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Late Breaking Abstracts

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1 - Late Breaking Abstracts

Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: Primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial

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Objective: Avelumab monotherapy showed modest antitumor activity (objective response rate, ORR, 9.6%) and a manageable safety profile in a phase 1b study of patients with recurrent/refractory ovarian cancer (OC, $n = 125$). This randomized, open-label, phase 3 trial (JAVELIN Ovarian 200; NCT02580058) evaluated avelumab (Ave) alone or in combination with pegylated liposomal doxorubicin (PLD) versus PLD alone in patients with platinum-resistant or refractory OC (PRROC).

Method: Eligible women (PRROC, ≤ 3 prior lines for platinum-sensitive disease and no prior therapy for platinum-resistant disease) were randomized 1:1:1 to Ave (10 mg/kg Q2W), Ave plus PLD (40 mg/m² Q4W), or PLD. Primary endpoints were PFS (by blinded independent central review per RECIST version 1.1) and OS. Retrospective analysis of efficacy based on PD-L1 status (PD-L1 expression $\geq 1\%$ of tumor cells or $\geq 5\%$ of immune cells) was a secondary endpoint.

Results: A total of 566 patients were randomized, including 142 (25%) with platinum-refractory disease, 273 (48%) with only 1 prior line of therapy, and 210 (37%) with bulky disease (tumor ≥ 5 cm). At data cutoff (September 19, 2018), all patients had been followed for ≥ 16 months or had died, withdrew consent, or were lost to follow-up. Ave did not improve PFS or OS versus PLD, and PFS or OS prolongation with Ave plus PLD versus PLD did not reach significance (**Table 1**). ORRs were 3.7% (95% CI 1.5–7.5) for Ave, 13.3% (95% CI 8.8–19.0) for Ave plus PLD, and 4.2% (95% CI 1.8–8.1) for PLD. At the time of writing, in patients evaluable for PD-L1 status ($n = 442$), median PFS was similar between PD-L1+ and PD-L1- subgroups in both the Ave and Ave plus PLD arms but differed in the PLD arm (1.9 vs 3.7 months). In patients with PD-L1+ tumors (58% of patients), trends for longer PFS and OS were seen for Ave plus PLD versus PLD (**Table 1**). In the Ave plus PLD arm, the ORR was 18.5% (95% CI 11.1–27.9) in the PD-L1+ subgroup and 3.4% (95% CI 0.4–11.9) for the PD-L1- subgroup. No new safety signals were observed; in the Ave, Ave plus PLD, and PLD arms, grade ≥ 3 treatment-emergent adverse events occurred in 49.7%, 68.7%, and 59.3% of patients, respectively.

Conclusion: Ave plus PLD showed clinical activity in patients with PRROC, but the trial did not meet its primary objectives of significantly improving PFS or OS versus PLD in the overall population. Planned analyses suggested improved PFS and OS for Ave plus PLD versus PLD in the PD-L1+ subgroup.

Table 1. Avelumab alone or in combination with pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase 3 JAVELIN Ovarian 200 trial

All patients	Ave (N=188)		Ave+PLD (N=188)		PLD (N=190)	
OS						
Median (95% CI), mo	11.8 (8.9; 14.1)		15.7 (12.7; 18.7)		13.1 (11.8; 15.5)	
Stratified hazard ratio vs PLD (repeated CI [RCI])	1.14 (0.948; 1.580)		0.89 (0.744; 1.241)		-	
<i>P</i> value vs PLD, 1-sided log-rank test	0.8253 (significance level, <0.0095)		0.2082 (significance level, <0.0103)		-	
PFS						
Median (95% CI), mo	1.9 (1.8; 1.9)		3.7 (3.3; 5.1)		3.5 (2.1; 4.0)	
Stratified hazard ratio vs PLD (RCI)	1.68 (1.320; 2.601)		0.78 (0.587; 1.244)		-	
<i>P</i> value vs PLD, 1-sided log-rank test	>0.999 (significance level, <0.0003)		0.0301 (significance level, <0.0002)		-	
PD-L1 evaluable	Ave		Ave+PLD		PLD	
	PD-L1+ (N=91)	PD-L1- (N=62)	PD-L1+ (N=92)	PD-L1- (N=58)	PD-L1+ (N=73)	PD-L1- (N=66)
OS						
Median (95% CI), mo	13.7 (9.6; not estimable)	10.5 (6.8; 15.3)	18.4 (13.7; 22.0)	12.7 (7.8; 18.7)	13.8 (10.5; 17.7)	13.1 (10.9; 15.7)
Hazard ratio vs PLD (95% CI)	0.797 (0.526; 1.207)	1.374 (0.879; 2.147)	0.719 (0.478; 1.079)	1.105 (0.685; 1.783)	-	-
<i>P</i> value vs PLD, 2-sided log-rank test	0.2828	0.1617	0.1098	0.6822	-	-
PFS						
Median (95% CI), mo	1.9 (1.8; 2.3)	1.8 (1.8; 1.9)	3.7 (2.2; 5.6)	3.9 (1.9; 5.5)	1.9 (1.9; 3.6)	3.7 (3.2; 5.5)
Hazard ratio vs PLD (95% CI)	1.263 (0.881; 1.812)	1.776 (1.194; 2.641)	0.588 (0.406; 0.853)	0.924 (0.601; 1.421)	-	-
<i>P</i> value vs PLD, 2-sided log-rank test	0.2026	0.0041	0.0048	0.7174	-	-

2 - Late Breaking Abstracts

Worry and regret in the prospective multicentre TUBA study in *BRCA1/2* mutation carriers

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Objective: Currently, risk-reducing salpingo-oophorectomy (RRSO) around the age of 40 is recommended for *BRCA1/2* mutation carriers. To prevent premature menopause, risk-reducing salpingectomy (RRS) is considered, because recent data indicate the fallopian tube and not the ovary as the origin of high-grade serous ovarian carcinoma (HGSC). The TUBA-study (NCT02321228) (510 participants) compares quality of life after standard RRSO with RRS followed by delayed risk-reducing oophorectomy (RRO).

Method: A multicenter preference trial in 13 Dutch oncology centers started in 2015. *BRCA1/2* mutation carriers choose between RRSO at age 35–40 years (*BRCA1*) or 40–45 years (*BRCA2*) and the innovative strategy (RRS with

delayed RRO) at age 40-45 years (*BRCA1*) or 45-50 years (*BRCA2*). We present preliminary data on cancer worry and decision regret.

Results: Until now, 384 participants were included with a mean age of 37 years: 51% carried a *BRCA1* and 49% carried a *BRCA2* mutation. In total, 72% of women chose RRS with RRO. Three-month and 1-year follow-up was completed in 289 and 197 women, respectively. At first, there was an equal decline on the cancer worry scale 3 months after surgery for both strategies (RRSO -1.9 vs RRS -1.4). At 1 year of follow-up, a decline of 2.2 points (14.7 at baseline) was found after RRSO, compared to a decline of 1.0 point (13.9 at baseline) after RRS. The mean score on the decision regret scale was 13.4 (SD 14.5) and 13.0 (SD 14.0) 1 year after RRSO and RRS, respectively. Women choosing RRSO without hormone replacement therapy (HRT) had the highest decision regret (mean 18.8, SD 17.4).

Conclusion: Cancer worry declines after RRSO and RRS, with only low levels of decision regret. The baseline value of cancer worry is higher in women choosing RRSO, which might explain the larger decline in these women. Furthermore, the levels of regret were comparable for both strategies. At last, there was a notable high level of regret after RRSO without HRT, which might be caused by more severe menopausal complaints.

3 - Late Breaking Abstracts

WISP: A prospective, multi-center trial of salpingectomy with delayed oophorectomy versus risk reducing salpingo-oophorectomy in women at increased risk for hereditary ovarian cancer

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Objective: The purpose of the Women Choosing Surgical Prevention (WISP) study is to evaluate the option of salpingectomy with delayed oophorectomy (SDO) versus risk-reducing salpingo-oophorectomy (RRSO) in women at high risk secondary to inherited mutations in ovarian cancer predisposition genes.

Method: A prospective, nonrandomized, multicenter study is ongoing at 8 sites in the United States with planned enrollment of 270 women. Eligible women are premenopausal between the ages of 30 and 50 years and carrying a pathogenic germline mutation in an ovarian cancer susceptibility gene (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *BARD1*, *PALB2*, *MSH2*, *MLH1*, *MSH6*, *PMS2*, and *EPCAM*). Women choose either SDO or RRSO and complete questionnaires at baseline and 6 months. Absolute and change in cancer distress and menopausal symptoms are compared at baseline and post-surgery. Discrete variable SDO/RRSO comparisons are performed using Fisher exact tests. Continuous variable SDO/RRSO comparisons are performed using Wilcoxon rank sum or Kruskal-Wallis tests.

Results: A total of 190 women have enrolled (91 SDO and 99 RRSO). Median age for SDO is 37 (34.0-41.0 years) and for RRSO 40.0 (38.0-45.0) years. Fifty-one percent of enrolled patients are *BRCA1+*, and 39% are *BRCA2+*. SDO and RRSO participants are statistically similar for race, mutation, marital status, education ($P = 0.4567$), and income. High-grade intraepithelial neoplasia was found in 1 RRSO specimen from a *PALB2* mutation carrier; to date, no ovarian cancers have been identified at initial surgery, between surgeries, or at time of completion oophorectomy. Women in both arms had a significant decrease in distress at 6 months post-surgery, with the RRSO women experiencing a greater decrease compared to the SDO arm ($P < 0.0006$). Compared to the SDO women, RRSO women had significant worsening of menopausal symptoms, including hot flashes ($P < 0.0001$), night sweats ($P = 0.008$), vaginal dryness ($P = 0.004$), and weight gain ($P = 0.02$) after surgery. There was higher decision regret in women who underwent RRSO compared to SDO ($P < 0.009$), which held true regardless of whether women went on hormone replacement post-RRSO.

Conclusion: Women at high risk of ovarian cancer who undergo RRSO or SDO have a significant decrease in cancer distress. Women choosing RRSO have significant worsening of menopausal symptoms and higher decision regret,

compared to women undergoing SDO. To date, the lack of ovarian cancers identified in WISP is reassuring, and safety of the trial continues to be closely monitored.

4 - Late Breaking Abstracts

A phase II trial of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer

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Objective: Single-agent immune checkpoint inhibitors are largely ineffective treating recurrent ovarian cancer. Our objective was to determine whether the efficacy of anti-PD1 pembrolizumab could be enhanced by combining it with anti-VEGF bevacizumab (to improve lymphocyte endothelial trafficking and restore DC function) and oral metronomic cyclophosphamide (to selectively deplete circulating regulatory T cells and restore the cytotoxic potential of T cells and NK cells) in patients with recurrent EOC.

Method: This is an open-label phase II study (with a safety lead-in cohort of $n = 5$) of pembrolizumab 200 mg IV in combination with bevacizumab 15 mg/kg IV every 3 weeks and oral cyclophosphamide 50 mg every day until disease progression or unacceptable toxicity. Key eligibility included RECIST 1.1 measurable platinum-resistant recurrent ovarian cancer or patient declines platinum retreatment, no active autoimmune disease, and normal organ function. The primary objectives were to assess safety, clinical benefit (CR plus PR plus SD > 6 months), response rate, PFS, and quality of life, along with translational objectives.

Results: A total of 40 patients with recurrent EOC were enrolled. The median age of patients was 62 (44–88) years. Ten (25%) patients were platinum-sensitive and declined platinum-based therapy. Median number of prior chemotherapy lines was 5. The combination was well tolerated; most common grade 3 toxicities were decreased lymphocyte count and hypertension. At the time of interim data analysis in November 2018, the median follow-up was 14.7 months. The ORR was 37.5% (15 PR), and the 6-month PFS rate was 70% (15 PR and 13 SD). Twelve patients are still on treatment (7 PR, 5 SD), and 18% (7/40) of the patients have continued on treatment over 12 months. The 6-month PFS rates for the platinum-sensitive and nonsensitive patients were 100% and 59%, respectively ($P = 0.024$).

Conclusion: Pembrolizumab is safe and well tolerated when combined with IV bevacizumab and oral metronomic cyclophosphamide. Tumor responses are higher and more durable compared to those reported for pembrolizumab monotherapy or patients treated with combination of bevacizumab and oral cyclophosphamide.

5 - Late Breaking Abstracts

Phase I evaluation of lenvatinib and weekly paclitaxel in patients with recurrent endometrial, ovarian, fallopian tube, or primary peritoneal cancer

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Objective: Lenvatinib is an oral tyrosine kinase inhibitor of VEGF receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor- β , RET, and KIT. The objective of this study was to estimate the maximally tolerated dose (MTD) and describe toxicities associated with lenvatinib and weekly paclitaxel in patients with recurrent endometrial and platinum-resistant epithelial ovarian cancer.

Method: Using a 3+3 design, patients were given weekly paclitaxel 80 mg/m² IV days 1, 8, and 15 and oral lenvatinib daily on a 28-day cycle. Lenvatinib dose levels (DL) were 8 mg, 12 mg, 16 mg, and 20 mg. After determining the MTD, 6 additional patients were enrolled to the expansion cohort. Toxicities were recorded using CTCAE version 4.03, and response was determined with imaging after cycle 2 and then every third cycle, using RECIST 1.1 criteria.

Results: Twenty-six patients were enrolled, 20 with ovarian cancer (15 high-grade serous, 2 low-grade serous, 2 clear cell, and 1 carcinosarcoma) and 6 with endometrial cancer (3 serous and 3 endometrioid). Six patients

completed DL4 (MTD, lenvatinib 20 mg with weekly paclitaxel 80 mg/m²): however, the frequent need for dose reductions for grade 3 toxicity at this DL led us to establish the phase II dose at lenvatinib 16 mg and weekly paclitaxel 80 mg/m². Toxicities (all grades) occurring in ≥25% of patients included leukopenia, anemia, neutropenia, leukopenia, lymphopenia, mucositis, nausea, diarrhea, anorexia, hypertension, fatigue, nausea, proteinuria, epistaxis, hoarseness. Grade ≥3 toxicities were hypertension (19%), neutropenia (15%), leukopenia (12%), anemia (12%), lymphopenia (8%), fatigue (8%), diarrhea (8%), mucositis (4%), vomiting (4%), hematuria (4%), rash (4%), and thrombocytopenia (4%). Twenty-three patients are evaluable for response; 1 had a complete response (4%), 14 (61%) partial response, 7 (30%) stable disease, and 1 (4%) progressive disease. The ORR was 12/18 (67%) in ovarian cancer and 3/5 (60%) in endometrial cancer. Median PFS is 14.0 months (95% CI 5.1–not reached); 54% had a PFS >6 months. See **Figure 1**.

Conclusion: The regimen was tolerable with manageable side effects. Activity was seen in both endometrial and ovarian cancer (ORR 65%, CBR 96%), is favorable compared to the response seen in other studies with weekly paclitaxel (ORR 20%–28%), and warrants further development.

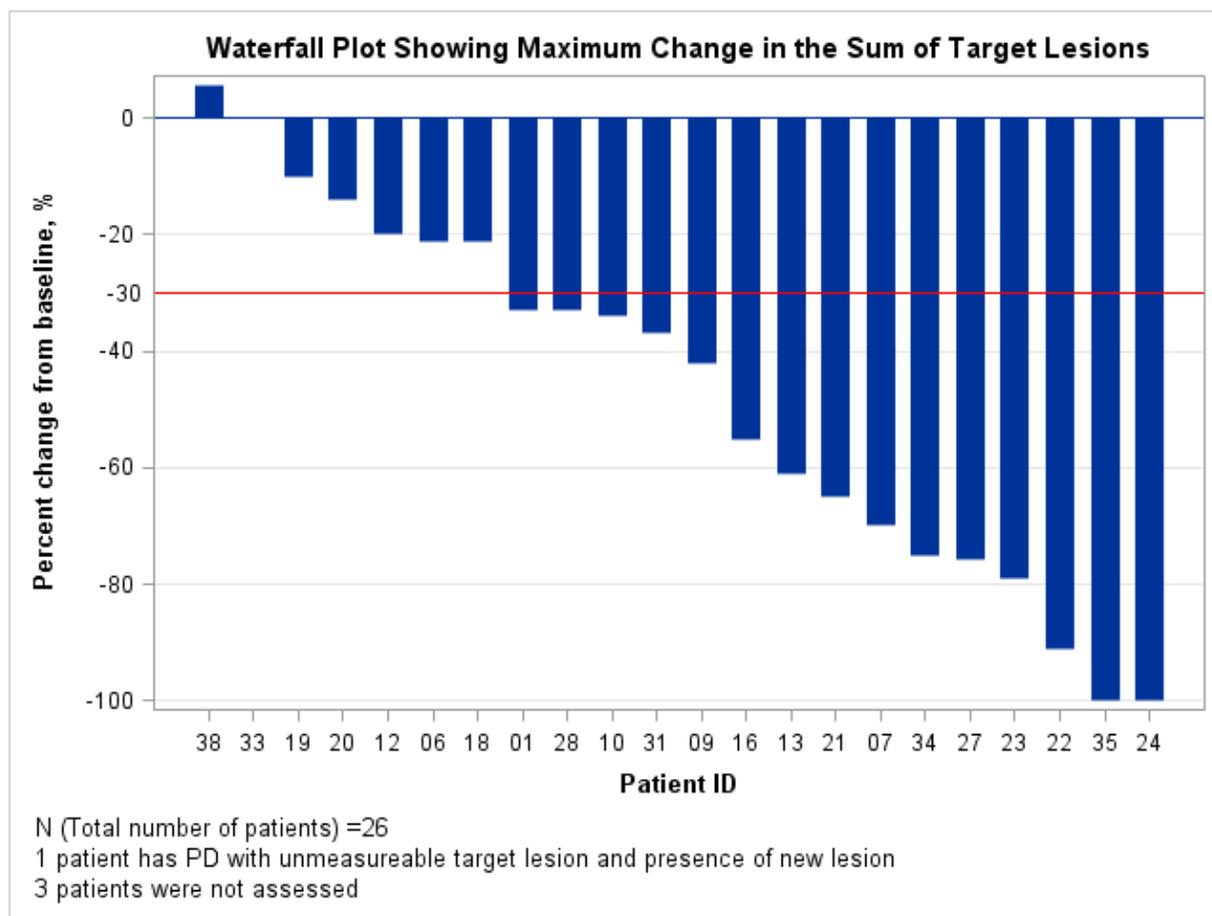


Fig. 1.