Molecular testing and patient selection in ovarian cancer

Moderators: Rebecca Arend, Chip Landen

May 7, 7:00 p.m. CST

Safety of veliparib in combination with chemotherapy and as maintenance in front-line ovarian cancer: Results in BRCAm, hrd, and whole populations from the velia trial

E.M. Swisher[a], R.L. Coleman[b], M.A. Bookman[c], M.F. Brady[d], G.F. Fleming[e], M. Friedlander[f], M.J. Cunningham[g], K.S. Tewari[h], B. Edraki[i], K. Moxley[j], G.M. Mantia-Smaldone[k], C. Ratajczak[l], M.H. Dinh[l], D.M. Sullivan[l], S. McClain[l], S. Okubo[m], K.D. Steffensen[n] and C. Aghajanian[o]. *[a]University of Washington Medical Center, Seattle, WA, USA, [b]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [c]Kaiser Permanente Northern California, San Francisco, CA, USA, [d]NRG Oncology Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, USA, [e]The University of Chicago Medicine, Chicago, IL, USA, [f]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia, [g]SUNY Upstate Medical University, Syracuse, NY, USA, [h]University of California Irvine Medical Center, Orange, CA, USA, [i]John Muir Medical Center, Walnut Creek, CA, USA, [j]The University of Oklahoma, Oklahoma City, OK, USA, [k]Fox Chase Cancer Center, Philadelphia, PA, USA, [l]AbbVie Inc., Chicago, IL, USA, [m]AbbVie GK, Osaka, Japan, [n]Lillebaelt University Hospital of Southern Denmark, Vejle, Denmark, [o]Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Objective: The phase 3 VELIA trial demonstrated that veliparib dosed concurrently with carboplatin/paclitaxel and continued as maintenance monotherapy resulted in a statistically significant improvement in progression-free survival compared to carboplatin/paclitaxe alone in patients with newly diagnosed stage III–IV high-grade serous ovarian, fallopian tube, and peritoneal cancer. It has been hypothesized that while DNA repair deficiencies may improve response to PARP inhibition, they may also render patients with *BRCA* mutations *(BRCAm)* or homologous recombination-deficient (HRD) tumors more sensitive to treatment-related toxicities.

Method: Patients were eligible regardless of biomarker status and were randomized to 1 of 3 treatment arms. This analysis is limited to patients randomized to carboplatin/paclitaxel plus veliparib followed by veliparib maintenance. Patients received 6 cycles (21 days/cycle) of carboplatin (AUC 6) and paclitaxel (175 mg/m^2 q3w or 80 mg/m^2 weekly). Veliparib was continuously dosed at 150 mg BID PO with carboplatin/paclitaxel and then at 300 mg BID, increasing to 400 mg BID if tolerated, for 30 additional cycles. Patients receiving ≥1 dose of study drug were included in safety analyses. Adverse events in patients randomized to carboplatin/paclitaxel plus veliparib followed by veliparib maintenance are reported for the whole patient population, as well as for the *BRCAm* and HRD patient subsets.

Results: During the entire treatment period (combination chemotherapy and maintenance), grade 2–4 nonhematologic adverse events were predominantly gastrointestinal. Grade 3–4 hematologic adverse events included neutropenia and anemia in more than one-third of patients. Frequency of common adverse events was generally comparable in the whole population and the *BRCAm* and HRD patient subsets. Frequency of adverse events leading to dose reduction was also comparable. In the whole population, the prevalence of all-grade neutropenia, anemia, thrombocytopenia, and nausea decreased substantially from cycles 7–9 to cycles 10–12 (in which cycle 7 was the first cycle of monotherapy maintenance). See **Table 1**.

Conclusion: In VELIA, adverse event frequencies were generally similar among the whole patient population and biomarker-positive patient subsets.

Table 1. Common treatment-emergent AEs during entire treatment period (combination and maintenance) in patients randomized to veliparib in combination with C/P and continued as maintenance monotherapy.

Adverse event, *n* (%)	**Whole Population (*n* = 377)**	***BRCA*m Population (*n* = 106)**	**HRD Population (*n* = 211)**
AE leading to dose reduction	89 (23.6)	26 (24.5)	55 (26.1)
Hematologic AEs (Grade 3-4)			
Neutropenia	218 (57.8)	67 (63.2)	129 (61.1)
Anemia	144 (38.2)	39 (36.8)	80 (37.9)
Thrombocytopenia	105 (27.9)	27 (25.5)	56 (26.5)
Leukopenia	66 (17.5)	18 (17.0)	38 (18.0)
Non-hematologic AEs (Grade 2-4)			
Nausea	167 (44.3)	46 (43.4)	100 (47.4)
Fatigue	137 (36.3)	44 (41.5)	73 (34.6)

Alopecia	126 (33.4)	37 (34.9)	75 (35.5)
Vomiting	70 (18.6)	19 (17.9)	40 (19.0)
Peripheral sensory neuropathy	63 (16.7)	17 (16.0)	37 (17.5)
Urinary tract infection	61 (16.2)	16 (15.1)	32 (15.2)
Diarrhea	58 (15.4)	27 (25.5)	37 (17.5)
Constipation	47 (12.5)	17 (16.0)	30 (14.2)

Exploring the relationship between homologous recombination score and progression-free survival in *BRCA* wildtype ovarian carcinoma: Analysis of veliparib plus carboplatin/paclitaxel in the velia study

E.M. Swisher[a], S.H. Kaufmann[b], M.J. Birrer[c], D.A. Levine[d], K.N. Moore[e], G.F. Fleming[f], R.L. Coleman[g], M.A. Bookman[h], K.M. Timms[i], D.M. Sullivan[j], B.A. Bach[j], B. Chen[j], V. Sehgal[j], P.J. Ansell[j], M.H. Dinh[j] and C. Aghajanian[k]. *[a]University of Washington Medical Center, Seattle, WA, USA, [b]Mayo Clinic, Rochester, MN, USA, [c]University of Alabama at Birmingham, Birmingham, AL, USA, [d]NYU Langone Health, New York, NY, USA, [e]The University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA, [f]The University of Chicago Medicine, Chicago, IL, USA, [g]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [h]Kaiser Permanente Northern California, San Francisco, CA, USA, [i]Myriad Genetics Inc., Salt Lake City, UT, USA, [j]AbbVie Inc., North Chicago, IL, USA, [k]Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Objective: The phase 3 VELIA trial demonstrated that veliparib dosed concurrently with carboplatin and paclitaxel and continued as maintenance monotherapy resulted in significantly better progression-free survival (PFS) compared to carboplatin and paclitaxel alone in patients with newly diagnosed advanced high-grade serous ovarian carcinoma (HGSC). VELIA enrolled patients without regard to germline or somatic *BRCA* mutations (*BRCA*m), homologous recombination deficiency (HRD), or platinum sensitivity, providing a unique opportunity to evaluate the prognostic and predictive role of the HRD assay.

Method: Patients with untreated stage III–IV HGSC received 6 cycles (21-day interval) of carboplatin and paclitaxel following primary cytoreduction or as neoadjuvant chemotherapy with interval cytoreduction. HRD score was determined by Myriad myChoice HRD CDx assay with cutoff ≥33 for HRD+ and <33 for non-HRD status. Randomization was stratified by disease stage, timing of surgery, residual disease post primary surgery, paclitaxel schedule, geographic region, and germline *BRCA* status (but not HRD). This analysis was restricted to patients randomized to carboplatin and paclitaxel with placebo then placebo maintenance (control), and carboplatin and paclitaxel with veliparib, and then veliparib maintenance (veliparib-throughout). Correlation of HRD score with outcome was limited to patients with *BRCA*wt HGSC to understand the predictive power of HRD score in *BRCA*wt HGSC using the PFS endpoint in veliparib-throughout versus control.

Result: A total of 532 patients from veliparib-throughout and control arms with HGSC confirmed *BRCA*wt and known HRD status were included in this exploratory analysis to evaluate HRD independent of *BRCA* status. Within the *BRCA*wt population, the HRD+ population had a PFS hazard ratio (HR) of 0.77 (95% CI 0.54–1.10) favoring use of veliparib, and the non-HRD population had a similar PFS HR of 0.76 (95% CI 0.55–1.03), both upper confidence intervals crossing threshold of 1.00 in this post hoc analysis. Comparing HRD score versus observed HR between veliparib-throughout and control, no clear cutoff score could be identified to accurately determine who would benefit most from the veliparib-throughout regimen.

Conclusion: In patients with *BRCA*wt carcinomas, HRD score was not predictive of patient outcomes for veliparib-throughout versus control. Veliparib-throughout suggests veliparib benefit even at low HRD scores compared to carboplatin and paclitaxel. This analysis of *BRCA*wt HRD+ and non-HRD populations suggests veliparib benefit is similar in both groups.

Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-sensitive recurrent ovarian cancer.

L. Loverix[a], A. Vanderstichele[a], S. Olbrecht[a], E. Van Niewenhuysen[a], T. Van Gorp[a], S.N. Han[a], R. Salihi[a], N. Concin[a], P. Neven[a], P. Busschaert[a], D. Lambrechts[b] and I. Vergote[c]. *[a]Leuvens Kanker Instituut, Leuven, Belgium, [b]Vesalius Research Center, Leuven, Belgium, [c]Leuven Cancer Institute, Leuven, Belgium*

Objective: The CLIO trial (NCT02822157) evaluated Olaparib single-agent therapy versus standard-of-care chemotherapy in platinum-sensitive recurrent epithelial ovarian cancer (relapse ≥6 months after platinum-based chemotherapy) (PSOC).

Method: Eligible patients with measurable germline *BRCA* wildtype PSOC disease and ≥1 prior line of chemotherapy were randomized 2:1 to olaparib (OLA) monotherapy (300-mg tablets, BID) or physician's choice chemotherapy (CT; carboplatin

AUC 5 pegylated liposomal doxorubicin 30 mg/m^2 q4w or carboplatin AUC 4 d1 gemcitabine 1,000 mg/m^2 d1 d8 q3w). Response was evaluated according to RECIST v1.1. Prior bevacizumab was allowed. Disease control rate (DCR) was defined as response or stable disease at 12 weeks

Results: A total of 60 patients were randomized 2:1 to OLA (*n* = 40) or CT (*n* = 20). Baseline characteristics, summarized in **Table 1**, were not significantly different between both arms. Objective response rate (ORR) was 40% (14/40) for OLA and 60% (12/20) for CT (*P* = 0.12). DCR was 80% (32/40) for OLA and 85% (17/20) for CT. Progression-free survival (PFS) was similar in both arms (median PFS 6.4 vs 8.5 months for OLA and CT, respectively, HR = 1.11, 95% CI 0.60–2.04, *P* = 0.7) as well as for overall survival (OS; median OS 23.9 vs 27.7, respectively, HR = 1.01, 95% CI 0.40–2.51). Adverse events in the OLA and CT arms did not reveal any unexpected events. Somatic *BRCA* testing is ongoing and will be presented at the meeting.

Conclusions: PFS and OS were similar between olaparib monotherapy and chemotherapy in recurrent germline *BRCA* wildtype platinum-sensitive epithelial ovarian cancer.

Table 1.

Baseline characteristics	**OLAPARIB**	**CHEMOTHERAPY**
Number of patients	40	20
Median age at randomization (years)	70 (IQR 63-76)	66 (IQR 58-73)
WHO score		
0	25 (62.5%)	12 (60%)
1	15 (37.5%)	8 (40%)
Histology		
High-grade serous	38 (95%)	19 (95%)
Clear-cell	1 (2.5%)	1 (5%)
Carcinosarcoma	1 (2.5%)	0 (0%)
Median months since diagnosis	34.1 (IQR 19.8-52.9)	43.3 (IQR 22-60)
Median prior lines	2 (IQR: 1-2.3, range 1-6)	2 (IQR:1-3, range 1-5-)
1	16 (40%)	7 (35%)
2	14 (35%)	5 (25%)
3	5 (12.5%)	4 (20%)
4 or more	5 (12.5%)	4 (20%)
Prior bevacizumab	21 (52.5%)	10 (50%)
Prior PARPi/placebo (in trial)	0	1 (5%)

Postprogression outcomes in patients with ovarian carcinoma associated with a mutation in a non-*BRCA* homologous recombination repair gene receiving rucaparib maintenance treatment: Results from the phase III study ARIEL3

D.M. O'Malley[a], A.M. Oza[b], D. Lorusso[c], C. Aghajanian[d], A. Oaknin[e], A. Dean[f], N. Colombo[g], J.I. Weberpals[h], A.R. Clamp[i], G. Scambia[c], A. Leary[j], R.W. Holloway[k], M. Amenedo Gancedo[l], P.C. Fong[m], J.C. Goh[n,o], D.K. Armstrong[p], S. Banerjee[q], J. García-Donas[r], E.M. Swisher[s], T. Cameron[t], L. Maloney[u], S. Goble[u], K.K. Lin[u], J.A. Ledermann[v] and R.L. Coleman[w]. *[a]The Ohio State University, James Cancer Hospital, Columbus, OH, USA, [b]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [c]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [d]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [e]Vall d'Hebrón University Hospital, Vall d'Hebrón Institute of Oncology (VHIO), Barcelona, Spain, [f]St John of God Subiaco Hospital, Subiaco, Australia, [g]European Institute of Oncology IRCCS and University of Milan-Bicocca, Milan, Italy, [h]Ottawa Hospital Research Institute, Ottawa, ON, Canada, [i]The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom, [j]Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Villejuif, France, [k]Florida Hospital Cancer Institute, Orlando, FL, USA, [l]Oncology Center of Galicia, La Coruña, Spain, [m]Auckland City Hospital, Grafton, New Zealand, [n]Cancer Care Services, Royal Brisbane and Women's Hospital, Herston, QLD, Australia, [o]University of Queensland, St Lucia, QLD, Australia, [p]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [q]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom, [r]HM Hospitales—Centro Integral Oncológico Hospital de Madrid Clara Campal, Madrid, Spain, [s]University of Washington, Seattle, WA, USA, [t]Clovis*

Oncology UK Ltd., Cambridge, United Kingdom, [u]Clovis Oncology, Inc., Boulder, CO, USA, [v]UCL Cancer Institute, University College London and UCL Hospitals, London, United Kingdom, [w]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective: In the ARIEL3 study (NCT01968213), rucaparib maintenance treatment significantly improved progression-free survival (PFS) versus placebo in all predefined, nested cohorts (*BRCA* mutant; *BRCA* mutant + wildtype *BRCA*/high loss of heterozygosity; and intent-to-treat population). Here we analyzed postprogression outcomes to evaluate the durability of the clinical benefit of rucaparib maintenance treatment following disease progression in the subgroup of patients with tumors associated with a mutation in a prespecified, non-*BRCA*, homologous recombination repair (HRR) gene.

Method: Archival specimens from all patients in ARIEL3 (*n* = 564) were sequenced to identify deleterious mutations in a prespecified list of 30 HRR genes. Patients were randomized 2:1 to receive oral rucaparib 600 mg BID or placebo. Exploratory postprogression endpoints of chemotherapy-free interval (CFI), time to first subsequent therapy (TFST), time to disease progression on subsequent line of therapy or death (PFS2), and time to second subsequent therapy (TSST) were assessed in patients with a non-*BRCA* HRR gene mutation.

Results: In the rucaparib group, 28 patients (7.5%) had a mutation in a non-*BRCA* HRR gene, most commonly in *RAD51C* or *RAD51D* (*RAD51C/D, n* = 10). In the placebo group, 15 patients (7.9%) had a non-*BRCA* HRR gene mutation, most commonly in *BRIP1* (*n* = 5) and *RAD51C/D* (*n* = 3). Among patients with a tumor associated with a *RAD51C/D* mutation, there was significantly longer PFS in those receiving rucaparib than in those receiving placebo (log rank *P* value, 0.0184); 9/10 rucaparib versus 0/3 placebo patients were progression-free at 12 months. Treatment with rucaparib versus placebo was associated with improvements in all the postprogression efficacy endpoints examined in patients with tumors associated with a non-*BRCA* HRR gene mutation (**Table 1**). Safety in this subgroup was consistent with that in the overall ARIEL3 safety population.

Conclusion: Although the number of patients in this subgroup was small, rucaparib improved the clinically meaningful endpoints CFI, TFST, PFS2, and TSST versus placebo in patients with platinum-sensitive, recurrent ovarian cancer harboring a non-*BRCA* HRR gene mutation. Mutations in a subset of HRR genes, such as *RAD51C/D*, may confer greater sensitivity to PARP inhibitor treatment.

Table 1. Postprogression outcomes for paitents with a Non-*BRCA* HRR mutation.

	Median, mo		
	Rucaparib (n=28)	**Placebo (n=15)**	**HR (95% CI)**
PFS[a]	11.1	5.5	0.21 (0.09-0.50)
CFI	18.2	7.7	0.21 (0.09-0.52)
TFST	16.9	6.3	0.16 (0.06-0.40)
PFS2	21.1	17.3	0.30 (0.12-0.72)
TSST	24.2	17.9	0.43 (0.18-1.04)

Visit cutoff December 31, 2017, unless otherwise noted.
HRs estimated with a Cox proportional hazards model.
[a]Visit cutoff April 15, 2017 (date of unblinding for primary efficacy analysis). Previously reported in O'Malley et al. *Mol Cancer Ther*. 2018;17(suppl 1):abst LB-A12.
CI, confidence interval; HR, hazard ratio