BERLIN 2025 ESMO congress

LBA40

WES-derived aneuploidy score (W-AS) identifies MMRd patients with reduced benefit from immunotherapy in endometrial cancer: Multi-omic analysis of the phase III AtTEnd/ENGOT-EN7 trial

L. Mazzarella[1], N. Colombo[2], K. Harano[3], E. Rulli[4], Y. Antill[5], E. Hudson[6], Y.M. Kim[7], F. Heitz[8], M. Rabaglio[9], E. Piovano[10], J.F. Cueva Banuelos[11], K. Takehara[12], J. Lombard[13], K. Allan[14], G. Tasca[15], E. Bignotti[16], S. Uggeri[4], G. Frige[1], M. Barberis[1], M.P. Barretina Ginesta[17]

[1] DIMA, Dept of Advanced Molecular Diagnostics, Istituto Europeo di Oncologia IRCCS, Milan, Italy, [2] Department of Medicine and Surgery, University of Milan–Bicocca, and Division of Gynecologic Oncology, European Institute of Oncology IRCCS, Milan, Italy, [3] 3. Department of Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4] Clinical Oncology, Istituto di Ricerche Farmacologiche Mario Negri - IRCCS, Milan, Italy, [5] Dept Medical Oncology, Peninsula Health, Melbourne, Australia, [6] Velindre Cancer Centre, Velindre University NHS Trust, Cardiff, United Kingdom, [7] Obstetrics and Gynecology / Gynecologic Cancer Center, Asan Cancer Institute, Seoul, Republic of Korea, [8] AGO Germany, Department of Gynecology & Gynecologic Oncology, Evangelische Kliniken Essen-Mitte Essen, Germany and Department for Gynecology with the Center for Oncologic Surgery Charité Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [9] Medical Oncology Department, Inselspital - Universitatsspital, Bern, Switzerland, [10] Obstetrics and Gynecology Academic Unit, AOU Città della Salute e della Scienza di Torino - Presidio Sant'Anna, Turin, Italy, [11] Dept. Medical Oncology, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain, and GEICO, Santiago de Compostela, Spain, [12] Gynecologic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [13] Medical Oncology, Calvary Mater Hospital Newcastle, Newcastle, Australia, [14] Glasgow Oncology Clinical Trials Unit, The Beatson WoS Cancer Centre, Glasgow, University of Glasgow, Glasgow, United Kingdom, [15] Oncology Unit 2, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy, [16] UO Ostetricia-Ginecologia, ASST Spedali Civili di Brescia, Brescia, Italy[17] Medical Oncology Department- Institut Català d'Oncologia-Girona, IDIBGI-CERCA, and GEICO, Girona, Spain

Background

The addition of Atezolizumab to standard chemotherapy significantly improves outcome in advanced/metastatic endometrial cancer with mismatch repair deficiency (MMRd). However, not all MMRd tumors benefited from the addition, and predictive biomarkers are not established.

Methods

Baseline surgical/biopsy specimens from 125 MMRd and 409 non-MMRd tumors from patients randomized in the AtTEnd trial were processed for multiomic analysis, including RNAseq (ongoing), Whole Exome Sequencing (WES by Twist Exome 2.0, analysed through Dragen v.4.2.4 and ASCETS) and multiplexed immunofluorescence with an 18-antibody panel. Univariable Cox proportional hazards models were used to explore the prognostic and predictive effect on progression free survival (PFS) and overall survival (OS).

Results

WES was finalized for 234 patients overall, including all available MMRd samples (110/125, 88.0%). Key findings from the analysis of individual mutations include: low incidence of POLE mutations (1/234); a dual MMRd/BRCA1/2-mutated profile (14/234); a high frequency of MSH3 mutations in MMRd patients (29/110). No individual mutation was associated with outcome, but MMRd tumors with combined alterations in APC and CTNNB1 (WNT pathway) (23/110, 20.9%) showed worse PFS (HR 1.91, 95% CI 1.10-3.33, p=0.0201). W-AS > 0.2 was found in 10/110 (9.1%) MMRd tumors and was associated with worse PFS (HR 2.81, 95%CI 1.33-5.97, p=0.0049) and OS (HR 2.51, 95%CI 1.12-5.65, p=0.0211). W-AS-high tumors did not benefit from atezolizumab in PFS (interaction p=0.0016. Low AS: HR 0.28, 95%CI 0.16-0.47, p<0.0001; High AS: HR 3.60, 95%CI 0.71-18.29, p=0.1006). Preliminary data suggested a lower immune cell infiltration in W-AS-high tumors, characterized by a reduced proportion of CD4+ helper T cells and an increased proportion of M2 macrophages.

Conclusions

If externally validated, W-AS may identify patients with MMRd tumors who derive limited benefit from adding immunotherapy to standard chemotherapy. Genetic assessment of W-AS, MSH3 and WNT genes should be considered in the prognostic workup of advanced/metastatic endometrial cancer.

Clinical trial identification

EudraCT 2018-001072-37; NCT03603184.

Legal entity responsible for the study

Istituto di Ricerche Farmacologiche Mario Negri, IRCCS.

Funding

Pharmaceutical Company (F Hoffmann-La Roche). Italian Ministry of Health, Ricerca Corrente 2020-2022 and Ricerca Corrente di Rete (ACCORD) 2022-2024s. IEO/Monzino Foundation.

Disclosure

L. Mazzarella: Financial Interests, Personal, Advisory Board, member of Scientific advisory board: Tethis; Financial Interests, Institutional, Research Grant, research grant: Bristol Myers Squibb International. N. Colombo: Financial Interests, Personal, Advisory Board, Various: Roche, AstraZeneca, MSD/Merck, GSK, Immunogen; Financial Interests, Personal, Invited Speaker, Congress, Symposia, Lectures: AstraZeneca; Financial Interests, Personal, Advisory Board, Lectures: Eisai; Financial Interests, Personal, Advisory Board, Advisory Role: Onxerna; Financial Interests, Personal, Invited Speaker: MSD/MERCK; Financial Interests, Personal, Invited Speaker, Speaker: GSK; Financial Interests, Personal, Advisory Board: Novocure, BioNTech, Gilead, AbbVie; Financial Interests, Institutional, Research Grant: AstraZeneca, GSK; Non-Financial Interests, Leadership Role, Chair, Scientific Committee: ACTO (Alleanza contro il tumore ovarico). K. Harano: Financial Interests, Personal, Invited Speaker: AstraZeneca, MSD, Takeda, Chugai Pharmaceutical; Financial Interests, Personal, Advisory Board: Takeda, AstraZeneca, Eisai; Financial Interests, Institutional, Research Grant: Merck, Daiichi Sankyo; Financial Interests, Institutional, Local PI: MSD, Daiichi Sankyo, Takeda, AstraZeneca, Chugai, Sumitomo Pharma, AbbVie. E. Rulli: Financial Interests, Institutional, Research Grant, Roche supported an investigator initiated trial, coordinated by our group.: Roche; Financial Interests, Institutional, Research Grant, AstraZeneca supported investigator initiated trials, coordinated by our group.: AstraZeneca; Financial Interests, Institutional, Research Grant: MSD, Gilead. Y. Antill: Financial Interests, Personal, Advisory Board, DUO-E: AstraZeneca; Financial Interests, Personal, Invited Speaker, various educational symposia: AstraZeneca; Financial Interests, Personal, Advisory Board, Pembrolizumab in Advanced endometrial cancer and Locally Advanced Cervical cancer: MSD; Financial Interests, Personal, Invited Speaker, various local and international educational symposia (CTIO): MSD; Financial Interests, Personal, Invited Speaker, Educational meetings: Eisai; Financial Interests, Personal, Advisory Board, RUBY trial- dostarlimab in advanced endometrial cancer: GSK; Financial Interests, Personal, Invited Speaker, educational symposia: GSK; Financial Interests, Personal, Writing Engagement, Breast Cancer patient related outcomes relating to immune therapy use (pembrolizumab): MSD. F. Heitz: Financial Interests, Personal, Financially compensated role: F Hoffmann-La Roche, GSK, AbbVie, Pharma&. E. Piovano: Financial Interests, Personal, Other, Speaker at Pharma& Symposium: Pharma&; Financial Interests, Personal, Advisory Board: Eisai; Financial Interests, Institutional, Local PI, Local PI in institutional studies sponsored by MSD, Roche, Gilead, Ascendis Pharma: Roche; Financial Interests, Institutional, Local PI, Local PI institutional studies sponsored by MSD, Roche, Gilead, Ascendis Pharma: MSD, Gilead, Ascendis Pharma; Other, Other, travel and accommodation expenses for scientific meetings: AstraZeneca, MSD, AbbVie. J.F. Cueva Banuelos: Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, Novartis; Financial Interests, Personal, Invited Speaker: AstraZeneca, MSD, GSK, Clovis, Pfizer, Novartis, Lilly, Roche, Pierre Fabre, Palex, Pharmamar, Eisai; Financial Interests, Personal, Other, Attending and accommodation scientific meetings: AstraZeneca, Lilly, MSD. J. Lombard: Financial Interests, Personal, Advisory Board, Ad Board for durvalumab + olaparib in uterine cancer: AstraZeneca; Financial Interests, Personal, Invited Speaker, educational dinner talk June 2023: Novartis; Financial Interests, Personal, Other, registration for virtual ESMO attendance October 2023: Novartis; Financial Interests, Personal, Invited Speaker, Speaker educational dinner March 2023: Eisai; Financial Interests, Personal, Invited Speaker, educational dinner speaker: Gilead; Financial Interests, Personal, Other, payment for registration for international virtual meeting (ASCO) June 2022: GSK; Financial Interests, Personal, Invited Speaker, Cervical Education Cancer Nurses Australia Webinar: Merck Serono; Financial Interests, Personal, Invited Speaker, Feb 2025: Novartis; Financial Interests, Personal, Invited Speaker, Nov 2024: Novartis. G. Tasca: Financial Interests, Personal, Advisory Board: GSK, MSD, Eisai; Financial Interests, Personal, Invited Speaker: GSK, AstraZeneca, Pharma&; Financial Interests, Personal, Steering Committee Member: GSK; Non-Financial Interests, Member, Collaborative Group in Gynecologial Oncology: MaNGO; Other, Travel Grant: PharmaMar. S. Uggeri: Financial Interests, Institutional, Research Grant: F Hoffmann-La Roche. M.P. Barretina Ginesta: Financial Interests, Personal, Advisory Board: AstraZeneca, GSK, MSD, Eisai, PharmaMar, Pharma&, Genmab, AbbVie; Financial Interests, Personal, Invited Speaker: AstraZeneca, GSK, MSD, Eisai, AbbVie, Regeneron Pharmaceuticals, GSK; Financial Interests, Personal, Steering Committee Member: MSD. All other authors have declared no conflicts of interest.