,Inc., Janssen Pharmaceutical K.K., Kyowa Kirin Co., Ltd., Life Technologies Japan Ltd., Loxo Oncology, Inc., Lunit Inc., Medical & Biological Laboratories CO., LTD., MSD K.K., Merus N.V., Nuomaixi Biopharma (HK) Limited, Nippon Boehringer Ingelheim Co., Ltd., Nippon Kayaku Co.,Ltd., Novartis Pharma K.K., Nuvation Bio Inc., Ono Pharmaceutical Co., Ltd., Partner Therapeutics, Inc., Pillar Biosciences Inc., Precision Medicine Asia Co., Ltd., Riken Genesis CO., LTD., Revolution Medicines, Inc., Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Turning Point Therapeutics,Inc., Wellmira Inc., Guardant Health AMEA, INC., Pfizer Inc., Pfizer R&D Japan G.K., Spectrum Pharmaceuticals, Inc., Summit Pharmaceuticals International Corporation; Non-Financial Interests, Member: American Society of Clinical Oncology, The Japan Lung Cancer Society, Japanese Society of Medical Oncology, The Japanese Cancer Association, Japanese Society of Clinical Oncology, International Association for the Study of Lung Cancer. M. Ahn: Financial Interests, Personal, Advisory Board: AstraZeneca, Takeda, MSD, Yuhan, Amgen, Janssen, Bristol-Myers Squibb, Roche, Daiichi Sankyo, Merck, VORONOI, Genexin, Boehringer Ingelheim, AIMED BIO. P.K. Cheema: Financial Interests, Personal, Advisory Board: AstraZeneca, Amgen, Bristol Myers Squibb, Merck, Novartis, F. Hoffmann-La Roche, Janssen, GSK, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, iTEOS, Bayer; Financial Interests, Personal, Invited Speaker: Janssen, Merck, Daiichi Sankyo, Hoffman La Roche, Pfizer, Amgen, oncologyeducation.ca; Financial Interests, Personal, Writing Engagement: Amgen; Financial Interests, Institutional, Other, Grant: Eisai; Financial Interests, Personal, Steering Committee Member: AstraZeneca, Merck; Financial Interests, Institutional, Local PI: AstraZeneca, Bristol-Myers Squibb, Taiho, Takeda, F. Hoffmann La Roche, iTEOS Therapeutics, Merck, Gilead, GSK, AbbVie. J. Mazieres: Financial Interests, Personal, Advisory Board: Roche, AstraZeneca, Merck, BMS, Takeda, DAIICHI, Pierre Fabre, Amgen; Financial Interests, Personal, Invited Speaker: Roche, AstraZeneca, Pierre Fabre; Financial Interests, Institutional, Research Grant: Roche, Pierre Fabre; Financial Interests, Institutional, Funding: BMS. A. Passaro: Financial Interests, Personal, Advisory Board: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson Innovative Medicine, Pfizer, Roche, Bayer; Financial Interests, Personal, Invited Speaker: AstraZeneca, Boehringer Ingelheim, Johnson & Johnson Innovative Medicine,

Merck Sharp & Dohme, Mundipharma, Daiichi Sankyo, Medscape, eCancer, AbbVie; Financial Interests, Institutional, Steering Committee Member: Johnson & Johnson Innovative Medicine, MSD, Arrivent, Bayer, BMS, AbbVie; Financial Interests, Institutional, Local PI: Daiichi Sankyo, Janssen, Cullinan Oncology; Financial Interests, Institutional, Trial Chair: AstraZeneca. E. Nadal: Financial Interests, Personal, Advisory Board: Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Boehringer Ingelheim, Lilly, Pfizer, Merck Serono, Daiichi Sankyo, AstraZeneca, Takeda, Amgen, Sanofi, Qiagen, Janssen, Regeneron, Pierre Fabre, Genmab, Apollomics, BeiGene, PharmaMar, GSK, Gilead; Financial Interests, Personal, Invited Speaker: Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Lilly, Pfizer, Sanofi, AstraZeneca, Takeda, Amgen, Qiagen, Janssen, Daiichi Sankyo, Illumina, AbbVie; Financial Interests, Institutional, Funding, Clinical trial funded by Roche: Roche; Financial Interests, Institutional, Funding, Merck Serono funded a clinical trial: Merck Serono; Financial Interests, Institutional, Funding, BMS funded a clinical trial: Bristol-Myers Squibb; Non-Financial Interests, Advisory Role: Pfizer, Roche, Transgene, Boehringer Ingelheim; Other, Other, Member of the Steering Committee: Spanish Lung Cancer Group (GECP); Other, Other, Director of Research and Innovation: Catalan Institute of Oncology. H. Ko: Financial Interests, Institutional, Local PI, DL-04: AstraZeneca. N.S. Menon: Financial Interests, Institutional, Invited Speaker, Outside Submitted work: BMS; Financial Interests, Institutional, Invited Speaker: Pfizer, Zydus; Financial Interests, Institutional, Local PI, Outside the submittred workLocal (site) PI for Destiny Lung -04 trial: AstraZeneca; Financial Interests, Institutional, Local PI, Outside submitted work Local PI for PROSpect study (to determine the prevalence of HRRm in Indian mCRPC patients).: AstraZeneca; Financial Interests, Institutional, Local PI, Local PI for phase 3 ASIAD-3 trial: AURIGENE; Financial Interests, Institutional, Local PI: MSD. E. Bria: Financial Interests, Institutional, Coordinating PI: AstraZeneca, Roche; Financial Interests, Personal, Speaker, Consultant, Advisor, Speaker: Merck Sharp & Dohme, AstraZeneca, Pfizer, Eli Lilly, Bristol-Myers Squibb, Novartis, Takeda, Roche; Financial Interests, Personal, Speaker, Consultant, Advisor, Advisor: Merck Sharp & Dohme, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Roche, Amgen, Daiichi Sankyo, Celltrion. S. Padda: Financial Interests, Personal, Advisory Board, Member of aIndependent Data Monitoring Committee (IDMC): Revolution Medicine; Financial Interests, Personal, Advisory Board: Daiichi Sankyo, Natera Oncology, AstraZeneca, Regeneron, Bayer, Eli Lilly, BMS, Takeda, Summit; Financial Interests, Personal, Steering Committee Member: AstraZeneca. W. Nassib William Junior: Financial Interests, Personal, Invited Speaker: Amgen, Genentceh/Roche, Eli Lilly, BMS, Pfizer, Janssen, United Medical; Financial Interests, Personal, Advisory Board: AstraZeneca, Boehringer Ingelheim, Merck, Bayer, Sanofi, Takeda, Novartis, Daiichi Sankyo, BeiGene; Financial Interests, Institutional, Coordinating PI: AstraZeneca, MSD, Daiichi Sankyo, Johnson and Johnson; Financial Interests, Institutional, Local PI: Eli Lilly, Pfizer, Merus. S. Mannix: Financial Interests, Personal, Full or part-time Employment, Full-time employment: Evinova, AstraZeneca Group; Financial Interests, Personal, Stocks/Shares, As part of full-time employment: AstraZeneca. L. Jung: Financial Interests, Personal, Full or part-time Employment, Full-time employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares, As part of full-time employment: AstraZeneca. E. Schreffler: Financial Interests, Personal, Full or part-time Employment, Full-time employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares, As part of full-time employment: AstraZeneca. B.T. Li: Financial Interests, Personal, Full or part-time Employment, Full-time employment: AstraZeneca. Y. Wu: Financial Interests, Personal, Invited Speaker: AstraZeneca, BMS, Boehringer Ingelheim, BeOne, Hengrui, Merck, MSD, Pfizer, Roche; Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, Amgen, Daiichi Sankyo; Financial Interests, Coordinating PI: AstraZeneca, Boehringer Ingelheim, BMS, Hengrui, Merck, MSD, Pfizer, Roche, Eli Lilly; Financial Interests, Steering Committee Member: Sanofi, Yunhan; Non-Financial Interests, Leadership Role: Chinese Thoracic Oncology Group (CTONG); Non-Financial Interests, Other, WCLC 2020 Conference Chair: IASLC; Non-Financial Interests, Leadership Role, Past President: Chinese Society of Clinical Oncology (CSCO); Non-Financial Interests, Other, Editorial Board member of Ann Oncology and ESMO Open: ESMO. All other authors have declared no conflicts of interest.

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