BERLIN 2025 ESMO congress

1065MO

First-in-human study of AZD5335, a folate receptor α (FRα)-targeted antibody-drug conjugate, in patients with platinum-resistant recurrent ovarian cancer

A. Oaknin[1], R. Perets[2], R. Shapira-Frommer[3], A.M. Oza[4], J.E. Ang[5], K. Sudo[6], K. Wilkinson[7], R. Yin[8], L.M. Manso Sanchez[9], J. Garcia-Corbacho[10], S.A. Welch[11], Q. Zhou[12], M. Song[13], L. Mileshkin[14], E. Chow[15], C. Myers[16], P. Mitchell[17], S. Upadhyay[18], T. Brier[19], F. Meric-Bernstam[20]

[1] Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain, [2] Division of Oncology, Rambam Health Care Center, Haifa, Israel, [3] Oncology Department, The Ella Institute for Treatment and Research of Melanoma and Skin Cancer - Sheba Medical Center, Ramat Gan, Israel, [4] Surgical Oncology – Division of Urology GU Clinic, Princess Margaret Cancer Centre, Toronto, Canada, [5] Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust Cambridge, Cambridge, United Kingdom, [6] Department of Medical Oncology, National Cancer Center Hospital, Chuo-ku, Japan, [7] Liverpool Cancer Therapy Centre, Liverpool Hospital, Liverpool, Australia, [8] Department of Gynecology and Obstetrics, West China Second University Hospital, Chengdu, China, [9] Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain, [10] Medical Oncology/Phase 1 Clinical Trials Unit, Hospital Universitario Virgen de la Victoria, Malaga, Spain, [11] Oncology, London Health Sciences Centre London Regional Cancer Program, London, Canada, [12] Department of Gynecologic Oncology, Chongqing Cancer Hospital, Chongqing, China, [13] Department of Surgery, Orange County Lennar Foundation Cancer Center, Irvine, United States of America, [14] Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia, [15] Clinical Pharmacology, AstraZeneca, Gaithersburg, United States of America, [16] Translational Medicine, AstraZeneca, Gaithersburg, United States of America, [17] Statistical Science, AstraZeneca, Waltham, United States of America, [18] Global Medicines, AstraZeneca, Cambridge, United Kingdom, [19] Early Global Development, AstraZeneca, Cambridge, United Kingdom[20] Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, United States of America

Background

AZD5335 is an antibody-drug conjugate that binds FRα on tumour cells and delivers a topoisomerase 1 inhibitor payload. FONTANA (NCT05797168) is a Phase 1/2a, first-in-human, modular open-label study of AZD5335 in patients (pts) with advanced solid tumours. Initial results from monotherapy dose escalation (Part A) have been presented (Shapira-Frommer ESMO 2024). We report the initial data from AZD5335 monotherapy dose optimization (Part B1).

Methods

Pts aged ≥18 years with platinum-resistant ovarian cancer were recruited to Part A (FRα expression-unselected, no restriction on prior lines of therapy [LOT]) and Part B1 (FRα-selected, ≤3 prior LOT, randomized allocation to dose cohorts). AZD5335 was administered Q3W IV at 5 dose levels (0.8–3.0 mg/kg) in Part A and at 1.6, 2.0 and 2.4 mg/kg in Part B1 until disease progression or unacceptable toxicity. The primary objective was safety and tolerability; secondary objectives included preliminary efficacy.

Results

As of 14 March 2025, 183 pts had received treatment (Part A, n=59; Part B1, n=124). Median duration of exposure was 3.8 months (range 0.3–15.5) with 107 pts (58.5%) remaining on-treatment at the data cut-off. The most common possibly treatment-related adverse events (TRAEs) (any grade [G], G3–4) were nausea (72.7%, 4.9%), fatigue (45.9%, 3.8%), neutropenia (44.8%, 22.9%), vomiting (40.4%, 4.9%), and anaemia (38.8%, 14.2%). Possible TRAEs led to dose reduction in 19.7% of pts and discontinuation in 7.1%. The maximum tolerated dose was not defined. The objective response rate for the 1.6, 2.0 and 2.4 mg/kg dose levels combined was 60.7% (95% CI: 46.8, 73.5) in pts with high FRα expression (≥75% tumour cells staining at ≥2+ intensity, n=56), and 47.5% (95% CI: 34.6, 60.7) in pts with low FRα expression (≥25% tumour cells staining at ≥1+ intensity, n=61). Progression-free survival data will be presented.

Conclusions

AZD5335 is associated with a manageable safety profile and has demonstrated competitive efficacy across all dose levels selected for dose optimization and in both high and low FRα-expressing tumours. Data from this trial will inform future monotherapy and combination opportunities in ovarian and additional solid tumours.

Clinical trial identification

NCT05797168; release date: 4 April 2023.

Editorial acknowledgement

Medical writing support for the development of this abstract, under the direction of the authors, was provided by Taylor Stepien, PhD (Chicago, IL, USA) of Ashfield Medcomms, an Inizio company, and was funded by AstraZeneca.

Legal entity responsible for the study

AstraZeneca.

Funding

AstraZeneca.

Disclosure

A. Oaknin: Financial Interests, Personal, Advisory Board: AbbVie, Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Daiichi Sankyo, Debiopharm International, Deciphera Pharmaceuticals, Eisai, Exelixis, F. Hoffmann-La Roche, GSK, Genmab, Immunogen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncXerna Therapeutics, Inc, PharmaMar, Regeneron, Sattucklabs, Seagen/Pfizer, Sutro Biopharma, TORL Therapeutics, Zentalis, Zymeworks, Stemline Therapeutics; Financial Interests, Personal, Other, Travel and accommodation: AstraZeneca, PharmaMar, Roche; Financial Interests, Institutional, Funding: Amgen, AbbVie Deutschland, Advaxis Inc., Aeterna Zentaris, Aprea Therapeutics AB, Regeneron Pharmaceuticals, Clovis Oncology Inc, Eisai limited Ltd, F. Hoffmann–La Roche Ltd, Immunogen Inc, Merck, Sharp & Dohme de España SA, Millennium Pharmaceuticals Inc, PharmaMar SA, Tesaro Inc., Bristol Myers Squibb; Non-Financial Interests, Leadership Role, on behalf of GEICO: GCIG; Non-Financial Interests, Officer, Chair of Gynaecological Track ESMO 2019. Scientific Track Member Gynaecological Cancers ESMO 2018, ESMO 2020, ESMO 2022. Member of Gynaecological Cancers Faculty and Subject Editor Gyn ESMO Guidelines: ESMO; Non-Financial Interests, Leadership Role, ESMO GYN Co-Chair 2023 - 2025: ESMO; Non-Financial Interests, Leadership Role, Chair de Cervix Committee. 2022-2024: GCIG; Non-Financial Interests, Member: ESMO, ASCO, GCIG, SEOM, GOG. R. Perets: Financial Interests, Personal, Advisory Board: Third Arc Bio; Financial Interests, Personal, Advisory Role: Nevia Bio, Simplivia; Financial Interests, Personal, Invited Speaker: GSK, AstraZeneca; Financial Interests, Personal and Institutional, Local PI: AstraZeneca, AbbVie, MSD, Genentech, Regeneron, Gilead, Amgen, Sanofi, Biomica, BMS, Bind Biologics, Third Arc Bio; Financial Interests, Institutional, Research Grant: Gilead; Financial Interests, Personal, Speaker, Consultant, Advisor: GSK, AstraZeneca, Neopharm. R. Shapira-Frommer: Financial Interests, Personal, Advisory Board: MSD; Financial Interests, Personal, Invited Speaker: MSD, AstraZeneca, Merck, Sanofi, BMS; Financial Interests, Institutional, Research Grant: MSD. A.M. Oza: Financial Interests, Institutional, Research Grant, Funding for investigator initiated studies received within the last 36 months: AstraZeneca; Financial Interests, Institutional, Coordinating PI: Ontario Institute for Cancer Research; Non-Financial Interests, Advisory Role, Uncompensated: AstraZeneca, GSK; Non-Financial Interests, Principal Investigator, Investigator-initiated studies with agents from AstraZeneca: AstraZeneca; Non-Financial Interests, Principal Investigator, Investigator-initiated studies with agents from GSK: GSK; Non-Financial Interests, Advisory Role, Oncology Tumor Advisory Council: Bristol Myers Squibb. J.E. Ang: Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, GSK; Financial Interests, Personal, Invited Speaker: AstraZeneca, GSK; Financial Interests, Institutional, Local PI: AstraZeneca, GSK, MSD, Daiichi Sankyo, Mersana Therapeutics; Financial Interests, Institutional, Coordinating PI: GSK, Daiichi Sankyo. K. Sudo: Financial Interests, Institutional, Principal Investigator: NanoCarrier, Daiichi Sankyo, AstraZeneca, Pfizer, Amgen, PRA Health Sciences, Takeda, Merck, Gilead Sciences, Loxo/Lilly; Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, Pfizer, Eisai, Nihon Medi-Physics, Janssen, Bayer Yakuhin, MSD. K. Wilkinson: Financial Interests, Personal, Invited Speaker: MSD; Non-Financial Interests, Institutional, Principal Investigator: A2, GSK, Innovent, Merck; Financial Interests, Personal, Sponsor/Funding: MSD. L.M. Manso Sanchez: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, pharma&, Genmab, GSK, MSD, Novartis, Roche, Seagen; Financial Interests, Personal, Other, Honoraria: AstraZeneca, GSK, MSD, Roche; Financial Interests, Personal, Other, Travel: AstraZeneca, GSK, MSD, Roche. J. Garcia-Corbacho: Financial Interests, Institutional, Funding: AstraZeneca, BMS, Pfizer, Regeneron, Amgen, Novartis, Daiichi Sankyo, GEICAM, Boehringer Ingelheim, MSD, Bayer, GSK; Non-Financial Interests, Personal, Local PI: AstraZeneca, BMS, Pfizer, Regeneron, Amgen, Novartis, Daiichi Sankyo, GEICAM, Boehringer Ingelheim, MSD, Bayer, GSK; Financial Interests, Institutional, Other, Event organization support: AstraZeneca, Pfizer, Regeneron, GSK; Non-Financial Interests, Personal, Principal Investigator: AstraZeneca, BMS, Pfizer, Regeneron, Amgen, Novartis, Daiichi Sankyo, GEICAM, Boehringer Ingelheim, MSD, Bayer, GSK. S.A. Welch: Financial Interests, Personal, Advisory Board: AstraZeneca, GSK, Merck, Eisai, AbbVie; Financial Interests, Personal, Advisory Role: Eisai; Financial Interests, Institutional, Local PI: AstraZeneca, Merck, Alkermes, Novartis, GSK; Financial Interests, Institutional, Speaker, Consultant, Advisor: AstraZeneca; Financial Interests, Personal, Speaker, Consultant, Advisor: GSK, Merck, Eisai. L. Mileshkin: Financial Interests, Personal, Advisory Board, Participation in Dostarlimab advisory board: GSK; Financial Interests, Personal, Invited Speaker, Remuneration for talk given at educational event: GSK; Financial Interests, Personal, Invited Speaker, Renumeration for talk at education event: The Limbic; Financial Interests, Institutional, Coordinating PI, Institutional funding from Beigene for an investigator-initiated trial: Beigene; Financial Interests, Personal, Coordinating PI, Support for flights to attend ESMO meetings in Madrid and Singapore to present results of the CUPISCO trial: Roche; Financial Interests, Personal, Other, Medical writing support for publications related to the CUPISCO trial: Roche; Non-Financial Interests, Other, Co-chair of the Steering Committee for the CUPISCO trial in CUP (non-remunerated): Roche; Non-Financial Interests, Member, Member of multiple other cancer organisations as above: ASCO, MOGA, COSA, IGCS, GCIG. E. Chow, S. Upadhyay, T. Brier: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. C. Myers, P. Mitchell: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares:

AstraZeneca. F. Meric-Bernstam: Financial Interests, Personal, Other, Consultant: AstraZeneca, OnCusp Therapeutics, Zymeworks, Debiopharm; Financial Interests, Personal, Other, Consulting: Calibr, Ecor1, Exelixis, GT Aperion, Infinity Pharmaceuticals, Loxo-Oncology, LegoChem Bio, Lengo Therapeutics, Tallac Therapeutics, Becton Dickinson, eFFECTOR Therapeutics, Jazz Pharmaceuticals, Elevation Oncology, Molecular Templates, Tempus; Financial Interests, Personal, Advisory Board: Daiichi Sankyo, Incyte, Karyopharm, Protai, TheraTechnologies, Zentalis, FogPharma, Harbinger Health, Mersana Therapeutics, Sanofi Pharmaceuticals; Financial Interests, Personal, Other, Consulting: Menarini Group; Financial Interests, Personal, Advisory Board, Advisory Board/Consultant: Seagen; Financial Interests, Personal, Invited Speaker: Dava Oncology; Financial Interests, Personal, Other, Consulting: Ribometrix; Financial Interests, Institutional, Other, Local PI / Research Grant: Aileron Therapeutics, Bayer Healthcare, CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., eFFECTOR Therapeutics, Taiho Pharmaceutical Co.; Financial Interests, Institutional, Other, Local PI / Research Grant / Coordinating PI: AstraZeneca; Financial Interests, Institutional, Local PI: Calithera Biosciences, Curis Inc., Debiopharm International, Guardant Health Inc., Klus Pharma, Novartis, Jazz Pharmaceuticals, Zymeworks; Financial Interests, Institutional, Other, Local PI / Steering Committee Member: Genentech Inc.; Financial Interests, Institutional, Research Grant: Takeda Pharmaceutical Co., Puma Biotechnology Inc., Repare; Other, Travel support: European Organisation for Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO); Other, Travel Support: Cholangiocarcinoma Foundation, Dava Oncology; Other, Honoraria: Dava Oncology. All other authors have declared no conflicts of interest.