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HexAgon-HN: A phase 2/3 study of the hexavalent OX40 agonist ordastobart (INBRX-106) in combination with pembrolizumab as first-line treatment (1L tx) of PD-L1–high recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) - Phase 2 primary analysis

J.C. Park¹, L.F.L. Licitra², E.J. Kang³, D.P. Zandberg⁴, J. Fayette⁵, K.J. Harrington⁶, M-H. Yang⁷, A. Gupta⁸, C.V. Lungulescu⁹, I. Hernandez Garcia¹⁰, M. Cossu Rocca¹¹, A. Carral Maseda¹², S. Sheth¹³, W. Ince¹⁴, C.C. Wang¹⁵, Y. Li¹⁶, Y. Diaz De Durana¹⁷, J. Martinalbo¹⁸, J. Garcia¹⁹, D.R. Adkins²⁰

¹ Department of Medicine, MGH - Massachusetts General Hospital, Boston, United States of America, ² Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori and University of Milan, Milan, Italy, ³ Department of Haemato-Oncology, Korea University Guro Hospital, Seoul, Republic of Korea, ⁴ Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, United States of America, ⁵ Medicine Department, Centre Léon Bérard, Lyon, France, ⁶ Department of Radiotherapy and Imaging, The Royal Marsden NHS Foundation Trust, London, United Kingdom, ⁷ Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan, ⁸ Clinical Oncology, Mount Vernon Cancer Centre, Middlesex, United Kingdom, ⁹ Department of Oncology, SC ONCOLAB SRL, Craiova, Romania, ¹⁰ Oncology, HUN - Hospital Universitario de Navarra, Pamplona, Spain, ¹¹ Division of Urogenital and Head and Neck Medical Oncology, IEO - Istituto Europeo di Oncologia IRCCS, Milan, Italy, ¹² Medical Oncology, CHUAC - Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, ¹³ Department of Hemato-Oncology, UNC - Lineberger Comprehensive Cancer Center, Chapel Hill, United States of America, ¹⁴ Oncology Department, Addenbrooke's Hospital, Cambridge, United Kingdom, ¹⁵ Department of Otolaryngology, Taichung Veterans General Hospital, Taichung City, Taiwan, ¹⁶ Department of Research, Inhibrx Biosciences, Inc., La Jolla, United States of America, ¹⁷ Clinical Research, Inhibrx Biosciences, Inc., La Jolla, United States of America, ¹⁸ Drug Development Oncology Department, Inhibrx Biosciences, Inc., La Jolla, United States of America, ¹⁹ Development Department, Inhibrx Biosciences, Inc., La Jolla, United States of America, ²⁰ Robert Ebert and Greg Stubblefield Head and Neck Tumor Center, Alvin J. Siteman Cancer Center, and Barnes Jewish Hospital, Washington University School of Medicine in St. Louis, St. Louis, United States of America

Background

Pembrolizumab (P) is a standard 1L tx option for R/M HNSCC, but response rates remain low. Addition of INBRX-106 (106), a hexavalent agonist engineered to promote higher-order OX40 clustering, to P may amplify and prolong the antitumor immune response.

Methods

In the phase 2 part of HexAgon-HN (NCT06295731), patients (pts) with 1L R/M HNSCC with high PD-L1 combined positive score (CPS; ≥ 20) were randomized 1:1 to open-label 106+P or P. The primary endpoint was confirmed objective response rate (ORR) by investigator per RECIST v1.1, with success defined as an observed Δ ORR ≥ 8 percentage points favoring 106+P; key secondary endpoints included progression-free survival (PFS) and safety.

Results

At data cutoff (19 Aug 2026), 68 pts were randomized (median follow-up, 7.0 mo); median age was 64.5 years; 85.3% were male; 57.4% had distant and 27.9% HPV+ disease. In response-evaluable pts (n=63), ORR (95% CI) with 106+P (n=29) was 48.3% (29.4, 67.5) vs 26.5% (12.9, 44.4) with P (n=34), ie, absolute Δ ORR of 21.8%. A greater effect was observed in pts with HPV+ disease: ORR 80.0% (3 CR + 5 PR) with 106+P (n=10) vs 33.3% (3 PR) with P (n=9); Δ ORR was 46.7%. Preliminary PFS analyses suggest a substantial improvement in PFS with 106+P; updated analyses will be presented. In the safety population (n=65), treatment-emergent adverse events (AEs) with 106+P vs P were reported in 100% vs 85.3% of pts, Grade (G) ≥ 3 AEs in 58.1% vs 47.1%, and serious AEs in 38.7% vs 35.3%. The most frequent treatment-related AEs (any G/G ≥ 3) with 106+P were rash (32.3%/3.2%), rash maculo-papular (32.3%/9.7%), diarrhea (29.0%/9.7%), and fatigue (29.0%/3.2%). Infusion-related reactions (22.6%/3.2%) were manageable and occurred mainly at first dose.

Conclusions

Addition of 106 to P as 1L tx for PD-L1 CPS ≥ 20 R/M HNSCC demonstrated an increase in ORR and showed a preliminary PFS benefit, with no new safety signals identified. A more pronounced effect in the prespecified HPV+ subgroup warrants further investigation. These positive randomized phase 2 results establish clinical proof of concept for OX40 agonism in cancer immunotherapy.

Clinical trial identification

NCT06295731.

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D.P. Zandberg: Financial Interests, Personal, Advisory Board: Merck, Coherus; Financial Interests, Personal, Advisory Board, Steering: Bicara, Seagen, Inhibrx Biosciences, Inc.; Financial Interests, Institutional, Research Funding: Merck, BMS, ISA Therapeutics, Bicara, Novasenta, Inhibrx Biosciences, Inc. K.J. Harrington: Financial Interests, Institutional, Advisory Board: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Merck, MSD, Pfizer, Replimune, Oncolys, Vyriad, Idera, BeiGene, GSK, Johnson and Johnson, QBiotech, AbbVie, Nanobiotix; Financial Interests, Institutional, Other, Honoraria for lectures: Amgen, AstraZeneca, BMS, Boehringer Ingelheim; Financial Interests, Institutional, Advisory Board, Advisory board for CD47 assets: Arch Oncology; Financial Interests, Institutional, Advisory Board, Development of DDR assets: ARTIOS; Financial Interests, Institutional, Advisory Board, Development of exosomal STING agonist: Codiak; Financial Interests, Institutional, Advisory Board, Development of oncolytic adenovirus: PsiVac; Financial Interests, Institutional, Advisory Board, Steering committee: ALX Oncology; Financial Interests, Institutional, Advisory Board, Development of preclinical asset: Onchilles; Financial Interests, Personal, Advisory Board, Consultancy: PDS Biotech; Financial Interests, Institutional, Funding, Research: AstraZeneca, Boehringer Ingelheim, MSD; Financial Interests, Institutional, Funding, Development of oncolytic HSV platform.: Replimune; Financial Interests, Institutional, Research Grant, Development of intratumoural therapy: Johnson & Johnson; Non-Financial Interests, Leadership Role, Chair of Steering Committee: ART NET; Non-Financial Interests, Other, Member of Global Steering Committee: MR - Linac. I. Hernandez Garcia: Financial Interests, Personal, Other, Educational Activities: Roche, AstraZeneca, MSD, Merck; Financial Interests, Personal, Other, Clinical Session Performance: Servier, Roche, AstraZeneca. A. Carral Maseda: Financial Interests, Personal, Advisory Board: Amgen, Bayer, BMS, Servier, Merck KGaA, Leo Pharma; Financial Interests, Personal, Invited Speaker: Grunenthal, Kyowa Kirin, Lilly, Novartis, Pierre Fabre, Sanofi, MSD, BeiGene, Roche; Financial Interests, Institutional, Local PI: Inhibrx, Regeneron Pharmaceuticals; Non-Financial Interests, Member of Board of Directors: TTCC. S. Sheth: Financial Interests, Personal, Advisory Board: Coherus Oncology, Eisai, Inhibrx Biosciences, Inc., Johnson & Johnson, Genmab; Financial Interests, Personal, Speaker's Bureau: Exelixis; Financial Interests, Personal, Research Funding: AstraZeneca, Exelixis, Inovio, Pharmaceuticals, Merck, Regeneron; Financial Interests, Personal, Advisory Board, Travel, Accommodations, Expenses: Merus. W. Ince: Non-Financial Interests, Personal, Other, Travel: MSD, Recordait, Merck, Johnson & Johnson, Novartis; Financial Interests, Personal, Advisory Role: Regeneron, Johnson & Johnson, Eisai, MSD; Financial Interests, Personal, Research Grant: MSD. Y. Li: Financial Interests, Personal, Full or part-time Employment: Inhibrx Biosciences, Inc.; Financial Interests, Personal, Stocks/Shares: Inhibrx Biosciences, Inc. Y. Diaz De Durana: Financial Interests, Personal, Full or part-time Employment: Inhibrx Biosciences, Inc.; Financial Interests, Personal, Stocks/Shares: Inhibrx Biosciences, Inc. J. Martinalbo: Financial Interests, Personal, Full or part-time Employment: Inhibrx Biosciences, Inc.; Financial Interests, Personal, Stocks/Shares: Inhibrx Biosciences, Inc. J. Garcia: Financial Interests, Personal, Full or part-time Employment: Inhibrx Biosciences, Inc.; Financial Interests, Personal, Stocks/Shares: Inhibrx Biosciences, Inc. All other authors have declared no conflicts of interest.