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A first-in-human study of oral IAG933 in adult patients with advanced mesothelioma and other solid tumours

E. Garralda[1], M. Florescu[2], J.G. Aerts[3], T. Yoshida[4], S. Postel-Vinay[5], I. Dagogo-Jack[6], M.G. Krebs[7], M. Metzenmacher[8], T. John[9], H.L. Kindler[10], M. Altan[11], L. Bankel[12], D. Shepard[13], Z.A.A. Wainberg[14], M. Duca[15], V.K. Lam[16], K. Parhiala[17], M-A. Altzerinakou[18], J. Faris[19], A. Santoro[20]

[1] Hospital Vall D Hebron, Vall D Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2] Hemato-oncology, Centre de recherche du CHUM, Montreal, Canada, [3] Pulmonary medicine, Erasmus MC University Hospital, Rotterdam, Netherlands, [4] Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [5] DITEP and U981 INSERM, Gustave Roussy, Villejuif, France and Cancer Institute, University College of London, London, United Kingdom, [6] Department of Medical Oncology, Massachusetts General Hospital, Boston, MA, United States of America, [7] The University of Manchester and, The Christie NHS Foundation Trust, Manchester, United Kingdom, [8] Department of Medical Oncology, University Hospital Essen, Essen, Germany, [9] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [10] Department of Medicine - Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL, United States of America, [11] Thoracic/ Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, United States of America, [12] Medical Oncology Department, University Hospital Zürich, Zurich, Switzerland, [13] Medical oncology, Cleveland Clinic, Cleveland, United States of America, [14] Medicine Haematology and Oncology Dept., University of California Los Angeles, Los Angeles, United States of America, [15] Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [16] Oncology Dept., Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, United States of America, [17] Translational Clinical Oncology, Novartis Biomedical Research, Cambridge, United States of America, [18] Early Dev. Analytics, Novartis Pharma AG, Basel, Switzerland, [19] Translation Clinical Oncology, Novartis Biomedical Research, Cambridge, MA, United States of America[20] Humanitas University, And Humanitas Research Hospital-Humanitas Cancer Center, Milan, Italy

Background

Hyperactivation of the YAP/TAZ–TEAD transcriptional complex occurs in many cancers, particularly in pleural mesothelioma (PM) owing to frequent hippo pathway alterations such as NF2 or LATS1/2 inactivating mutations. IAG933 directly disrupts the interface between YAP/TAZ and all four TEADs leading to tumour regression in preclinical models. We report dose escalation data from the ongoing first-in-human study of IAG933 in patients (pts) with mesothelioma, which did not require mutational testing for eligibility, and other solid tumours with key Hippo pathway alterations, or with functional YAP-TAZ fusions (e.g. epithelioid haemangioendothelioma [EHE]).

Methods

This is a phase I, open-label, multi-centre, dose escalation and expansion study of IAG933 (NCT04857372). IAG933 is administered orally, using an intermittent 3 days on, 4 days off (INT) or continuous (CONT) schedule. Key aims are to assess safety and tolerability, recommended dose/schedule, and antitumor activity of IAG933.

Results

As of 14 Feb 2025, 130 pts were treated (INT [n=42], and CONT dosing [n=88]). Diagnoses included PM (n=100), peritoneal mesothelioma (PeriM; n=10), EHE (n=9), meningioma (n=6), and other solid tumours (n=5). Median (range) age was 65.0 (21.0–84.0) years. Most treatment-related adverse events (TRAEs) were grade (G) G1/G2. TRAEs occurred in 83 pts (63.8%); 9 pts (6.9%) had ≥G3 TRAEs. The most common TRAEs were fatigue (20.0%), peripheral oedema and proteinuria (10.8% each). G3 QTc prolongation was a dose-limiting toxicity in 4 pts (2 pts at 600 mg INT, 2 pts at 400 mg CONT). Five confirmed partial responses (4 PM and 1 PeriM) were observed. In the pooled 300/400 mg CONT cohorts in PM, the overall response rate was 12% (3/25), with a disease control rate of 36%. Overall, 28 pts had a duration of treatment ≥ 6 months, including 6 pts with ≥ 12 months and 2 pts with ≥18 months.

Conclusions

IAG933 is a direct inhibitor of the YAP-TEAD protein-protein interaction. In the dose escalation phase of this trial, IAG933 was well-tolerated and demonstrated clinical efficacy.

Clinical trial identification

NCT04857372.

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Legal entity responsible for the study

Novartis Pharmaceuticals Corporation.

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Disclosure

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Florescu: Financial Interests, Personal, Invited Speaker: Astra-Zenéca, Roche, Takeda, Bristol Myers Squibb; Financial Interests, Personal, Other, Honorarium: Astra-Zenéca, Roche, Takeda, ristol-Myers Squibb. J.G. Aerts: Financial Interests, Personal, Advisory Board: MSD, AstraZeneca, Amphera, Danone; Financial Interests, Personal, Invited Speaker: Eli-lily, MSD, Bristol Myers Squibb. T. Yoshida: Financial Interests, Personal, Advisory Board: Pfizer, MSD, Amgen, Boehringer Ingelheim; Financial Interests, Personal, Invited Speaker: AstraZeneca, Chugai pharmaceutical, Pfizer, Takeda, Lilly, Ono pharmaceutical, Novartis, Daiichi sankyo, MSD, BMS, Amgen; Financial Interests, Institutional, Local PI: AstraZeneca, Novartis, Amgen, Daiichi sankyo, BMS, MSD, Ono pharmaceutical, Chugai pharmaceutical, AbbVie, Astellas, Boehringer Ingelheim, Nuvalent. S. Postel-Vinay: Financial Interests, Institutional, Advisory Board, Steering Committee: Daiichi Sankyo; Financial Interests, Institutional, Advisory Board, Steering committee: AMGEN; Financial Interests, Personal, Advisory Board: Epics therapeutics; Financial Interests, Institutional, Local PI, As part of the Drug Development Department (DITEP) SPV is Principal/sub-Investigator of Clinical Trials for AbbVie, Adaptimmune, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co, Clovis Oncology, Cullinan-Apollo, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Tharapeutics, Gamamabs, Genentech, GSK, H3 Biomedicine, Hoffmann La Roche Ag, Imcheck Therapeutics, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Janssen Cilag, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharm. 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Dagogo-Jack: Financial Interests, Personal, Advisory Board: AstraZeneca, Bayer, BostonGene, Bristol Myers Squibb, Catalyst, Eli Lilly, Genentech, Janssen, Merus, Novocure, Pfizer, Sanofi/Genzyme, ThermoFisher Scientific; Financial Interests, Institutional, Research Funding: Array, BostonGene, Genentech, Pfizer; Financial Interests, Personal and Institutional, Research Funding: Novartis. M.G. Krebs: Financial Interests, Personal, Advisory Board: Bayer, Roche, Janssen, Guardant Health, Zai Lab; Financial Interests, Personal, Invited Speaker: Roche, Janssen, Eisai; Financial Interests, Institutional, Advisory Board: AstraZeneca, Seattle Genetics; Financial Interests, Personal, Invited Speaker, Invited speaker - Finland: BMS; Financial Interests, Institutional, Coordinating PI: AstraZeneca, Carrick, Janssen, Pyramid Biosciences, Ellipses, Oric Pharmaceuticals; Financial Interests, Institutional, Local PI: Blueprint, Astex, Bayer, BerGenBio, Immutep, Novartis, Nurix, Nuvalent, Roche, Seattle Genetics, Turning Point Therapeutics, Relay Therapeutics, BMS; Financial Interests, Institutional, Research Grant: Roche, Novartis; Other, Other, Travel expenses for congress: Immutep, Janssen; Other, Other, Travel expenses: Roche, Zai Lab; Other, Other, Travel Expenses: BMS. M. Metzenmacher: Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, Johnson&Johnson, MSD, Novartis, Novocure, Pfizer, Roche, Takeda. T. John: Financial Interests, Personal, Invited Speaker, Speaker tour Vietnam: AstraZeneca; Financial Interests, Personal, Advisory Board: BMS, AstraZeneca, Bayer, Specialised Therapeutics; Financial Interests, Institutional, Advisory Board: Roche, Novartis, Pfizer, Amgen, Takeda, PharmaMar, Johnson and Johnson, Seagen Pharmaceuticals, Merck Serono, Bayer; Financial Interests, Institutional, Invited Speaker: Beigene; Non-Financial Interests, Principal Investigator, Oceanic study: AstraZeneca. H.L. Kindler: Financial Interests, Personal, Other, Consultant: Amgen, AstraZeneca, Enlaza. M. Altan: Financial Interests, Institutional, Research Funding: Genentech, Nektar Therapeutics, Merck, GSK, Novartis, Jounce Therapeutics, Bristol Myers squibb, Eli Lilly, Adaptimmune, Shattuck lab, Gilead, Verismo Therapeutics, Lyell; Financial Interests, Personal, Advisory Board: GSK, Shattuck Lab, Bristol Myers Squibb, AstraZeneca, Insightec, Regeneron, Genprex, Lyell; Financial Interests, Personal, Invited Speaker: AstraZeneca, Nektar Therapeutics, SITC, Regeneron. D. shepard: Financial Interests, Personal, Advisory Board: Deciphera, Parabilis, Bayer, Ipsen; Financial Interests, Personal, Other, Steering committee; Speaker: Aadi Bioscience; Financial Interests, Personal, Invited Speaker: ngsworks TherapeuticsSpri; Financial Interests, Institutional, Research Funding: Eli Lilly, Polaris Pharmaceuticals,

Kinnate Biopharma, Pfizer, Novartis, Servier, Inhibrx, Cogent Biosciences, Abbisko Therapeutics, PMV Pharmaceuticals, Nucmito Pharmaceuticals, Numab Therapeutics AG. Z.A.A. Wainberg: Financial Interests, Personal, Advisory Board: Amgen, Astellas, Arcus, Bayer, AstraZeneca, Novartis, Roche, Ipsen, Daiichi, Merck, BMS, Alligator, Jannsen, Boehringer Ingelheim, Phanes; Financial Interests, Personal, Other, DMC: Pfizer; Financial Interests, Institutional, Steering Committee Member: Novartis, AstraZeneca; Financial Interests, Institutional, Coordinating PI: Ipsen; Financial Interests, Institutional, Local PI: Merck; Financial Interests, Institutional, Research Grant: BMS, Arcus. V.K. Lam: Financial Interests, Personal, Other, consultant/advisory role: Pfizer, Genentech/Roche, Lovance Biotherapeutics, Takeda, Seattle Genetics, Bristol Myers Squibb, AstraZeneca, Guardant Health, Eli Lilly, Nuvation Bio; Financial Interests, Personal, Research Funding: GSK, Bristol Myers Squibb, AstraZeneca, Merck, Novartis. K. Parhiala: Financial Interests, Institutional, Full or part-time Employment: Novartis Pharmaceuticals Corporation. M. Altzerinakou: Financial Interests, Institutional, Full or part-time Employment: Novartis Pharma AG. J. Faris: Financial Interests, Institutional, Full or part-time Employment: Novartis Pharmaceutical Corporation. A. Santoro: Financial Interests, Institutional, Other, Consultancy: Sanofi, Incyte; Financial Interests, Institutional, Advisory Board: BMS, Servier, Gilead, Pfizer, Eisai, Bayer, MSD; Financial Interests, Institutional, Other, Speaker's Bureau: Takeda, BMS, Roche, AbbVie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, MSD, BeiGene. All other authors have declared no conflicts of interest.