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Commentary

Ovarian Cancer Maintenance: Practice-Changing Data Calls for Changing Practice

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A significant challenge for clinicians is staying current on the rapidly evolving therapeutic landscape in oncology. Treatment options for recurrent ovarian cancer are rapidly expanding based upon multiple important prospective randomized clinical trials, all of which included maintenance therapy. These data have led to six U.S. Food and Drug Administration (FDA) approvals of four separate drugs across three treatment settings: adjuvant or maintenance treatment following cytoreductive surgery for newly diagnosed, advanced disease and second- or third-line treatment for patients with platinum-sensitive recurrence (≥6 months from prior platinum therapy) who have achieved complete response (CR) or partial response (PR) to platinum-based therapies. It is imperative that clinicians consider these options and counsel patients appropriately in lieu of these robust data sets that demonstrate improved patient outcomes. Contemporary data assessing current patterns of care indicate that a significant proportion of eligible platinum-sensitive patients are not being offered maintenance therapy [1].

The concept of extending treatment time beyond the standard of approximately six cycles has been controversial in the management of patients with ovarian cancer. The rationale for this approach is predicated upon the existence of nonresistant, slowly dividing tumor cells that have been inadequately exposed to cycle-dependent cytotoxic agents during the initial treatment period and may be eliminated with further therapy [2]. Improvements in cytotoxic treatment have helped epithelial ovarian cancer become a relapsing and remitting disease course where most patients will have a high response rate to multiple lines of treatment. The duration of remission, however, generally is shorter with each subsequent regimen [3, 4]. Therefore, development of a maintenance option that could extend these treatment-free intervals is especially attractive in ovarian cancer. Accordingly, multiple approaches to maintenance including extended platinum-based chemotherapy [5, 6], therapeutic vaccines [7, 8], and reduced-dose, extended taxane administration [9, 10] have been investigated. Of these, none had sufficient efficacy, and some were associated with significant toxicity. Therefore, drug development in this space shifted from not only extending remission time but also minimizing adverse events while maintaining quality of life. These balanced goals have finally been accomplished with four FDA approvals of both biologic and targeted therapies, bevacizumab and three different poly adenosine diphosphate ribose polymerase (PARP) inhibitors, respectively.

Bevacizumab is an antiangiogenic agent that was first found to be efficacious as a single agent for both platinum-sensitive and -resistant disease [11] and then subsequently first FDA approved in combination with single-agent cytotoxics for the treatment of platinum-resistant disease [12]. Given the biologic mechanism of action, low incidence of serious adverse events, and efficacy, there was a high priority for its development as a maintenance agent. Table 1 lists the outcome measures for bevacizumab maintenance studies across the recurrent and front-line settings. First, the OCEANS trial investigated bevacizumab maintenance in the platinum-sensitive recurrent setting in addition to the carboplatin/gemcitabine [13, 14]. In OCEANS, bevacizumab was administered at 15 mg/kg every 3 weeks during chemotherapy and continued as maintenance if women had achieved CR or PR. OCEANS reported a prolongation of median progression-free survival (mPFS) from 8.4 to 12.4 months with a hazard ratio (HR) of 0.484 that was statistically significant (95% confidence interval [CI] 0.388–0.605; Table 1). GOG 213 also demonstrated improvement in PFS when bevacizumab was added to the carboplatin and paclitaxel combination and continued as maintenance, with a trend toward an improvement in overall survival (OS), leading to a second FDA approval [15]. Finally, when studied in the front-line setting, bevacizumab maintenance resulted in a significant improvement in PFS, for women with advanced (FIGO stage III or IV) ovarian cancer following primary cytoreductive surgery on GOG 218 [16]. An OS advantage was not seen in front-line treatment, but is possibly biased by the postprogression use of bevacizumab in the control group.

Bevacizumab is generally well tolerated, with the most common side effects being hypertension, proteinuria, epistaxis,

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Table 1. Efficacy of ovarian cancer maintenance therapeutics by line of treatment, maintenance drug, and biomarker where applicable

Clinical trial	Study drug (manufacturer)	Biomarker	*n*	Efficacy: Median PFS (mPFS) + HR (95% CI); Median OS (mOS) + HR (95% CI) (where available)		
				***BRCA*^{mut}**	**HRD marker positive**	**Intent to treat (all subjects or *BRCA*wt)**
Front-line treatment setting						
GOG 218 [16, 34]	Bevacizumab (Genentech/Roche)	None	1,873	N/A	N/A	$mPFS_{exp}$ 14.1 mos $mPFS_{cont}$ 10.3 mos PFS 0.72 (0.63–0.82) mOS_{exp} 33.6 mos mOS_{cont} 32.9 mos OS 0.96 (0.85–1.09)
SOLO-1 [27]	Olaparib (AstraZeneca)	Restricted to g*BRCA*mut and s*BRCA*mut	391	$mPFS_{exp}$ > 36 mos (NR) $mPFS_{cont}$ 13.8 mos HR PFS 0.30 (0.23–0.41)	N/A	N/A
Platinum-sensitive recurrent setting						
GOG 213 [15]	Bevacizumab (Genentech/Roche)	None	674	N/A	N/A	$mPFS_{exp}$ 13.8 mos $mPFS_{cont}$ 10.4 mos HR PFS 0.63 (0.53–0.74) mOS_{exp} 42.2 mos mOS_{cont} 37.3 mos HR OS 0.82 (0.68–0.996)
OCEANS [13, 14]	Bevacizumab (Genentech/Roche)	None	484	N/A	N/A	$mPFS_{exp}$ 12.4 mos $mPFS_{cont}$ 8.4 mos HR PFS 0.48 (0.39–0.61) mOS_{exp} 33.6 mos mOS_{cont} 32.9 mos HR OS 0.95 (0.77–1.18)
Study 19 [23, 33]	Olaparib (AstraZeneca)	Unrestricted	265	$mPFS_{exp}$ 11.2 mos $mPFS_{cont}$ 4.3 mos HR PFS 0.18 (0.10–0.31) mOS_{exp} 34.9 mos mOS_{cont} 30.2 mos HR OS 0.62 (0.41–0.94)	N/A	$mPFS_{exp}$ 8.4 mos $mPFS_{cont}$ 4.8 mos HR PFS 0.54 (0.34–0.85) mOS_{exp} 29.8 mos mOS_{cont} 27.8 mos HR OS 0.73 (0.55–0.96)
ARIEL3 [26]	Rucaparib (Clovis)	Sequential: g*BRCA*mut if efficacious, then s*BRCA*mut, then unselected	564	$mPFS_{exp}$ 16.6 mos $mPFS_{cont}$ 5.4 mos HR PFS 0.23 (0.16–0.34)	$mPFS_{exp}$ 13.6 mos $mPFS_{cont}$ 5.4 mos HR PFS 0.32 (0.24–0.42)	$mPFS_{exp}$ 10.8 mos $mPFS_{cont}$ 5.4 mos HR PFS 0.36 (0.30–0.45)
SOLO-2 [25]	Olaparib (AstraZeneca)	Restricted to g*BRCA*mut	295	$mPFS_{exp}$ 19 mos $mPFS_{cont}$ 5.5 mos HR PFS 0.30 (0.22–0.41)	N/A	N/A
NOVA [24]	Niraparib (Tesaro)	Two cohorts; g*BRCA*mut or unselected	503	$mPFS_{exp}$ 21.0 mos $mPFS_{cont}$ 5.5 mos HR PFS 0.27 (0.17–0.41)	$mPFS_{exp}$ 12.9 mos $mPFS_{cont}$ 3.8 mos HR PFS 0.38 (0.24–0.59)	$mPFS_{exp}$ 9.3mos $mPFS_{cont}$ 3.9 mos HR PFS 0.45 (0.34–0.61)

Abbreviations: *BRCA*wt, *BRCA* wildtype; CI, confidence interval; cont, control arm; exp, experimental arm; *gBRCA*mut, germline *BRCA* mutated; HR, hazard ratio; HRD, homologous recombination deficiency; N/A, not investigated; NR, not reached; OS, overall survival; PFS, progression-free survival; *sBRCA*mut, somatic *BRCA* mutated.

and headaches [17]. Rare but serious adverse events include vascular toxicities such as stroke, acute myocardial infarction, venous thromboembolism, and reversible posterior leukoencephalopathy syndrome in addition to poor wound healing and hemorrhage. Finally, bowel perforation is an adverse event unique to bevacizumab that appears to be increased in women with ovarian cancer. Although low in incidence (0.3%–3%) across all studies, it occurs more commonly when bevacizumab is given in later lines of therapy or concurrent with bowel obstruction, and it carries a high mortality rate. GOG 218 found no detriment in quality of life endpoints in women receiving bevacizumab as maintenance during full remission [18].

Data supporting a second maintenance platform have emerged with use of oral PARP inhibitors (PARPi), which have shown unprecedented activity, especially for women with germline *BRCA* (g*BRCA*) mutations. The primary mechanism of action of PARPis is to inhibit the cancer cell's ability to repair single strand breaks, which leads to collapse of the DNA replication fork and double-strand (dsDNA) breaks [19]. Cells harboring a defect in homologous recombination, such as g*BRCA* mutation, are unable to effectively repair these dsDNA breaks, resulting in cell death and, thus, synthetic lethality [20]. PARPis were first shown to be active in treating g*BRCA*^{mut} [21] and somatic *BRCA*^{mut} (s*BRCA*^{mut}) recurrent ovarian cancers [22]. Four randomized trials supported the FDA approval of three different PARPis for maintenance in the platinum-sensitive recurrent space following a CR or PR to second- or third-line platinum-based treatment: Study 19 [23], NOVA [24], SOLO-2 [25], and ARIEL 3 [26] (Table 1). These studies demonstrated differential benefit among biomarker-defined populations. Specifically, the median PFS improvement (delta) in g*BRCA*^{mut} groups ranged from 11.2 to 15.5 months in PARPi-treated patients, which was highly statistically significant and translated to a 70%–77% reduction in the risk of progression in the proportional HR model (HR 0.23–0.30). PFS in the non-g*BRCA*^{mut} groups was still significantly improved, with HR ranging from 0.36 to 0.54 across the trials.

At this time, it is unclear whether the PFS advantages will translate into improvements in OS or if one PARPi is superior to another. Although there are distinct preclinical differences among the three approved agents in terms of PARP trapping, selectivity for PARP isoenzymes, half-life, and volume of distribution, clinically they have behaved similarly in trials reported to date, despite having unique toxicity profiles. It is clear, however, that they all demonstrate significant activity regardless of biomarker status in the platinum-sensitive recurrent setting. The SOLO-1 trial recently confirmed that the benefit of olaparib in g*BRCA*^{mut} patients who are responding to front-line chemotherapy might be even greater in terms of absolute gains in PFS, where the mPFS difference between the olaparib group and placebo is approximately 36 months, and the HR for progression is 0.30 (95% CI 0.23–0.41; $p < .001$) [27].

Like bevacizumab, PARPis are well tolerated, with the most common side effects being hematologic (neutropenia and anemia), gastrointestinal (nausea, vomiting, diarrhea), and fatigue. Niraparib is associated with more thrombocytopenia, which is manageable with dose reduction [28]. Most PARPi adverse events occur within the first month of treatment and are either self-limited or managed by dose reduction with or without temporary dose interruption. The only serious adverse event associated with PARPis is myelodysplastic syndrome (MDS), which was observed in the earlier-phase studies of each drug in class. The incidence of MDS, however, is equal to that observed in the placebo groups in the randomized trials of both PARPi and bevacizumab. Quality-of-life studies for olaparib and niraparib have shown no decrement in PARPi-treated women [29–31].

When weighing the options of maintenance for women with ovarian cancer, decisions should be based on the balance of efficacy, toxicity, convenience, compliance, presenting symptoms, and quality of life. There have been no head-to-head comparisons between bevacizumab and PARPi, and the clinical trial constructs have differed between these classes of agents; therefore, decisions regarding their use and sequencing between front line and recurrence must be individualized and based on numerous clinical parameters including goals of therapy, toxicity, and biomarker status. Several trials combining the use of PARPi and antiangiogenesis therapies with and without checkpoint inhibitors (both anti-programmed death 1 and anti-programmed death-ligand 1 targets) are ongoing, with many nearing completion. In reality, many women will be eligible for both bevacizumab and PARPi during their disease course, and these ongoing trials will better inform combinations and sequencing.

The barriers to the incorporation of this novel treatment strategy into standard practice are likely complex. Potential contributors include lack of awareness of emerging clinical trial data, which may be most problematic for low-volume ovarian cancer providers. Additionally, concerns about cost, quality of life, and the logistical challenges of prolonged therapy may play a role. Lastly, there is a bias against treatments that have yet to demonstrate improvement in OS. Currently available data demonstrate that there is no detriment to quality of life [18, 29–31] and that OS benefit is desired but not required to declare a treatment effective for ovarian cancer [32]. Furthermore, the PFS2 (time from randomization to progression on next-line of treatment or death from any cause) data further support a clinical benefit for patients in this setting [24]. Education of clinical providers to at minimum counsel eligible women regarding these data is critical in advancing care of patients with platinum-sensitive ovarian cancer.

Based on these practice-changing data, it's time to change practice! All eligible patients with ovarian cancer deserve informed counseling regarding the pros and cons of maintenance therapy, and the option of maintenance treatment in these regulatory approved settings.

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Leslie M. Randall: Genentech, Tesaro, Clovis, AstraZeneca (C/A), Tesaro, AstraZeneca (H), Genentech (RF); **Michael J. Birrer:** Tesaro, Clovis, Merck Sharp & Dohme, Genentech USA, AstraZeneca (C/A); **Thomas J. Herzog:** AstraZeneca, Caris, Clovis Oncology, Johnson & Johnson, Tesaro (SAB).

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References

1. Mahner S. Proceedings of ESMO Educational Symposium. Presented October 22, 2018. Available at https://cslide.ctimeetingtech.com/library/esmo/browse/search/262N#2Ea4M. Accessed November 1, 2018.

2. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med 1995;332:1004–1014.

3. Hanker LC, Loibl S, Burchardi N et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012;23:2605–2612.

4. Lorusso D, Mancini M, Di Rocco R et al. The role of secondary surgery in recurrent ovarian cancer. Int J Surg Oncol 2012;2012:613980.

5. Lambert HE, Rustin GJ, Gregory WM et al. A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. Ann Oncol 1997;8:327–333.

6. Bertelsen K, Jakobsen A, Strøyer J et al. A prospective randomized comparison of 6 and 12

cycles of cyclophosphamide, adriamycin, and cisplatin in advanced epithelial ovarian cancer: A Danish Ovarian Study Group trial (DACOVA). Gynecol Oncol 1993;49:30–36.

7. Berek J, Taylor P, McGuire W et al. Oregovomab maintenance monoimmunotherapy does not improve outcomes in advanced ovarian cancer. J Clin Oncol 2009;27:418–425.

8. Sabbatini P, Harter P, Scambia G et al. Abagovomab as maintenance therapy in patients with epithelial ovarian cancer: A phase III trial of the AGO OVAR, COGI, GINECO, and GEICO–The MIMOSA study. J Clin Oncol 2013;31:1554–1561.

9. Markman M, Liu PY, Wilczynski S et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: A Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol 2003;21:2460–2465.

10. Copeland LJ, Brady MF, Burger RA et al. A phase III trial of maintenance therapy in women with advanced ovarian/fallopian tube/peritoneal cancer after a complete clinical response to first-line therapy: An NRG oncology study. Late-breaking abstract #1. Presented at: SGO; March 14, 2017: Washington, DC.

11. Burger RA, Sill MW, Monk BJ et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group Study. J Clin Oncol 2007;25:5165–5171. Erratum in: J Clin Oncol 2014;32:3686.

12. Pujade-Lauraine E, Hilpert F, Weber B et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302–1308. Erratum in: J Clin Oncol 2014;32:4025.

13. Aghajanian C, Goff B, Nycum LR et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol 2015; 139:10–16.

14. Aghajanian C, Blank SV, Goff BA et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039–2045.

15. Coleman RL, Brady MF, Herzog TJ et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:779–791.

16. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365:2473–2483.

17. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. Gynecol Oncol 2010;117:497–504.

18. Monk BJ, Huang HQ, Burger RA et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: A Gynecologic Oncology Group Study. Gynecol Oncol 2013;128:573–578.

19. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nat Rev Drug Discov 2005;4:307–320.

20. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defects in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917–921.

21. Domchek SM, Aghajanian C, Shapira-Frommer R et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol 2016; 140:199–203.

22. Swisher EM, Lin KK, Oza AM et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicenter, open-label, phase 2 trial. Lancet Oncol 2017;18:75–87.

23. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366: 1382–1392.

24. Mirza MR, Monk BJ, Herrstedt AM et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–2164.

25. Pujade-Lauraine E, Ledermann JA, Selle F et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274–1284. Erratum in: Lancet Oncol 2017;18:e510.

26. Coleman RL, Oza AM, Lorusso D et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390:1949–1961.

27. Moore K, Colombo N, Scambia G et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495–2505.

28. Lord R, Mirza MR, Woelber L et al. Safety and dose modification for patients with low body weight receiving niraparib in the ENGOT-OV16/NOVA phase III trial. Abstract #20. Presented at: Society of Gynecologic Oncology Annual Meeting on Women's Cancer; 2018; New Orleans, LA.

29. Friedlander M, Gebski V, Gibbs E et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): A placebo-controlled, phase 3 randomised trial. Lancet Oncol 2018;19:1126–1134.

30. Oza AM, Matulonis UA, Malander S et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): Results from a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2018;19:1117–1125.

31. Ledermann JA, Harter P, Gourley C et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer 2016;115:1313–1320.

32. Herzog TJ, Ison G, Alvarez RD et al. FDA ovarian cancer clinical trial endpoints workshop: A Society of Gynecologic Oncology White Paper. Gynecol Oncol 2017;147:3–10.

33. Ledermann JA, Harter P, Gourley C et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: An updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol 2016; 17:1579–1589.

34. Burger RA, Enserro D, Tewari KS et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (bev) in the primary treatment of advanced ovarian cancer: An NRG Oncology/Gynecologic Oncology Group (GOG) study. J Clin Oncol 2018;36(suppl 15):5517a.