None - Scientific Plenary

Avutometinib plus defactinib in recurrent low-grade serous ovarian cancer: A subgroup analysis of ENGOT-OV60/GOG-3052/RAMP 201 Part A

Susana Banerjee, MBBS, MA, PhD, FRCP[1], Els Van Nieuwenhuysen, MD[2], Alessandro Santin, MD[3], Kari Ring, MD[4], Nicoletta Colombo, MD, PhD[5], Premal Thaker, MD[6], Emily Prendergast, MD[7], Andrew Clamp, PhD[8], Isabelle RAY-COQUARD, MD, PhD[9], Hye Sook Chon, MD[10], Kathleen Moore, MD[11], Erin Salinas, MD[12], Peter Rose, MD[13], David O'Malley, MD[14], Ana Oaknin, MD, PhD[15], Bradley Monk, MD, FACS, FACOG[16], Robert Holloway, MD[17], Gregg Newman, MD[18], John Moroney, MD[19], Toon Van Gorp, MD, PhD[2], Elsa Kalbacher[20], Christine Gennigens, MD, PhD[21], Nicholas Wojtynek, PhD[22], Stephanie Lustgarten, PhD[22], Rachel Grisham, MD[23]

[1]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, NCRI, London, United Kingdom, [2]Leuven Cancer Institute, BGOG, Leuven, Belgium, [3]Yale School of Medicine, New Haven, CT, United States, [4]University of Virginia, Charlottesville, VA, United States, [5]University of Milan-Bicocca, MaNGO, Milan, Italy, [6]Washington University in St. Louis School of Medicine, St. Louis, MO, United States, [7]Minnesota Oncology, Minneapolis, MN, United States, [8]The Christie NHS Foundation Trust and University of Manchester, NCRI, Manchester, United Kingdom, [9]Centre Léon Bérard and University Claude Bernard Lyon 1, GINECO, Lyon, France, [10]H. Lee Moffitt Cancer Center, Tampa, FL, United States, [11]Stephenson Oklahoma Cancer Center at the University of Oklahoma, Oklahoma City, OK, United States, [12]Compass Oncology, Beaverton, OR, United States, [13]Cleveland Clinic Foundation, Cleveland, OH, United States, [14]The Ohio State University, James Comprehensive Cancer Center, Columbus, OH, United States, [15]Vall d'Hebron Barcelona Hospital Campus, GEICO, Barcelona, Spain, [16]HonorHealth, University of Arizona, Creighton University, Phoenix, AZ, United States, [17]Advent Health Cancer Institute, Orlando, FL, United States, [18]Sansum Clinic, US Oncology, Santa Barbara, CA, United States, [19]University of Chicago, Chicago, IL, United States, [20]CHU J Minjoz, GINECO, Clermont Ferrand, France, [21]Centre Hospitalier Universitaire de Liège, BGOG, LIEGE, Belgium, [22]Verastem Oncology, Needham, MA, United States, [23]Memorial Sloan Kettering Cancer Center, New York, NY, United States

Objectives:

Low-grade serous ovarian cancer (LGSOC) is a rare, clinically distinct cancer broadly driven by RAS/MAPK pathway alterations. There are no treatment options specifically approved for LGSOC. Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity and induces a dominant negative RAF-MEK complex, preventing phosphorylation of MEK by ARAF, BRAF, and CRAF. Defactinib is a selective inhibitor of focal adhesion kinase (FAK), a signaling target that has been shown to mediate resistance to multiple anticancer agents. Avutometinib + defactinib demonstrated a 45% objective response rate (ORR; 13/29, 95% CI: 26–64%) and tumor shrinkage in 86% (25/29) of patients in Part A of ENGOT-OV60/GOG-3052/RAMP 201 (RAMP 201; NCT04625270). These findings were consistent with earlier data (FRAME; NCT03875820) that led to an FDA breakthrough therapy designation for avutometinib + defactinib in recurrent LGSOC.

Methods:

This planned subgroup analysis of RAMP 201 (April 6, 2023 data cutoff) was performed to assess the efficacy (Part A; confirmed ORR, blinded independent central review; *n*=29) and safety (all treated patients; *n*=81) of avutometinib + defactinib in the context of 1) lines of prior systemic therapy (LoT; 1–3, ≥4) and 2) best response to most recent prior treatment in the metastatic/recurrent setting (partial response/complete response [PR/CR], no PR/CR; investigator-assessed). Patients who experienced stable disease (SD) and patients who previously received a MEK inhibitor (MEKi) were further characterized.

Results:

Similar ORRs were observed among patients treated with 1–3 (5/11; 45.5%) and ≥4 (8/18; 44.4%) LoT. Prior to

enrollment in RAMP 201, 23/29 patients presented in the metastatic/recurrent setting, with 2/23 (8.7%) patients having a response to their last LoT; avutometinib + defactinib yielded a 43.5% (10/23) ORR in this subgroup. At the time of data cutoff, 13/29 patients receiving avutometinib + defactinib had the best response of SD, with 10/13 SD patients achieving tumor shrinkage and 6 achieving ≥15% tumor regression. For these patients, the median time from the last LoT was 1.84 months, with the majority (9/13) having received chemotherapy or hormonal therapy as their last LoT. The best response to the last LoT could be determined for 8/13 patients, with 5/8 having the best response of progressive disease (PD). Four of the 29 efficacy-evaluable patients had previously received MEKi (2 as last LoT), with 3 discontinuing due to disease progression and 1 due to an unknown cause. The best response to prior MEKi therapy included 1 SD, 1 PD, and 2 unknown. Treatment with avutometinib + defactinib in 3/4 patients who previously received MEKi achieved confirmed PRs. The safety profiles of avutometinib + defactinib were similar in the 1–3 and ≥4 LoT subgroups and were consistent with previously reported safety data. The majority of treatment-related adverse events (TRAEs) were mild to moderate, manageable/reversible.

Conclusions:

In RAMP 201 Part A, avutometinib + defactinib achieved high response rates in heavily pre-treated recurrent LGSOC, regardless of the previous line of therapy. Notably, tumor regression was observed in the majority of patients, including those with stable disease or progressive disease with the last line of therapy, including previous MEKi.

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UPLIFT (ENGOT-OV67/GOG-3048): Results from the phase II trial of upifitamab rilsodotin (UpRi; XMT-1536), a NaPi2b-directed dolaflexin antibody-drug conjugate in platinum-resistant ovarian cancer

Debra Richardson, MD[1], Nicole Concin, MD, PhD[2], John Hays, MD, PhD[3], Jose Alejandro Perez Fidalgo, MD, PhD[4], Bhavana Pothuri, MD[5], Susana Banerjee, MBBS, MA, PhD, FRCP[6], Sharad Ghamande, MD[7], Isabelle Ray Coquard, MD, PhD[8], Anna Germanova, MD, PhD[9], Bobbie Rimel, MD[10], Domenica Lorusso, MD, PhD[11], Noelle Cloven, MD[12], Jean-Francois Baurain, MD, PhD[13], Leslie Randall, MD[14], Birute Brasiuniene, MD, PhD[15], Jill Tseng, MD[16], Dagmara Klasa-Mazurkiewicz, MD, PhD[17], Theresa Werner, MD[18], Ana Oaknin, MD, PhD[19], Joo Ern Ang[20], Alexandra Leary, MD, PhD[21], Erin Bishop, MD[22], Christian Marth, MD, PhD[23], Chelsea Bradshaw, MS[24], Robert Burger, MD[24], Antonio Jose Gonzalez Martin, MD, PhD[25]

[1]Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK, Oklahoma City, OK, United States, [2]Ev. Kliniken Essen-Mitte, Essen, Germany, Innsbruck, Austria, [3]Ohio State University, James Cancer Center, Columbus, OH, Columbus, OH, United States, [4]Hospital Clinico Universitario de Valencia, Valencia, Spain, Valencia, Spain, [5]NYU Langone Health, NY, New York, NY, United States, [6]The Royal Marsden NHS, NCRI, London, UK, London, United Kingdom, [7]Augusta University, Georgia Cancer Center, Augusta, GA, Augusta, GA, United States, [8]Centre Leon Berard, Lyon, France, Lyon, France, [9]Charles University in Prague, Prague, Czech Republic, Prague, Czech Republic, [10]Cedars Sinai Medical Center, Los Angeles, CA, Los Angeles, CA, United States, [11]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Rome, Italy, [12]Texas Oncology-Fort Worth Cancer Center, Fort Worth, TX, Fort Worth, TX, United States, [13]Cliniques universitaires Saint-Luc, Bruxelles, Belgium, Bruxelles, Belgium, [14]Massey Comprehensive Cancer Center, VCU Health, Richmond, VA, Richmond, VA, United States, [15]National Cancer Institute of Lithuania, Vilnius University, Vilnius, Lithuania, Vilnius, Lithuania, [16]UC Irvine Health, Orange County, CA, IRVINE, CA, United States, [17]Medical University of Gdansk, Gdansk, Poland, Gdansk, Poland, [18]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, SALT LAKE CITY, UT, United States, [19]Vall d'Hebron Institute of Oncology, Barcelona, Spain, Barcelona, Spain, [20]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, Cambridge, United Kingdom, [21]Institut de Cancérologie Gustave Roussy, Villejuif, France, villejuif, France, [22]Medical College of Wisconsin, Milwaukee, WI, Milwaukee, WI, United States, [23]Medical University Innsbruck, Innsbruck, Austria, Innsbruck, Austria, [24]Mersana Therapeutics, Cambridge, MA, United States, [25]Cancer Center Clinica Universidad de Navarra, Madrid, Spain, Madrid, Spain

Objectives:

Effective and well-tolerated treatments for platinum-resistant ovarian cancer (PROC) remain an unmet medical need; standard of care single-agent chemotherapy has limited efficacy, with response rates of ~12%. Upifitamab rilsodotin (UpRi) is a dolaflexin, high drug-to-antibody ratio antibody-drug conjugate (ADC) targeting NaPi2b, a sodium-dependent phosphate transporter broadly expressed in high-grade serous epithelial ovarian cancer, with limited expression in normal tissues. UPLIFT was a single-arm phase II trial evaluating the efficacy and safety of UpRi in PROC.

Methods:

UPLIFT enrolled patients with up to 4 prior lines of therapy; patients were dosed at 36mg/m^2 Q4W. Patients enrolled regardless of