A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naïve patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial.

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Background: Gynecologic carcinosarcomas (CS) are rare yet aggressive epithelial malignancies for which optimal therapy is debated. PI was shown to be superior to I. PC demonstrated compelling phase 2 activity with improved safety and convenience. Methods: Main inclusion: ≥ 18 y; chemotherapy naïve stage I-IVB or recurrent uterine (U) or ovarian (O) CS. Treatment randomised 1:1 to PC (P 175mg/m² with C: AUC 6 or 5 if prior RT on D1) or PI (P: 135 mg/m² D1-3; I 1.6 g/m² D1-3; G-CSF support with dose escalation & de-escalation based on nadir counts) q21 days for 6-10 cycles. Quality of life (QOL) (FACT-En TOI) and neurotoxicity (FACT/GOG-Ntx subscale) administered at 4 timepoints. A stratified log-rank test compared primary endpoint of overall survival (OS) from entry between treatment groups for non-inferiority (NI) of PC to PI. With 264 events, power was 80% for a null hazard ratio of 1.2 against a 13% greater death rate on PI when type I error is limited to 5% for a one-tail test. NCT00954174. Results: 637 pts accrued with a median follow-up of 61 months. The primary (U, n = 536) and secondary (O, n = 101) cohorts are analyzed separately and included 449 and 90 pts eligible pts, respectively. For the U cohort: PC and PI were randomly assigned to 228 and 221 eligible pts. Stage distribution: I (40%); II (6%); III (31%); IV (15%) and recurrent (8%). The study met its primary objective with PC not inferior to PI (intention-to-treat analysis; Median OS 37 vs. 29 mo, HR = 0.87; 90% CI = 0.70 to 1.075; p < 0.01 for NI, p > 0.1 for superiority (S)). PFS (median on PC 16mo vs PI 12mo; HR = 0.73; p = 0.01 for NI, p < 0.01 for S). Toxicity (grade 1/2/3/4/5: PC 1/8/40/48/2%; PI 1/32/39/25/1%). Most of increase toxicity for PC was hematologic with G-CSF rarely used (N = 6). Confusion and genitourinary hemorrhage were significantly worse with PI. Both groups had decline in QOL and neurotoxicity scores. Similar trends were noted for the O cohort (OS: PC 30mo vs PI 25mo; and PFS: 15 mo vs 10 respectively). Conclusions: PC was not inferior to PI for OS with longer PFS and similar QOL and neurotoxicity. These results establish a new standard regimen for women with CS. Clinical trial information: NCT00954174.
Activity of durvalumab in advanced endometrial cancer (AEC) according to mismatch repair (MMR) status: The phase II PHAEDRA trial (ANZGOG1601).

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Background: Deficient DNA mismatch repair (dMMR) occurs in approximately 15% of AEC and is associated with a high tumour mutation burden. Expression of PD-1 and PD-L1 has been reported in up to 90% of ECs, including those with proficient DNA mismatch repair (pMMR). We report here preliminary results of PHAEDRA, a single-arm phase 2 trial designed to determine the activity of single-agent durvalumab, an antibody to PD-L1, in 2 cohorts of women with AEC. Methods: Participants (pts) had pMMR AEC progressing after 1-3 lines of chemotherapy, or dMMR AEC progressing after 0-3 lines of chemotherapy, and were treated with durvalumab 1500mg IV Q4W. The primary endpoint was objective tumour response (OTR = complete response [CR] or partial response [PR] by iRECIST). Secondary endpoints included disease control at 16 weeks (DC16w = CR, PR, or stable disease at 16 weeks [SD16w]), immune-related adverse events (irAEs), PD-L1, germline mutations and MLH1 methylation. Other secondary endpoints include: OTR and DC by RECIST1.1, other AE, PFS, OS & quality of life will be reported later. Results: 71 pts with AEC were recruited from Feb 2017 to Sep 2018: 35 dMMR and 36 pMMR. Median follow-up were 8.3 vs 14.8 months in dMMR vs pMMR pts. Median age: 67 (range 36-81); ECOG PS: 0–1 in 68, and 2 in 3. Pathology: endometrioid in 94% and 58%; serous in 0% and 31%; grade: high in 42% and 83% (dMMR and pMMR respectively). Durvalumab was the 1st, 2nd and subsequent line of non-hormonal therapy in 15, 14, and 6 pts with dMMR and 0, 21, and 15 pts with pMMR. Among dMMR pts, the OTR rate was 40% (14/35, 95% CI 26-56), with 4 CR and 10 PR; 7 others had SD16w for a DC16w rate of 60% (21/35, 95% CI 44-74). OTR rate was 40% as 1st line, 43% as 2nd line, and 33% as subsequent line treatment. Among pMMR pts, the OTR rate was 1/36 (3%, 95% CI 1-14) with 1 PR; 6 others had SD16w for a DC16w rate of 19% (7/36; 95% CI 10-35). IrAEs occurred in 14 pts: hyperthyroidism in 6, hypothyroidism in 6, pneumonitis in 1 and hepatitis in 1. Conclusions: Durvalumab monotherapy showed promising activity and safety in AEC with dMMR regardless of prior lines of chemotherapy, but there was limited evidence of activity in AEC with pMMR. Clinical trial information: ACTRN12617000106336.
Phase 2, two-group, two-stage study of avelumab in patients (pts) with microsatellite stable (MSS), microsatellite instable (MSI), and polymerase epsilon (POLE) mutated recurrent/persistent endometrial cancer (EC).

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Background: This non-randomized phase 2 study evaluated the PD-L1 inhibitor avelumab in two cohorts of EC: i) MSI/POLE cohort including ECs with immunohistochemical (IHC) loss of expression of at least one of the mismatch repair (MMR) proteins and/or documented mutation in the exonuclease domain of POLE and ii) MSS cohort including ECs with normal IHC expression of all MMR proteins. Methods: Eligibility criteria included measurable disease, unlimited prior therapies, and any EC histology. Co-primary endpoints were confirmed objective response (OR) and progression-free survival rate at 6 months (PFS6). Avelumab 10 mg/kg IV was given every 2 weeks until progression or unacceptable toxicity. In the 1st stage, 16 pts were enrolled in each cohort; if there were $\geq 2$ ORs or $\geq 2$ PFS6 responses, accrual would continue to the 2nd stage with enrollment of 19 additional pts. Overall, if there are $\geq 4$ ORs or $\geq 8$ PFS6 responses, avelumab would be considered worthy of further study in each cohort.

Results: As of 12/2018, 33 pts were enrolled. The MSS cohort was closed at the 1st stage due to futility; of 16 pts in the MSS cohort, only 1 pt exhibited an OR and PFS6 response [ORR and PFS6 rate 6.25% (95% CI 0.16%-30.2%)]. Conversely, the MSI/POLE cohort reached the primary endpoint of 4 ORs after accrual of only 17 pts. Two pts in the MSI/POLE cohort did not initiate protocol therapy and were excluded from all analyses. Of 15 pts in the MSI/POLE cohort, 4 pts exhibited OR [1CR+3PRs, OR rate (ORR) 26.7% (95% CI 7.8%-55.1%)] and 6 pts (including the 4 pts with OR) exhibited PFS6 responses [PFS6 rate 40.0% (95% CI 16.3%-66.7%)], 4 ongoing and 3 approaching 2 yrs. Twenty-two pts (71%) reported treatment related toxicities, 6 patients (19%) G3 toxicities; there were no treatment-related G4 and G5 toxicities. In the MSI/POLE cohort, 5 of 6 PFS6 responses were observed in pts with $\geq 3$ lines of prior therapy ($p = 0.011$) and in tumors who were PD-L1 negative by IHC. Further correlative work will be reported at the meeting. Conclusions: In EC pts stratified by MSI/POLE status, MSI vs MSS status appears to be correlated with avelumab response even in PD-L1 negative tumors. Responses in the MSI/POLE cohort were more frequent in more heavily pretreated patients, a finding that warrants further investigation. Clinical trial information: NCT02912572.
Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994.

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Background: Conflicting evidence on the value of neoadjuvant chemotherapy followed by surgery compared to concomitant chemoradiation in Stage IB2-IIB cervical carcinoma led to this multinational multicenter trial. As the trial is approaching completion of its follow-up, preliminary results are presented. Methods: Between May 2002 and June 2014 a total of 620 patients with FIGO stage Ib2-IIb were randomized between neoadjuvant chemotherapy followed by surgery (NACTS, arm 1, N=311) with standard concomitant chemoradiotherapy (CCRT, arm 2, N=309). In arm 1, radical hysterectomy was required within 6 weeks after completion of cisplatin-based chemotherapy with a cumulative minimum of 225mg/m2, in arm 2, radiation consisted of 45-50 Gy plus boost concurrent with weekly cisplatin chemotherapy (40 mg/m2 per week). Primary endpoint was 5-ys overall survival (OS). Results: Median follow-up time was 8.2 years (95% CI = 7.8 yrs – 8.6 yrs) and similar between both arms. A total of 191 deaths (31%) occurred. Age, stage and histological cell type were balanced in both arms. Protocol treatment was completed in 459 (74%) patients (71% for NACTS; 82% for CCRT). In arm 1 238 (76%) patients underwent surgery. Main reasons for not having surgery as per protocol, were toxicity (25/74, 34%), progressive disease (18/74, 24%) and insufficient response to NACT (12/74, 16%). Additional radiotherapy was given to 113 patients (36.3%) in arm 1; additional surgery performed in 9 patients (2.9%) in arm 2. Short term severe adverse events (≥G3) occurred more frequently in arm 1 than in arm 2 (35% vs 21%, p < 0.001). The 5 year OS was 72% in arm 1 and 76% in arm 2 (not statistically significant, difference = 4.0% (95%CI: -4% - 12%); HR 0.87, 95%CI: 0.65-0.15, p=0.332). Conclusions: These preliminary results revealed no difference in 5-year OS between NACTS and CCRT, indicating that quality of life and long term toxicity are important to decide optimal treatment. The final results will be available by April 2019, including long-term toxicity and treatment effect across prognostic factors. Clinical trial information: NCT00039338.
Recurrence rates in cervical cancer patients treated with abdominal versus minimally invasive radical hysterectomy: A multi-institutional analysis of 700 cases.

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Background: Compare outcomes between open and minimally invasive radical hysterectomy. Methods: Retrospective multi-institutional review of patients undergoing radical hysterectomy for stage IA1, IA2 and IB1 squamous, adeno- or adeno-squamous carcinoma between 01/01/2010 - 12/31/2017. Results: From 704 cases that met the inclusion criteria, 185 (26.3%) underwent open and 519 (73.7%) underwent minimally invasive surgery (MIS). Women treated with open surgery were older, had larger tumors on preoperative assessment as well as on final pathology assessment, had higher proportion of patients with IB1 stage and adjuvant therapy. Patients undergoing open surgery had longer median follow-up compared to MIS (44 vs. 30.3 months, p < 0.001). The two groups were similar in regard to race distribution, body mass index, comorbidities and preoperative histology. There were 13/185 (7%) recurrences and 10/185 (5.4%) deaths in the open compared to 42/519 (8.1%) recurrences and 26/519 (5%) deaths in MIS (p = n.s for both). However, on multivariate analysis, after controlling for race, comorbidities, preoperative tumor size, histology, grade and smoking status, MIS had higher odds of recurrence (OR 2.24, 95% CI 1.04 - 4.87, p = 0.04). On a second model, in addition to prior mentioned factors, we included lymphovascular space invasion, receipt of adjuvant therapy and vaginal margin status. Undergoing MIS remained associated with higher odds of recurrence (OR 2.37, 95% CI 1.1 - 5.1, p = 0.031). On sub-group analysis of cases with preoperative tumor size less than equal to 2 cm, there were 5/121 (4.1%) recurrence in open and 25/415 (6%) recurrences in MIS group (p = 0.34). Multivariate analysis did not show a higher rate of recurrence in MIS arm in this subgroup. In 26 cases of MIS where no vaginal manipulator was used, no recurrences were noted. In comparison 19/270 (7%) recurrences were noted in intra-uterine manipulator (V-care/Zumi/Rumi) and 22/210 (11%) in vaginal manipulators (EEA sizer/Colpo Probe) groups (p = 0.119). Conclusions: In this large retrospective analysis, patients undergoing MIS for early stage cervical cancer had higher odds of recurrence. In patients with 2 cm or less tumor on preoperative assessment, recurrence rates were similar between the two groups. Role of manipulator in increasing recurrence should be further studied in this patient population.

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Background: Standard treatment of platinum-sensitive recurrent ovarian cancer (PSROC) is platinum based combination chemotherapy ± bevacizumab. However, this treatment modality is hardly curative, and is associated with significant toxicity. Both bevacizumab (BEV) and PARP inhibitors (PARPi) have demonstrated efficacy in PSROC. There is preclinical evidence of enhanced activity of the combination. This is the proof-of-concept randomized trial of PARPi-BEV combination against PARPi monotherapy as treatment in PSROC, regardless of number of previous lines of therapies. Methods: In this randomized, open-label, phase 2 study, women with measurable/evaluable, high-grade serous or endometrioid PSROC were randomized to niraparib 300mg once daily or the combination of niraparib 300mg once daily and BEV 15mg/kg IV every 3 weeks until disease progression (1:1 randomization). The primary endpoint was progression-free survival (PFS). Stratification was according to homologous recombination-deficiency(HRD) status (MyChoice HRD) and chemotherapy-free-interval (CFI)(6-12months (mo) vs. >12mo). First-line maintenance bevacizumab was permitted. Results: Of 97 enrolled patients, 48 were randomized to niraparib monotherapy and 49 to the chemotherapy-free combination. The combined treatment significantly improved PFS compared to niraparib alone: median 11.9 vs. 5.5 mo; hazard ratio (HR) adjusted for stratification factors 0.35; 95% confidence interval (CI),[0.21 to 0.57]; P<0.001. Pre-planned exploratory subgroup analyses: patients with HRD-positive tumors (n=54) HR 0.36 (CI, 0.18-0.69); HRD-negative disease (n=43) HR, 0.47 (CI, 0.24-0.95); gBRCAmut patients (n=34) HR 0.53 (CI, 0.23-1.21); non-gBRCAmut patients (n=63) HR 0.33; CI, 0.18-0.61); CFI of 6 to 12 mo (n=38) HR, 0.29 (CI, 0.14 to 0.62); CFI of ≥12 mo (n=59) HR, 0.42; (CI, 0.22 to 0.80). There was no difference in treatment-emergent grade 3-4 adverse events except for the rate of hypertension (26.5% vs. 0%) and neutropenia (12.2% vs. 2.1%). Patient-reported outcomes measured using EORTC QLQ-C30 and OV28 were similar for both treatment arms. Conclusions: Both niraparib alone and the combination had meaningful activity in PSROC. Compared to niraparib alone, the chemotherapy-free regimen of niraparib and BEV significantly improved PFS in women with PSROC, regardless of HRD status and duration of CFI. Clinical trial information: NCT02354131.
Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase III SOLO3 trial.

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Background: Data from a randomized Phase II trial (NCT00628251) of olaparib (capsules, 200 or 400 mg bid, n = 32 per arm) vs pegylated liposomal doxorubicin (PLD, n = 33) in gBRCAm OC pts with recurrence ≥12 months after prior platinum therapy indicated efficacy for olaparib (Kaye et al. JCO 2012). However, the efficacy of PLD was higher than previously reported in this setting. We led a confirmatory Phase III, open-label study of olaparib vs non-platinum chemotherapy in gBRCAm PSR OC pts (NCT02282020). Methods: Pts were randomized (2:1) to olaparib tablets (300 mg bid) or chemotherapy treatment of physician’s choice (TPC) (paclitaxel [P; 80 mg/m² on day 1 (D1), D8, D15, D22 every 4 weeks (q4w)], topotecan [T; 4 mg/m² D1, D8, D15 q4w], gemcitabine [G; 1000 mg/m² D1, D8, D15 q4w] or PLD [50 mg/m² D1 q4w]) until progression, stratified by: TPC, prior lines of chemotherapy (2–3 ✔️ 4) and platinum-free interval (6–12 vs >12 months). Primary endpoint: ORR (blinded independent central review [BICR]). Secondary endpoints included PFS and safety. Results: 266 gBRCAm PSR OC pts were randomized (olaparib, n = 178; TPC, n = 88 [PLD, n = 47; P, n = 20; G, n = 13; T, n = 8]); 12 in the TPC arm withdrew before receiving study treatment. 223 pts (84%) had baseline BICR measurable disease (olaparib, n = 151; TPC, n = 72). ORR was 72% with olaparib vs 51% with TPC (OR 2.53, 95% CI 1.40–4.58; P = 0.002). HR for PFS by BICR was 0.62 (95% CI 0.43–0.91; P = 0.013; median 13.4 vs 9.2 months [olaparib vs TPC]) and by investigator assessment was 0.49 (95% CI 0.35–0.70; P < 0.001; median 13.2 vs 8.5 months, respectively). Most common adverse events (AEs) with olaparib were nausea (65% vs 34% [TPC]) and anemia (50% vs 25%) and with TPC were palmar-plantar erythrodysesthesia (PPE; 36% vs 1% [olaparib]) and nausea. Most common grade ≥3 AEs in either arm were anemia (21% [olaparib] vs 0 [TPC]), PPE (0 vs 12%) and neutropenia (6% vs 11%). For olaparib vs TPC, serious AEs were reported by 24% vs 18% and AEs led to treatment discontinuation in 7% vs 20%. Conclusions: Pts with gBRCAm PSR OC receiving olaparib monotherapy had a significant, clinically relevant improvement in ORR and PFS vs TPC, with no new safety signals. Clinical trial information: NCT02282020.
Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-resistant ovarian cancer.

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Background: The CLIO trial (NCT02822157) evaluated olaparib single-agent therapy versus standard of care chemotherapy in platinum-resistant (recurrence within 6 months after last platin) ovarian cancer (PROC). Methods: Eligible patients with measurable 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; PLD 40 mg/m2 q 4 wks; Topotecan 1.25 mg/m2 day 1—5 q 3 wks; Paclitaxel 80 mg/m2 day 1, 8,15 q 3 wks; Gemcitabine 1000 mg/m2 day 1, 8 and 15 q 4 wks). Primary endpoint was objective overall response (ORR) per RECIST v1.1. Germline BRCA status was available for all patients. Disease control rate (DCR) was defined as response for at least 12 wks. Results: 100 patients with PROC were randomized 2:1 to OLA (N = 67) or CT (N = 33). Median prior lines of treatment was 3 (range: 1—8). ORR (unconfirmed) was 18% (12/67) for OLA and 6% (2/33) for CT. ORR for OLA was 38% (5/13) in gBRCAm and 13% (7/54) in gBRCAwt patients. Of note, 2 patients with gBRIP1 mutation had no response under OLA. DCR was 35.8% (24/67) for OLA and 42% (14/33) for CT. DCR under OLA in gBRCAm was 62% (8/13) compared to 30% (16/54) in gBRCAwt disease. The median duration of response (DOR) and the median progression-free survival (PFS) was similar: 5.4 months vs 4.5 months (DOR) and 2.9 vs 3.4 months (PFS) for OLA and CT, respectively. Grade ≥3 treatment-related AEs occurred in 60% vs 52% for OLA and CT, respectively. Somatic HRR mutation analysis is ongoing and will be presented. Conclusions: Olaparib monotherapy showed a favorable response rate in PROC compared with chemotherapy also in gBRCAwt patients. Analysis of clinical endpoints in relation to HRR is ongoing and will be presented. Clinical trial information: NCT02822157.
EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study.

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Background: The Geriatric Vulnerability Score (GVS) combining albumin, lymphocyte count, ADL, IADL and HADS scores has been reported (Falandry C Ann Oncol 2013) to identify vulnerable elderly OC patients (pts) as those with a GVS $\geq 3$. For such pts, Carboplatin (Cb) monotherapy or weekly Cb plus paclitaxel (Pa) are often proposed as an alternative to Cb-Pa given every 3 weeks.

Methods: Pts $\geq 70$ yrs with first line FIGO stage III/IV epithelial OC were screened for GVS. Those with GVS $\geq 3$ were randomized to receive either arm A: Cb AUC5-6 + Pa 175mg/m² d1q3week or arm B: Cb AUC5-6 d1q3week or arm C: weekly Cb AUC2 + Pa 60mg/m² d1-d8-d15 q4week. Primary endpoint is treatment feasibility defined as the ability to complete 6 chemotherapy courses without disease progression, early treatment stopping due to unacceptable toxicity or death. Inclusion of 240 pts was planned.

Results: Among 444 screened pts, 120 were randomized from 12/2013 to 04/2017 (armA = B = C = 40). Pts characteristics were well balanced between arms A-B-C respectively: median age (79-82-80 yrs), FIGO stage IV (32-37-27%), primary surgery (65-72-70%), absence of macroscopic residuals (CC-0) (7-5-047%), ECOG $\leq 2$ ( 5 0 - 5 0 - 47%). Feasibility per protocol for arms A-B-C is 65%, 47% and 60% (p = 0.15). Main reasons for treatment arrest are treatment toxicity (A:20%; B:15%; C:22.5%; p = 0.771) and disease progression (A: 7.5%; B:30%; C:2%; p = 0.004). Median PFS for arm A-B-C are 12.5 mos (95%CI 10.3-15.3), 4.8 (3.8-15.3) and 8.3 (6.6-15.3), respectively (p < 0.001) and median OS for arm A-B-C is not reached (NR) (21, NR), 7.4 (5.3-NR) and 17.3 (10.8-NR), respectively (p = 0.001). At the pre-planned intermediate analysis, the IDMC recommended to prematurely close the study as survival in armB was found significantly worse and the number of potential pts required to find a significant difference between both Cb-Pa regimens (arms A&C) was out of reach. Conclusions: Compared to 3-weekly and weekly Cb-Pa regimens, Cb single agent was reported to be less active with significant worse survival outcome in vulnerable elderly pts. In this population Cb-Pa combination remains a standard. Clinical trial information: NCT02001272.
Sex hormone, insulin, and insulin-like growth factor signaling in recurrence of high stage endometrial cancer: Results from the NRG Oncology/Gynecologic Oncology Group 210 trial.

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Background: Sex hormone and insulin/insulin-like growth factor (IGF) axis signaling pathways play an important role in endometrial cancer development but their role in endometrial cancer recurrence is unknown. In this study GOG-8015 we evaluated these pathways in a prospective cohort of patients diagnosed with the most common type of endometrial cancer, endometrioid adenocarcinoma. Methods: Stage II-IV endometrioid endometrial adenocarcinoma patients (N = 816) enrolled in the GOG-210 study with pre-treatment specimens were tested for tumor mRNA and protein expression levels of IGF1, IGF2, IGF binding proteins (IGFBP)-1 and -3, the insulin (IR) and IGF-I receptors (IGF1R), and phosphorylated (activated) IR/IGF1R as well as estrogen (ER) and progesterone receptors (PR) using quantitative PCR and immunohistochemistry (IHC). Serum concentrations of insulin, IGF-I, IGFBP-3, estradiol, estrone and sex hormone binding globulin were measured using ELISAs. Hazard ratios (HR) and 95% confidence intervals (CI) for risk of recurrence were obtained from multivariable Cox proportional hazard’s models with adjustment for age, stage and grade. Results: Recurrence occurred in 280 (34%) cases during a mean of 5.4 years of follow-up. ER-positivity (HR 0.67, 95% CI 0.47-0.95), IR-positivity (HR 0.53, 95% CI 0.29-0.98) and serum IGF-I levels (highest versus lowest quartile, HR 0.66, 95% CI 0.47-0.92) were inversely associated with recurrence risk. Conversely, circulating estradiol (highest versus lowest tertile, HR 1.55, 95% CI 1.02-2.36) and insulin (per 10 uU/ml, HR 1.52, 95% CI 1.12-2.06) and phosphorylated IGF1R/pIR expression (HR 1.40, 95% CI 1.02-1.92) were associated with increased risk of recurrence. Conclusions: We identified novel sex hormone and insulin/IGF axis tissue and circulating biomarkers of recurrence in a prospective study of high stage endometrioid endometrial cancer. Circulating insulin and estradiol, and tissue phosphorylated (activated) IGR1R/IR were independently associated with recurrence. These findings support prioritizing studies to establish their clinical utility as prognostic biomarkers and to investigate new strategies that target these pathways for prevention and treatment of endometrial cancer recurrence.
Results of a phase 2 trial of ribociclib and letrozole in patients with either relapsed estrogen receptor (ER)-positive ovarian cancers or relapsed ER-positive endometrial cancers.

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Background: Single agent aromatase inhibitor (AI) therapy is associated with limited clinical activity in ovarian cancer (OC) and endometrial cancers (EC). AI therapy was associated with a progression free survival (PFS) at 12 weeks of only 20% in relapsed OC (Bowman et al, 2002) and a median PFS of 1 month in relapsed EC (Rose et al, 2000). In Estrogen Receptor (ER) positive metastatic breast cancer, clinical studies had shown a significant prolongation of PFS with the addition of the cyclin kinase 4/6 inhibitor ribociclib to AI (Hortobagyi et al, 2016). Here, we report the results of a phase 2 clinical trial of the combination of ribociclib and letrozole in patients with relapsed ER positive OC or EC. Objectives: Primary endpoint was the proportion of patients with relapsed ER positive OC or EC alive and progression-free after 12 weeks of therapy (PFS12) with the combination of ribociclib given at a dose of 400 mg orally daily and letrozole 2.5 mg orally daily. A PFS of 45% was considered a favorable result based on the data referenced above from Bowman et al.

Methods: Eligibility criteria included patients with relapsed ER positive OC or EC, with measurable disease, not previously treated with ribociclib or AIs. Xenografts were created from CT guided tumor biopsies at baseline to assess feasibility. Results: A total of 40 patients were enrolled (20 with OC and 20 with EC) with a median age of 61 years (range: 30-82) and 64.5 (range: 52-75) in the OC and EC groups respectively. Among the OC patients, 17 had high grade serous carcinomas and 3 had low grade serous carcinomas. 11 EC patients had endometrioid cancers (3 with grade 1 tumors) and 9 had high grade serous tumors. Ten out of 20 OC patients and 11/20 EC patients were alive and progression-free at 12 weeks (PFS12 of 50 and 55%, respectively). The most common grade 3 or higher adverse events (occurring in at least 5 pts) were leukopenia (18%), lymphopenia (18%), neutropenia (13%), and fatigue (13%). 34 tumor biopsies were suitable for injection into mice and 44% engrafted. ER expression persisted through multiple passages in mice. Two of three EC PDX models exhibited improved PFS with letrozole/ribociclib compared to letrozole alone. Conclusions: The combination of ribociclib and letrozole is associated with a promising 50% and 55% PFS12 in patients with ER positive relapsed OC or EC respectively. Creation of xenograft tumor models from CT guided biopsies of OC and EC tumors was feasible. Clinical trial information: NCT02657928.
A phase II randomized study of avelumab plus entinostat versus avelumab plus placebo in patients (pts) with advanced epithelial ovarian cancer (EOC).

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Background: Preclinical evidence suggests that combining avelumab (A), a human anti-PD-L1 monoclonal antibody, and entinostat (E), a class I selective histone deacetylase (HDAC) inhibitor, may increase tumor immunogenicity and responsivity to checkpoint inhibition. This study evaluated whether A+E would lead to improved progression free survival (PFS) vs A in pts with advanced EOC. Methods: Pts with EOC which had progressed or recurred after 1st-line platinum-based chemotherapy and received 3-6 lines of therapy were randomized 2:1 to receive A (10 mg/kg IV Q2W) plus E (5 mg PO QW) or A plus placebo (P). Treatment continued until disease progression (PD) or unacceptable toxicity. The primary endpoint was PFS (investigator-assessed, RECIST 1.1), stratifying on the presence/absence of bulky disease (tumor ≥ 50 mm) and platinum-refractory disease. The hypothesis was that the combination would reduce the hazard of PD or death by 43%, representing a 75% improvement in median PFS. 97 events (from 120 pts) provided 90% power with 1-sided significance level of 0.10. Secondary endpoints included ORR, duration and time to response, toxicity, clinical benefit rate, and OS. Results: 126 pts were enrolled, median age 63 yrs (range 43-82), median 4 prior lines, 83% serous histology. Median PFS was 1.64 and 1.51 mos for A+E and A+P, respectively (p = 0.31; HR 0.90, 95% CI: 0.58-1.39). No significant differences in ORR (6% vs 5%), or OS (NE vs 11.3 mos) were observed. 4 pts (3%) had clear cell EOC, with no responses observed. The incidence of related adverse events (AEs) was higher in the A+E arm compared to A+P (any grade: 93% vs 78%, Grade 3/4: 41% vs 10%), and the most frequent (≥20%) related AEs with A+E were fatigue (46%), nausea (31%), diarrhea (26%), anemia (26%), and chills (20%). Grade 3/4 related AEs occurring in ≥5% with A+E were fatigue (9%), and neutropenia (8%). 47% of pts in A+E arm required E dose holds/reductions. Discontinuations due to AEs were similar between arms (21% vs 17.5% for A+E and A+P, respectively), as was duration of study therapy (median 4 and 5 cycles started). Conclusions: In pts with heavily pretreated EOC, median PFS was not prolonged when E was added to A compared to A alone and the combination resulted in greater toxicity. Clinical trial information: NCT02915523.
Impact of adding nintedanib to neoadjuvant chemotherapy (NACT) for advanced epithelial ovarian cancer (EOC) patients: The CHIVA double-blind randomized phase II GINECO study.

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Background: Nintedanib, an oral inhibitor of VEGF-FGF-PDGF receptors, has been shown to prolong progression-free survival (PFS) when added to adjuvant chemotherapy after primary surgery (duBois A, Lancet Oncol 2015). CHIVA trial explored the role of nintedanib in combination with NACT. Methods: Patients (pts) with FIGO stage IIIC-IV chemotherapy-naive AEOC considered as unresectable after laparoscopic evaluation were randomized (2:1) to be treated with 3 to 4 cycles (cy) of carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m²) (CP) before interval debulking surgery (IDS) followed by 2 to 3 cy of CP for a total of 6 cy, plus either 200 mg of Nin (armA) or placebo (armB) twice daily on days 2–21 q3week at cy 1&2, 5&6 and maintenance therapy for up to 2 years. The primary endpoint was PFS. Results: Between Jan. 2013 and May 2015, 188 pts were included (124 arm A, 64 arm B) with a median Peritoneal Cancer Index of 22 (range 19-27). Pts characteristics were well balanced between both arms. Median PFS was 14.4 mos (95%CI 12.2-15.4) and 16.8 (13.3-21.4) in arm A and B respectively (HR:1.50, p=0.02). Median OS was 37.7 mos (29.8-41.0) and 44.1 (32.7-not reached) in arm A and B respectively (HR:1.54, p=0.053). Arm A was associated with more toxicity compared to arm B respectively (Grade 3&4 adverse events: 92 versus 71%), with increased early treatment discontinuation before the 3rd cy (14.5 vs 6.2%) & CP dose reduction (12% vs 0%). Pts in Arm A reported inferior RECIST ORR to pre-IDS therapy compared to Arm B (35.1 vs 55.9%). IDS was performed significantly less frequently in arm A (58.1%) vs arm B (76.6%). However among pts who underwent IDS, complete surgical cytoreduction rate (76%) and peri/postoperative complication rate (11.2%) were similar in both arms. Conclusions: The addition of nintedanib to NACT increases toxicity and compromise chemotherapy efficacy leading to a reduced rate of IDS and worse PFS and OS for advanced EOC patient. Clinical trial information: 2011-006288-23.
5513 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Adavosertib with chemotherapy (CT) in patients (pts) with platinum-resistant ovarian cancer (PPROC): An open label, four-arm, phase II study.

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Background: Adavosertib (AZD1775; A), a highly selective WEE1 inhibitor, demonstrated activity and tolerability in combination with carboplatin (C) in primary PROC. This study (NCT02272790) assessed the objective response rate (ORR) and safety of A in PROC. Methods: Pts with recurrent RECIST v1.1 measurable PROC received A with C, gemcitabine (G), weekly paclitaxel (P), or pegylated liposomal doxorubicin (PLD) in 3- (C) or 4-week (G, P, PLD) cycles (Table). Tumor assessments were performed every 2 cycles until disease progression. Primary objective: ORR; other objectives: disease control rate (DCR), progression-free survival (PFS) and safety. Results: In the 94 pts treated (median treatment duration 3 months; range 0–16 months), outcomes were greatest with A (weeks [W]1–3 + C) with ORR of 67% and median PFS (mPFS) of 10.1 months for this cohort. Most common grade ≥ 3 treatment-emergent adverse events (TEAEs) are shown in the Table, with hematologic toxicity most notable with A (W1–3) + C. TEAEs led to A dose interruptions, reductions and discontinuations in 63%, 30% and 13% of the whole cohort, respectively. A possible positive relationship between CCNE1 amplification and response warrants further investigation. Conclusions: A shows preliminary efficacy when combined with CT. Pts receiving A (W1–3) + C showed greatest benefit. The increased but not unexpected hematologic toxicity is a challenge and could be further studied to optimize the dose schedule and supportive medications. Clinical trial information: NCT02272790.

<table>
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<th>175 mg daily (2 Ds, W1–3) + G</th>
<th>225 mg BID (2.5 Ds, W1–3) + P</th>
<th>225 mg BID (2.5 Ds, W1–3) + C</th>
<th>225 mg BID 175 mg BID (2.5 Ds, W1–3) + C + PLD</th>
<th>225 mg BID (2.5 Ds, W1–3) + PLD</th>
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<td>8 (21)</td>
<td>13 (57)</td>
<td>6 (50)</td>
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*Data from an interim analysis; †800 mg/m² IV D1, 8 and 15; ‡80 mg/m² D1, 8 and 15; §AUC5 D1; §40 mg/m² D1; ‡Affecting ≥ 20% of all pts. D, day
Dose-dense early postoperative intraperitoneal chemotherapy in ovarian cancer: Randomized, phase II trial.

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Background: Dose-dense early postoperative intraperitoneal chemo (DD-EPIC) had been carried out in advanced ovarian cancer (OC) pts in China over the past three decades but it was not proved by a prospective study. This trial was designed to confirm the benefit of DD-EPIC in delaying progression and improving survival.

Methods: In a multicenter, phase 2 trial, pts with FIGO IIIC-IV OC and optimal debulking surgery (residual disease ≤ 1 cm) were randomly allocated to receive 4 doses of weekly DD-EPIC with cisplatin (50mg/m²) and etoposide (100mg/m²) followed by 6 cycles of intravenous (iv) chemo with carboplatin and taxane every 3 weeks (DD-EPIC group), or standard iv chemo alone (iv group). (ClinicalTrials.gov, NCT01669226).

Results: Between 2009 and 2015, 218 pts were randomized, of whom 215 initiated treatment (106 to DD-EPIC and 109 to iv; for efficacy analyses). Totally, 36 pts (16.7%) were received neoadjuvant chemo. With a median of 61.9 mos follow-up, 122 pts died (54 in DD-EPIC and 68 in iv group). Remarkable OS benefit of DD-EPIC was recorded (67.5 mos for DD-EPIC vs. 46.3 mos for iv; HR 0.70, 95% CI 0.49-1.00, P=0.047). Pts in DD-EPIC had a significantly increased median PFS compared with those in iv group (21.7 vs. 16.8 mos; HR 0.64, 95% CI 0.47-0.86, P=0.003). Median TFST was 25.1 vs. 18.0 mos in favor of DD-EPIC (HR 0.62, 95%C 0.46-0.83, P=0.002). Similar findings were detected in TSST (42.2 vs. 29.3 mos; HR 0.66, 95% CI 0.47-0.94, P=0.019). Grade 3 and 4 Leucopenia (53.8% vs. 35.2%), anemia (23.6% vs. 5.6%) and gastrointestinal events (10.4% vs. 1.9%) were more common in DD-EPIC (P=0.006, P<0.001 and P=0.010, respectively). Ninety-one pts were detected by gBRCA testing, with 25.3% of cases carrying deleterious BRCAm, but PFS and OS benefit were observed in patients with BRCA-wild type (HR 0.46 and 0.55, 95%CI 0.27-0.81 and 0.27-1.11, respectively).

Conclusions: DD-EPIC with a higher completion rate and acceptable treatment burden was associated with longer OS than standard iv alone. Owing to the benefit of relatively long-term OS, DD-EPIC may be considered as a valuable option for OC, particularly in developing countries and BRCA-wild type pts. Clinical trial information: NCT01669226.

<table>
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<td></td>
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<td>DD-EPIC</td>
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<tr>
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The prognosis of patients with recurrent or persistent ovarian clear cell carcinoma: Results from a randomized phase III study (JGOG3017/GCIG).

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Background: There are currently no concise data on prognosis in patients with recurrent or persistent clear cell carcinoma (CCC). The JGOG3017/GCIG was a randomized phase III trial to compare paclitaxel plus carboplatin (TC) to CPT-11 plus cisplatin (CPT-P) for stage I to IV CCC patients who have been diagnosed by central pathological review (CPR). A total of 619 patients were eligible for efficacy analyses. The aim of this study was to investigate prognosis of these patients with recurrent or persistent CCC. Methods: We estimated median and restricted mean survival time (RMST) of post-progression survival (PPS) of patients with recurrent or persistent CCC by platinum sensitivity, treatment arm, crossover chemotherapy, primary stage, residual tumor, performance status and ethnicity. PPS rates at 6, 12, 18 and 24-month were also calculated. Results: Among the 619 patients, the recurrence rate of stages was as follows: 6.3% (6/96) in stage IA/IB, 14.6% (46/315) in stage IC, and 54.8% (114/208) in stage II- IV. The recurrence rate of surgical situations was as follows: 19.4% (106/544) in complete surgery, 75% (27/36) in optimal, and 84.6% (33/39) in suboptimal. Overall, 166 of 619 patients had recurrent disease. The median PPS were 14.0 months (95% confidence interval [CI], 12.6 – 17.9) for all patients, 13.5 months (95% CI, 11.4 – 19.6) in the TC group (n=77) and 14.4 months (95% CI, 11.0 - 18.8) in the CPT-T group (n=89), with no significant difference between the two groups (hazard ratio, 1.02; 95% CI, 0.71 - 1.47, log-rank P = 0.898). The RMST of PPS for all patients was 14.6 months (95% CI, 13.3 - 15.8). Median PPS for patients with platinum-resistant (44.6%, n=74) and platinum-sensitive (53.0%, n=88) disease were 10.9 months (95% CI, 8.9 - 13.3) and 18.8 months (95% CI, 15.0 - 28.7) (HR, 1.88; 95% CI, 1.30-2.72, p<0.001), respectively. Conclusions: The median PPS of patients with platinum-resistant recurrence was significantly shorter than that of patients with platinum-sensitive recurrence. Data on PPS in patients with recurrent CCC that will be the basis of a future clinical trial in such patients were obtained.
Surveillance in stage I MOGCTs (malignant ovarian germ cell tumors): A MITO prospective study (multicenter Italian trials in ovarian cancer).

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Background: The standard of treatment of stage I MOGCTs is surgery followed by BEP (bleomycin + etoposide + cisplatin) chemotherapy, except for stage IA dysgerminoma (D) and IAG1 immature teratoma (IT). Surveillance has emerged as a possible option to avoid adjuvant chemotherapy in IB-C1 D, IA-C G2 – G3 IT, and in stage IA mixed and yolk sac tumors (YST), after comprehensive surgical staging (CSS) with negative postoperative markers. The aim of this study was to analyze oncological outcome of stage I MOGCT patients included in the MITO9 study.

Methods: MITO9 was a prospective observational study analyzing data collected between 2013 and 2018. 41 patients with stage I conservatively treated MOGCTs were included. Three groups were identified: group A. IA D and IAG1 IT candidate to surveillance according to guidelines; group B. stages IB-C1 D, stage IA-C G2-G3 IT, stage IA mixed and YST were consulted about the option of close surveillance vs adjuvant chemotherapy in case of CSS; group C. all other patients receiving BEP.

Results: Median age was 25.6 years (range 14-40). Median follow up was 36.4 months. Group A included 12 patients, 5 IA G1 IT and 7 IA D. Group B included 24 patients. Of these, 2 out of 5 patients (40%) were positive at restaging and were excluded from surveillance protocol. Seven of the 22 remaining patients (31.8%) received chemotherapy, while 15 (68.1%) were enrolled in the surveillance protocol. Out of these 15 patients, 4 were stage IC D (one IC1, one IC2 and two IC3), 2 were mixed stage IA with YST tumor, 9 were G3 IT (four IA, three IC2, one IC3 and one IB). The 7 patients receiving chemotherapy were: 1 dysgerminoma IC2, 2 YST IA, 3 IT G3 (one IA and one IC2) and 1 mixed IA tumour. Group C included 5 patients, three IC YST and two mixed IC2 with YST. Survival of these patients was 100%, while disease free survival was 97.5%. Only one patient in C Group, a stage IA G3 IT treated with adjuvant BEP, relapsed as mature teratoma. None of the patients in the surveillance protocol experienced relapse. Conclusions: These data suggest that close surveillance could be an alternative option to avoid adjuvant chemotherapy in properly staged IB-C1 D, stage IA G2 – G3 IT, stage IA mixed and YST. These findings deserve further confirmation in an international cooperative setting.
A comparison of adjuvant therapy approaches for patients with early-stage uterine serous carcinoma.

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Background: Uterine serous carcinoma is a less common subtype of endometrial cancer that is associated with poorer survival. The optimal post-operative adjuvant treatment strategy for these patients remains uncertain. Methods: This multi-institutional, retrospective cohort study evaluated patients with early stage uterine serous carcinoma. Patients with FIGO Stage IA-II disease after surgery, whose tumors had serous or mixed serous/non-serous histology were included. Patients with carcinosarcoma were excluded. Clinical data were abstracted from local medical records. Summary statistics, Fisher’s exact, and Kruskal-Wallis tests were used to analyze demographic and clinical characteristics. Univariable and multivariable analyses were performed for recurrence-free survival (RFS) and overall survival (OS). Results: 634 patients were included. 77% of patients had Stage IA disease, 42% showed no myometrial invasion. The majority had pure serous histology (72%) and LVSI (76%). Adjuvant treatment varied: 12% received no adjuvant therapy, 7% had chemotherapy alone, 51% had cuff brachytherapy, 12% had cuff brachytherapy with chemotherapy (cuff/chemo), and 19% underwent pelvic radiation (EBRT). Complete RFS and OS data were available for 607 and 609 patients, respectively, and the median follow-up time was 58 months. As compared with patients who received no adjuvant therapy, patients who received cuff or cuff/chemo had improved RFS (cuff: HR 0.70, p = 0.02; cuff/chemo HR 0.53, p = 0.01) and OS (cuff HR 0.56, p = 0.001; cuff/chemo HR 0.48, p = 0.01). In a direct comparison, patients with cuff/chemo had better RFS and OS than those with chemotherapy alone (RFS HR 0.52, p = 0.03; OS HR 0.50, p = 0.05). There were no differences in RFS or OS for women who received chemotherapy alone or EBRT. Improved survival with cuff and cuff/chemo persisted on multivariable analyses (included age, stage, LVSI, adjuvant therapy type); additionally, EBRT was also associated with improved OS. In analyses limited to patients without myometrial invasion, patients with cuff or cuff/chemo had improved RFS and OS compared with observation alone. Conclusions: The use of adjuvant cuff brachytherapy with and without chemotherapy was associated with improved RFS and OS in patients with early stage uterine serous carcinoma.
A randomized double-blind placebo-controlled phase II trial comparing gemcitabine monotherapy to gemcitabine in combination with adavosertib in women with recurrent, platinum resistant epithelial ovarian cancer: A trial of the Princess Margaret, California, Chicago and Mayo Phase II Consortia.

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Background: Platinum resistant ovarian cancer (OC) remains a therapeutic challenge. High grade serous OC (HGSOC) harbors TP53 mutations leading to increased dependency on S- and G2-phase checkpoints. Wee1 inhibition with Adavosertib (AZD 1775) (A) induces G2 checkpoint escape. Gemcitabine (G) is an antimetabolite therapy and blocks the progression of cells through the G1/S phase. We hypothesized that combining G+A would be synergistic and overcome resistance. Methods: We conducted a multicentre double-blind 2:1 randomized phase 2 trial to assess the progression free survival (PFS) in women with recurrent platinum-resistant/refractory HGSOC receiving G+A or G+placebo (P) (NCT02151292). Eligibility required measurable disease and feasibility of paired tumor biopsies; no limitation in prior lines of therapy. Non HGSOC histologic subtypes were enrolled in a separate non-randomized exploratory cohort. A/P was given orally at 175mg OD on D1-2, D8-9 and D15-16 with G 1000mg/m² IV D1, D8 and D15 in a 28-day cycle until progression or unacceptable AE. Tumor staging was scheduled every 8 weeks. TP53 mutations were analyzed on archival tissue with Sanger sequencing, TAm-Seq and IHC. TP53 mutation will also be assessed in circulating tumor DNA (ctDNA). Whole exome and RNA sequencing were performed on paired tumor tissues. Results: 124 patients (pts) with median of 3 prior lines of therapy (range 1-10) from 12 centres across Canada and US were enrolled between Sep 2014 to May 2018, with 99 pts randomized (65 in Arm G+A and 34 in G+P). 5 pts were ineligible; 64 pts have died. The median follow-up was 14.3 months. Main related AE was hematologic toxicity (Anemia G ≥3: 31% in G+A vs 18% in G+P; Thrombocytopenia G ≥3: 31% vs 6%; Neutropenia G ≥3: 62% vs 30%). PFS was significantly improved from 3.0 to 4.6 months (HR 0.56 (95%CI: 0.35-0.90, p=0.015 Log rank). There was a significant improvement in overall survival (OS) from 7.2 to 11.5 months (HR 0.56 (95%CI: 0.34-0.92, P=0.022). Partial response by RECIST 1.1 was observed in 13 (21%) and 1 (3%) pts for Arms G+A and G+P, respectively (p=0.02). From the 25 pts in the exploratory cohort, 3 (12%) partial responses were observed. Final results will be reported at the meeting. Conclusion: Addition of adavosertib to gemcitabine in women with platinum resistant/refractory OC improved response rate, PFS and OS with manageable toxicity. Clinical trial information: NCT02151292.
Pembrolizumab with low dose carboplatin for recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer-interim results.

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Background: Pembrolizumab has shown activity in advanced recurrent ovarian cancer (AOC) with an 8% response rate and median progression-free survival (PFS) of 2.1 months reported in KEYNOTE-100. Because platinum chemotherapies also induce T cell proliferation and enhance tumor cell recognition through PD-1/PD-L, we assessed the safety and activity of pembrolizumab with carboplatin in platinum resistant AOC. Methods: Key eligibility criteria for this Phase 1/2 single arm trial were platinum resistant AOC, fallopian tube, or peritoneal cancer, progression after subsequent systemic therapy, and ECOG PS 0-1. Pembrolizumab 200mg was given on Day 1 and carboplatin AUC 2 on Day 8 and 15 of a 3 week cycle until progression, unacceptable toxicity, or consent withdrawal. Imaging was done before cycles 4 and 8, then every 3 months and unconfirmed objective response assessed by blinded independent review per RECIST 1.1. Adverse events (AEs) were reported per Common Terminology for Adverse Events v5.0. PD-L1 expression was assessed by immunohistochemistry. Results: 27 patients (median age: 64) had received a median of 5 (range: 2-9) prior lines of systemic therapy, which included bevacizumab in 74% of patients. The most common treatment related (TR) AEs were lymphopenia (18%) and anemia (9%). The majority of TR AEs were grade 1 or 2 (93%). 6% of AEs were grade 3 with lymphopenia the most common. Two grade 4 AEs were neutropenia and lymphopenia. Of 23 patients evaluable for best objective response, 13.0% (95% CI, 2.7-33.6) had partial response (PR), 65.2% (95% CI, 42.7-83.6) had stable disease (SD), and 21.7% (95% CI, 7.4-43.7) had progression. 7 of the 23 evaluable patients (30.4%) had archival tumor with modified percent scoring $\geq 5$ for PD-L1 and all achieved PR (3/7, 42.8%) or SD (4/7, 57.2%). Overall median PFS was 4.6 months (95% CI, 2.7-6.2). Rate of PFS at 6 months was 40.4% (95% CI, 25.5-65.5). Median follow-up is 6.2 months and PFS is based on current data, but 8 patients remain on study and estimates will be updated. Conclusions: Pembrolizumab with low dose carboplatin was well tolerated and showed activity in heavily pretreated platinum resistant AOC. Survival and biomarker analyses are ongoing. Clinical trial information: NCT03029598.
Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer: Final findings from the FORWARD II study.

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Background: Mirvetuximab soravtansine is an ADC comprising a FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. As part of the Phase 1b FORWARD II trial (NCT02606305), the combination of mirvetuximab soravtansine with bevacizumab (BEV) was evaluated in pts with FRα-positive, platinum-resistant ovarian cancer (recurrence within 6 months after last platinum).

Methods: Pts received mirvetuximab soravtansine (6 mg/kg; adjusted ideal body weight) and BEV (15 mg/kg) on Day 1 of a 21-day cycle. Responses were assessed according to RECIST 1.1 and adverse events (AEs) evaluated by CTCAE v4.03. Results: In total, 66 pts received combination dosing at this level: 11 during escalation and 55 in expansion. The median age was 63 years, pts received a median of 3 prior lines of systemic therapy (range 1-8), and 62% had received prior therapy with BEV. The most common AEs were diarrhea (58%), nausea (50%), and blurred vision (48%), and were primarily low grade (≤ grade 2). Serious AEs were largely gastrointestinal in nature, with small intestinal obstruction the most frequent individual event (4 pts, 6%). Objective responses were seen in 27 pts for a confirmed overall response rate (ORR) of 41% (95% CI, 29, 54), median progression-free survival (mPFS) interval of 7.1 months (95% CI, 4.9, 9.5), and median duration of response (mDOR) of 8.6 months (95% CI, 4.9, 14.9). In a subset analysis of pts (n = 16) who were bevacizumab-naïve, had 1-2 prior therapies, and medium/high FRα levels (i.e., ≥ 50% of cells with at least moderate staining intensity) the ORR was 56% (95% CI, 30, 80), mPFS 9.9 months (95% CI, 4.1, 15.9), and mDOR 12 months (95% CI, 6.0, 14.9). Conclusions: The combination of mirvetuximab soravtansine with BEV exhibits favorable tolerability in pts with platinum-resistant ovarian cancer, characterized by a manageable side-effect profile. The encouraging efficacy compares favorably to reported outcomes for BEV and chemotherapy seen in similar patient populations. These data support continued exploration of the combination in ovarian cancer. Clinical trial information: NCT02606305.
Evolve: A post PARP inhibitor clinical translational phase II trial of cediranib-olaparib in ovarian cancer—A Princess Margaret Consortium – GCIG Phase II Trial.

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Background: PARP inhibitors (PARPi) are approved therapies in high grade serous ovarian cancer (HGSOC). There are few studies after PARPi progression and correlation with dynamic changes in resistance. We hypothesized that PARPi resistance could be overcome by adding an anti-angiogenic.

Methods: We report the first phase 2 trial assessing the combination of olaparib and cediranib after PARPi failure in HGSOC. This investigator initiated study included three cohorts of 10 evaluable patients (pts): i) platinum sensitive post PARPi (PS), ii) platinum resistant post PARPi (PR) and iii) exploratory cohort of pts re-challenged with chemotherapy post PARPi progression (PE) (NCT 02681237). The primary objective was to determine objective response rate by RECIST v1.1 and progression free survival (PFS) at 16 weeks. Secondary objectives were to evaluate safety, PFS, overall survival (OS) and mechanisms of PARPi resistance. Pts who had radiographic progression on any PARPi were eligible. Archival tumor at initial diagnosis and baseline tumor biopsy at PARPi progression were mandatory. Pts received olaparib tablets 150mg BID with cediranib 20mg QD until progression or unacceptable toxicity. CT scans were performed every 8 weeks. Whole exome and RNA sequencing were performed on paired tumors tissues. Results: Thirty-four pts were enrolled. BRCA1/2 mutations were found in 9/11 PS, 8/10 PR and 7/13 PE pts. By RECIST1.1, four partial responses were observed (2 in PR and 2 in PE cohorts) and 18 stable disease. The 16-week PFS was 54.5% (31.8–93.6) in PS, 50% (26.9–92.9) in PR and 36% (15.6–82.8) in PE, respectively. OS at 1 year was 81.8% (61.9–100) in PS, 64.8% (39.3–100) in PR and 39.1% (14.7–100) in PE. Main related adverse events were anemia, hypertension, diarrhea and fatigue, grade 3 < 10%. Molecular analyses identified different mechanisms of PARPi resistance in ~77% of evaluable pts with matched pre-post PARPi progression biopsies such as reversion mutations in BRCA1/2 and other homologous repair (HR) genes; BRCA, HR and MDR upregulation, CCNE amplification and RIG-I like receptor downregulation.

Conclusions: Treatment with olaparib-cediranib after PARPi failure was feasible and met the predefined bar for efficacy in each cohort. This is the largest clinical trial prospectively evaluating PARPi failure and correlating tissue genomic mechanisms of resistance. Clinical trial information: NCT02681237.
Exploratory analysis of the effect of maintenance rucaparib on postprogression outcomes in patients (pts) with platinum-sensitive recurrent ovarian carcinoma (OC) and updated safety data from the phase 3 study ARIEL3.

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Background: In ARIEL3, rucaparib maintenance treatment significantly improved progression-free survival (PFS) vs placebo in all predefined, nested cohorts: BRCA mutation; BRCA mutation + wild-type BRCA/ high loss of heterozygosity (LOH); and intent-to-treat (ITT) population. Methods: Pts were randomized 2:1 to receive oral rucaparib 600 mg BID or placebo. Exploratory endpoints of time to first subsequent therapy (TFST), time to investigator-assessed PFS on the subsequent line of treatment or death (PFS2), and time to second subsequent therapy (TSST) were assessed in the predefined cohorts. Results: Exploratory efficacy endpoint data are given in the Table. As of Dec 31, 2017, the most common treatment-emergent adverse events (TEAEs) of any grade (rucaparib vs placebo) were nausea (75.8% vs 36.5%), asthenia/fatigue (70.7% vs 44.4%), dysgeusia (39.8% vs 6.9%), and anemia/decreased hemoglobin (39.0% vs 5.3%). The most common grade ≥3 TEAEs were anemia/decreased hemoglobin (21.5% vs 0.5%) and alanine/aspartate aminotransferase increase (10.2% vs 0.0%). Conclusions: Rucaparib significantly improved the clinically meaningful endpoints TFST, PFS2, and TSST vs placebo in all predefined cohorts of pts with platinum-sensitive, recurrent OC. The updated safety profile was consistent with prior reports. Clinical trial information: NCT01968213.
A phase I study of veliparib incorporated into front-line platinum based chemotherapy and bevacizumab in epithelial ovarian cancer (NCT00989651): A GOG/nrg trial.

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Background: Veliparib, a poly-(ADP-ribose)-polymerase inhibitor, increases anti-tumor activity when combined with platinum chemotherapy and has monotherapy activity in BRCA deficient tumors. This study was done to determine the recommended phase II dose (RP2D) of veliparib in combination with front line treatment for epithelial ovarian cancer (EOC).

Methods: Eligible patients had newly diagnosed, stage II-IV EOC. Six regimens were evaluated, 3 variations of chemo delivery with either continuous (D1-21) or intermittent (days-2-5) veliparib BID. Chemo included 1: IV q3week carboplatin (C) (AUC 6) and paclitaxel (T) (175mg/m2); 2, IV q3week C (AUC 6) and weekly T (80mg/m2); and 3, IV T (135mg/m2, day 1), IP cisplatin (75mg/m2, day 1 or 2) and IP T (60mg/m2, day 8). Bevacizumab 15mg/kg started cycle 2 and continued as monotherapy cycles 7-22. A 3+3 dose escalation design evaluated dose-limiting toxicities (DLTs) in cycles 1 and 2. Once < 2/6 patients experienced a DLT, that dose level was expanded to evaluate feasibility over 4 cycles.

Results: The study accrued 424 treated patients. For regimen 1, continuous (Reg1c) the maximum tolerated dose (MTD) was 250mg veliparib BID but the feasible dose was found to be 150mg BID. For regimen 1, intermittent (Reg1i) the MTD and feasible dose were 400 and 250mg BID respectively. For Reg2c the MTD and feasible dose were the same at 150mg BID. For Reg2i the MTG and feasible dose were 250 and 150mg BID respectively. For Reg3c the MTG and feasible dose are both 150mg BID and for Reg3i the MTG was 400mg BID and the feasible dose felt to be 300mg BID. Median PFS by residual disease and BRCA status is: (Positive residual disease) 14.6, 19.1 and 16.9 months for BRCA+, BRCAwt and BRCA ukn respectively. For no gross residual disease the PFS is NR, 34.2 and 24.5 months respectively.

Conclusions: Given the difficulty with toxicity not defined as a DLT, the RP2D for all regimens is veliparib 150mg BID. This data informed the dose that moved into the phase III trial GOG 3005/Velia: NCT02470585. Velia also incorporated maintenance veliparib instead of maintenance bevacizumab among all high grade serous patients (BRCA+ and wt). These results will determine utilization of veliparib in this space. Clinical trial information: NCT00989651.
Determination of eligibility criteria for salvage hysterectomy after definitive radiotherapy/concurrent chemoradiotherapy for residual cervical disease.

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Background: Patients with persistent cervical cancer after definitive radiotherapy/concurrent chemoradiotherapy (RT/CCRT) have a poor prognosis. Salvage hysterectomy (HT) is potentially curative, but eligibility criteria therefor have not been determined. Methods: Part 1) Retrospective review of patients with persistent cervical cancer treated with definitive RT/CCRT at 35 institutions of the Japanese Clinical Oncology Group (JCOG) from 2005–2014. Differences between a salvage HT group and a systemic chemotherapy (CT) group after definitive RT/CCRT for residual tumor were evaluated. Clinical variables influencing a salvage HT treatment decision were evaluated using logistic regression analysis. Part 2) Questionnaire-based survey conducted by JCOG gynecologic oncologists assessing treatment choice for patients with residual cervical disease after definitive RT/CCRT. Patients with residual cervical tumor before, during and after definitive RT/CCRT were surveyed for 86 conditions and appropriate candidates for salvage HT were evaluated using heat map analysis. Results: Part 1) We identified 298 patients who underwent salvage HT or systemic CT. Median overall survival was 3.8 and 0.9 year in the HT and CT groups, respectively (HR 0.4341, 95% CI 0.336-0.559, p < 0.01). FIGO stage and lymph node metastasis at initial treatment, performance status (PS) at diagnosis of residual cervical tumor and parametrial invasion of residual cervical tumor significantly influenced a salvage HT treatment decision. Part 2) Heat map analysis showed that surveyed variables segregated into 3 groups: i) in favor of salvage HT, ii) in favor of systemic CT, and iii) either. Conditions such as FIGO stage IB-IIB, PS of 0-1, residual tumor < 4 cm, no parametrial invasion and no residual lymph node metastasis were included in group i, in favor of salvage HT. Conclusions: Eligibility criteria could be determined based on the results of the current study, and a prospective clinical trial evaluating the survival benefit of salvage HT for residual cervical tumor after definitive RT/CCRT is being planned by JCOG.
Human papillomavirus genotype and prognosis of invasive cervical cancer: A nationwide cohort study.

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Background: The role of human papillomavirus (HPV) in development from oncogenic infection to invasive cervical cancer (ICC) has been well established. However, the association of HPV genotypes and prognosis of ICC is controversial. Methods: We identified all ICC diagnosed in Sweden during the years 2002-2011 (4254 confirmed cases after clinical and histo-pathological review), requested all archival formalin-fixed, paraffin-embedded blocks and subjected them to comprehensive HPV genotyping. Twenty out of twenty-five archives agreed to the study, contributing a total of 2845 confirmed cases with valid HPV results. Cases were followed up from date of cancer diagnosis to 31 December, 2015, migration from Sweden, or death; whichever occurred first. Five-year relative survival ratios (RSRs) were calculated and excess hazard ratios (EHRs) with 95% confidence intervals (CIs) were estimated using Poisson regression. Results: HPV was detected in 2365 tumors (83.1% of all cases). The five-year RSR by tumor HPV status was 0.54 (HPV negative), 0.76 (HPV16 positive), 0.73 (HPV18 positive), 0.72 (other high-risk HPV positive) and 0.56 (low-risk HPV positive) compared to the age-matched general female population. Compared to cases with HPV-negative tumor, a significantly lower excess mortality was seen if the tumor was positive for HPV16 (EHR:0.54, 95% CI 0.44-0.65), other high-risk HPV (EHR:0.47, 95% CI 0.37-0.60), and low-risk HPV (EHR:0.48, 95% CI 0.32-0.74), after adjustment for age, time since cancer diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, educational level and histology. However, the mortality among women with HPV18 positive tumors were not statistically significantly different from cases with HPV-negative tumors. In women with a single HPV infection of either HPV16 or HPV18, those with HPV18-positive tumors had 56% (EHR:1.56, 95% CI: 1.13-1.97) higher excess mortality compared to women with HPV16-positive tumors. Conclusions: HPV genotype in cervical cancer tumor is associated with prognosis of ICC. Single HPV18 positivity indicated a poorer prognosis than single HPV16 positivity. This could add information of value beyond the established clinical prognostic factors for women diagnosed with ICC.
Clinically significant discrepancy between clinical and pathologic stage of early-operable cervical cancer.

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Background: The cornerstone of the management of cervical cancer (CC) traditionally relies on clinical examination assessment (CE) of tumor size (TS) and local extension of disease. Previous reports demonstrate poor accuracy of CE, with the most common discrepancy being failure to identify parametrial involvement (PI). The goal of this study is to determine the accuracy of CE in comparison to final pathology (FP) in early operable CC. Methods: This is a multi-center retrospective review of patients with early CC (FIGO stage IB1, IIA1). Data on age, race, histology, stage, CE findings, FP report and receipt of adjuvant radiation therapy (RT) were collected. CE findings included TS, PI and vaginal involvement (VI). CE of TS, PI, and VI were compared to FP. Subanalysis was also conducted based on TS (< or ≥ 2cm) and location of tumor (exophytic vs endophytic). Analysis was performed using paired-T and Cohen’s Kappa tests. Results: Final analysis included 135 patients. Mean age was 52.6 years. The majority of patients had squamous cell carcinoma (72.6%). Overall, there was a significant difference between CE of TS compared to FP; mean error of 1.22 cm (p < 0.0001). In those with tumors ≥ 2cm the mean error was 1.28 cm (p < 0.0001). No significant discrepancy was observed in tumors < 2 cm (mean error: 1.10cm; p = 0.5). CE of TS of endophytic tumors was poor (mean error 1.68cm; p = 0.004) compared to exophytic tumors (mean error: 1.12 cm; p = 0.693). There was no significant difference in the identification of VI between CE and FP (3.7% vs 8.89%; p = 0.067). No patients with PI on CE were included in this analysis. However, 14.07% of patients were found to have PI on FP (p < 0.0001). There was no difference in the accuracy CE of TS between non-obese (< 30 kg/m²) and obese patients (≥30 kg/m²), mean error 1.13 and 1.3, respectively (p = 0.061). As a results of FP, 55 patients (40.7%) received adjuvant RT and 38 patients (28.14%) were upstaged from IB1 to IB2. Of these 38 patients, 36 (94.7%) went on to receive adjuvant RT. Conclusions: CE of TS and PI is inaccurate, especially in tumors ≥ 2cm and endophytic tumors. This suggests imaging should be strongly encouraged, particularly in the setting of the updated FIGO 2018 staging system and recent debate over surgical approach.
Feasibility of visual inspection with acetic acid (VIA) screening for cervical cancer in Tanzania with emphasis on special populations.

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Background: Following the report that VIA screening reduced cervical cancer mortality by 31% in India (ASCO LBA2 2013; Shastri SS, et al JNCI 2014), the W.H.O. endorsed VIA guidelines for Africa, where the global disease burden is highest. In Tanzania, cervical cancer is a major source of morbidity and mortality, with nearly 10,000 new cases and 7,000 deaths annually. Due to lack of resources, therapies are limited and patient outcomes are further confounded by the relatively high prevalence of concurrent HIV infection. We report on the feasibility of VIA screening in Tanzania with emphasis on unique populations. Methods: Our two 5-day VIA screen-and-treat workshops in Buzuruga and Sangabuye Health Centres in Mwanza, Tanzania were approved by the University of California, Irvine IRB and local health authorities. Participants were recruited from surrounding communities and offered free cervical VIA screening, cryotherapy when indicated, and HIV rapid testing. Acetowhite lesions and/or abnormal vascular markings were VIA+. Chi-square and Fisher exact tests were performed with statistical significance assigned at 0.05. Results: During July 2018, 825 of 917 registered participants underwent VIA screening and 25.1% (n=207) were VIA+. 147 VIA+ non-pregnant women received same day cryotherapy and 15 (1.8%) with lesions suspicious for cancer were referred to Bugando Medical Center. In the subanalysis of 64 HIV+ patients (23 diagnosed at the workshops, 41 with prior diagnosis on ART), HIV infection was not associated with VIA positivity (p=0.497). Additionally, a non-significant trend of higher VIA+ screens among newly diagnosed untreated HIV patients (27.7%) vs patients with known HIV on ART (17.5%) was observed (p=0.556). Conclusions: VIA screening for cervical cancer, while feasible in Tanzania, will require follow-up and repetitive screening. Although cervical cancer is an AIDS-defining illness, lack of correlation between HIV infection and VIA-positivity may reflect the availability of W.H.O.-subsidized ART in sub-Saharan Africa to attenuate HPV-mediated neoplastic transformation, as previously reported by others. Further study of this phenomenon is warranted.
Comparative benefit of interstitial needles in addition to intracavitary applicators in the treatment of locally advanced cervical cancer.

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Background: Cervical cancer is the leading cause of cancer mortality of women in Low and Middle Income Countries (LMIC). Interstitial needles (IN) have improved outcomes but the resources required in comparison to intracavitary brachytherapy (IC) alone has impeded uptake in endemic regions. We conducted a retrospective review of the utilisation of IN in the management of locally advanced cervical cancer and simulated 2D planning by loading the applicators using standard Manchester loading (ML) to explore the magnitude of benefit that interstitial needles provide. Methods: 72 brachytherapy plans of 18 patients who had undergone treatment using tandem and ring and had interstitial brachytherapy between 04/2016 and 10/2018 were reviewed. ML plans prescribed to point A were generated to represent a 2D scenario but the known HR-CTV was taken into consideration and its dosimetric outcomes were compared to those of the 3D based plans. Results: The median tumour volume was 23 cm³. IN was used in 82% of the insertions. The median number of IN was 2 (range 0–6) with median percentage of IN dwell time 6.6% (range 0.68–38.5). V100 was excellent 98.2% for ML 97.3% for 3D IN and 98.7% for 3D non-IN plans. The median HRCTV D90 was 8.5 Gy/fraction (cumulative EQD2 101.4 Gy) for ML plans and 8.0 Gy/fraction (cumulative EQD2 91.4 Gy) for 3D plans. The ML plans failed to meet the OAR goals except for the rectum, which was optimally distanced by the rectal paddle. The median bladder, sigmoid and small bowel doses were 24% above the recommended constraint in the individual plans and 15% cumulative EQD2. A statistically significant relationship was found between the number of needles utilised, tumour volume (p < 0.001) and coverage (p = 0.006) but not delivered dose (p > 0.068). Conclusions: 2D brachytherapy can provide adequate dose coverage for most tumours but IN provide a benefit in reducing the doses to OARs in a significant number of patients. This justifies investment in resources for uptake of interstitial needles to increase access to optimal treatment of cervical cancer for women in LMIC. This research was made possible an ASCO Conquer Cancer Foundation grant.
Prognostic significance of the number of pelvic lymph-nodes resection in patients with cervical adenocarcinoma: An analysis from JGOG 1070S study.

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Background: Although resection of more than 20 lymph-nodes is considered to be adequate in pelvic lymphadenectomy for cervical cancer patients, prognostic significance of the number of resected lymph-nodes (PLN-num) is clinically still unknown. Methods: This nationwide multicenter retrospective study (JGOG 1070S) examined consecutive 693 patients with clinical stage IB-IIB cervical cancer who underwent radical hysterectomy including pelvic and/or para-aortic lymphadenectomy between 2008-2009 at 87 institutions of the Japanese Gynecologic Oncology Group. Maximum number of enrollments from one institution was limited 10 or less to minimize the inter-institutional bias. Correlation between PLN-num and prognosis was analyzed using Cox hazard model with considering histological subtypes. Results: Of 473 eligible cases in this study, the average PLN-num per a case in each institution was positively correlated with the number of total cases treated in each institution per year. (R = 0.42, P = 0.012). Patients with high PLN-num showed favorable progression free survival (PFS) (P = 0.12). Focusing on adeno and adeno-squamous carcinomas, significantly improved PFS was shown in high PLN-num cases (P = 0.012), although no significance was found in squamous cell carcinoma (P = 0.754). Multivariate analysis in adeno and adeno-squamous cases showed PLN-num as an independent prognostic factor (HR; 0.46, 95%CI; 0.24–0.84, P = 0.026) along with disease stage and adjuvant therapeutics. Subset analysis of adeno and adeno-squamous cases without adjuvant therapeutics showed significant improvement of survival in high PLN-num group (P = 0.019). Conclusions: In our study, PLN-num in lymphadenectomy for patients with cervical adeno or adeno-squamous carcinoma was clarified to be a significant prognostic factor. Systematic total lymphadenectomy is recommended for these patients to obtain a favorable prognosis.
Association of detection of aflatoxin in plasma of Kenyan women with increased detection of oncogenic HPV.

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Background: Cervical cancer is the leading cause of cancer-related deaths among women living in Africa. Only a small proportion of HPV-infected women develop cervical cancer and other cofactors may increase a woman's risk of developing cervical cancer. Aflatoxin, a potent carcinogen and immunosuppressive agent, is produced by fungi that contaminate corn and other staple foods in sub-Saharan Africa. Women who ingest aflatoxin may be more likely to have persistent infections with oncogenic HPV type. Methods: Demographics, behavioral data, plasma, and cervical swabs were collected from HIV-uninfected women 18 and 45 years of age who presented for cervical cancer screening at Moi Referral and Teaching Hospital (Eldoret, Kenya) and had normal VIA examination. HPV testing was performed on cervical swabs using the Roche Linear Array Assay. Aflatoxin-albumin adduct (AFB1-lys) was detected and quantified in plasma. The association of plasma AFB1-lys detection and concentration and the detection of HPV was examined. Results: Sufficient plasma was available from 88 HIV-uninfected women and was transported to the U.S. for aflatoxin testing. Valid HPV testing results were available for 86 of these women (mean age 34.0 years); 49 women (57.0%) had detectable AFB1-lys and 37 (43.0%) had no detection. Substantial variation existed in plasma AFB1-lys concentrations among the 49 women (range 0.02 to 0.21 pg/μL). Detection of AFB1-lys was not associated with age, and other behavioral factors such as number of lifetime partners, marital status and age at first sex. AFB1-lys detection was associated with detection of A9 HPV types (HPV 16, 31, 33, 35, 52, and 58) as a group in cervical swabs (p = 0.029) as well as A9 types excluding HPV 16 (p = 0.020), but not with individual A9 types, A7 HPV types (such as HPV 18), or low-risk HPV types. A concentration dependent association of AFB1-lys was seen with detection of A9 HPV types as a group (p = 0.009), non-HPV 16 A9 types (p = 0.005), and HPV 52 (p = 0.042), but not with the A7 HPV types. Conclusions: AFB1-lys was detected in 57% of HIV-uninfected Kenyan women without cervical dysplasia. AFB1-lys-positive women were more likely than AFB1-lys-negative women to have oncogenic HPV A9 types detected. Higher plasma AFB1-lys concentrations were associated with increased likelihood of oncogenic HPV A9 type detection. Further studies are needed to determine if chronic exposure to aflatoxin interacts with HPV infection (and possibly HIV co-infection) to modulate the risk of cervical cancer in women in Kenya and other developing countries.
Cervical cancer harboring a Rb1 mutation may sensitize to cisplatin via PI3K/AKT pathway by regulating apoptosis.

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Background: Cervical cancer is one of the most common malignant tumors in women and major causes of cancer death in women. Although concurrent chemoradiotherapy has improved the treatment of cervical cancer, due to the heterogeneity of the tumor to chemotherapy or radiation therapy, especially the varied response to chemotherapy, the patients respond differently to the same therapeutic regimen, furthermore some patients get rapid progression. Therefore, we attempted to analyze the potential relationship between genomic mutation and chemotherapy response and survival in cervical cancer patients. Methods: Clinical information and sequencing data of Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC) in Genomic Data Commons (GDC) data portal were obtained through TCGAbiolinks. Only patients with stage IIB-IV CESC who received cisplatin only and were included. Cisplatin sensitivity data and sequencing data of CESC cell lines were obtained from the Genomics of Drug Sensitivity in Cancer (GDSC). Cox regression analysis, Kaplan-Meier survival analysis, differential analysis of gene expression and functional enrichment were used to explore the role of different mutations in survival and cisplatin sensitivity. Results: A total of 48 patients with stage IIB-IV CESC were enrolled. 77 genes with mutation frequency > 10% were included in final analysis. Multivariate analysis showed that the mutation of Rb1 was an independent predictor of overall survival (OS) (HR = 0.07, 95%CI 0.01-0.73, P = 0.026). Patients with mutant Rb1 had better overall survival (134.2 versus 86.8 months) compared with patients with wild-type Rb1. The half maximal inhibitory concentration (IC50) of the mutant Rb1 cell line to cisplatin was significantly lower than that of the wild-type cell line (3.49 versus 10.15 μM, P = 0.038). A total of 332 differently expressed genes (DEGs) were identified and the KEGG pathway enrichment analysis showed that most DEGs were enriched in the PI3K/AKT pathway (P = 0.015). Conclusions: We found that Rb1 mutation was an independent survival predictor in stage IIB-IV CESC, and CESC patients with Rb1 mutation may be more sensitive to cisplatin.
Background: To evaluate the safety and efficacy of nimotuzumab plus concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy for the treatment of locally advanced cervical squamous cell cancer (LACSCC).

Methods: From December 2013 to March 2017, 31 patients with stage (FIGO 2009) IB2-IVA cervical squamous cell cancer were enrolled in this single-arm clinical trial at an academic medical center and received concurrent chemoradiotherapy plus nimotuzumab. All patients underwent at least 1 year of follow-up. The prescription radiation dose was 50.4 Gy/28 F on the pelvic field with or without extended-field radiation. An additional 30-36 Gy to Point A was delivered with high-dose-rate techniques. Cisplatin 40 mg/m² and nimotuzumab 200 mg were infused intravenously once weekly during radiotherapy. The main and secondary outcome measures were toxicity evaluated using CTCAE 4.0., and the short-term outcome evaluated by RECIST 1.1.

Results: The median follow-up duration was 29.7 months (13.3-61.2 months). All patients received external beam radiotherapy, brachytherapy, and nimotuzumab six times. Twenty-seven patients received six cycles of chemotherapy while four received only 4-5 cycles. There was no life-threatening toxicity. The incidence of acute grade 3 bone marrow depression was 51.6% (16/31) and grade 3 gastrointestinal tract reaction was 9.7% (3/31). The incidence of late toxicities was 22.6% (7/31), and these included vaginal-rectal fistula, intestinal obstruction, rectal hemorrhage, hematuria, and vaginal stenosis. Complete response was achieved in 30 cases (96.8%). The 1-year disease-free survival (DFS), local progression-free survival (LPFS), and overall survival (OS) rates were 87.1%, 90.3%, and 100%, respectively. The corresponding 3-year values were 74.8%, 90.3%, and 86.7%.

Conclusions: Nimotuzumab plus concurrent IMRT and chemotherapy may represent a well-tolerated and effective treatment regimen in patients with LACSCC.
PD-L1 expression, DNA mismatch repair genes, and HPV types in cervical squamous cell carcinoma.

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Background: Previous studies observed low PD-L1 expression in cervical cancer, and that high PD-L1 expression is associated with deficient DNA mismatch repair genes and poor prognosis. No study has investigated the PD-L1 expression differences among HPV types in cervical cancer. We aim to determine PD-L1 expression in our patient population and its clinical significance. Methods: A total of 198 patients with SCC were identified and 60 had evaluable tumor specimens and clinical data. Immunohistochemistry on MMR genes and PD-L1 expression using tissue microarrays was performed. HPV analysis for 15 high-risk types was done by multiplex PCR and gel electrophoresis. Correlation between PD-L1 expression, MMR status, HPV types and other clinical parameters was analyzed using $\chi^2$ or Fisher’s exact test. Cumulative 5-year survival was analyzed by Kaplan-Meier curves and log rank test. Results: Of the 60 patients, 90% were black, 55% between ages of 30-55 and 40% older than 55. 33 patients had poorly, 20 moderately, and 7 well-differentiated tumors. At 5-year follow up, 11 had recurrence, 14 patients died of disease and 7 lost to follow up. 93.3% of tumors had positive staining for PD-L1 with 56.7% showing high expression. Patients aged 30-55 showed a higher rate of PD-L1 expression. Majority had intact MMR (91.7%). High-risk HPV DNA was extracted in 41 specimens (68.3%), 11 of these were infected with $\geq$2 or more types, identifying 6 high-risk types not included in vaccine. Correlation analysis showed that there is significant correlation between age and PD-L1 expression on tumor cells ($p = 0.047$). No correlation between MMR status and PD-L1 expression. Mean disease free survival (DFS) was 43.7, 36.5, and 6.3 months for high, low and negative PD-L1 expression, respectively ($p = 0.002$). In patients with stage I-II disease, mean DFS was 52.2, 42.6 and 7.6 months for high, low and negative PD-L1 expression, respectively ($p = 0.001$). Similar direct relationship is observed with overall survival. Cases with mixed HPV infection are associated with late clinical stage at diagnosis ($p = 0.037$) and lower PD-L1 expression. Conclusions: Contrary to previous studies, our results showed remarkably high rate of PD-L1 expression in cervical SCC, which is associated with longer DFS and OS, especially in early stage tumors. Mixed HPV infection is associated with late clinical stage at diagnosis and lower PD-L1 expression.
Comparison of definitive cervical cancer management with concurrent chemotherapy and radiation between two centers with variable resources and opportunities for improved treatment delivery.

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Background: Cervical cancer remains a global health challenge particularly in low to middle income countries with under resourced healthcare systems. We present the experiences of two centers practicing in variable resource environments to determine predictors of improved radiochemotherapy outcomes.

Methods: This retrospective review describes baseline demographic and clinicopathologic characteristics of cervical cancer patients treated with concurrent chemotherapy and radiation between 2014 and 2017 at the National Radiotherapy Oncology and Nuclear Medicine Center (NRONMC) in Korle Bu Teaching Hospital, Accra, Ghana and Moffitt Cancer Center, Tampa, Florida, USA. Results: Ghanaian patients presented at an older median age (56 vs. 49 years, p < 0.001), with predominantly stage IIIB disease (43% vs. 16%, p < 0.001) and squamous cell histology (89% vs. 79%, p < 0.001). Median treatment duration was longer for Ghanaian patients (58 vs. 52 days, p < 0.001). Ghanaian patients were less likely to receive concurrent chemotherapy (68% vs. 100%, p < 0.001) and interstitial brachytherapy implants (0 vs 19%, p < 0.001). No Ghanaian patients received a radiation boost to pelvic or paraortic lymph nodes (p < 0.001). Ghanaian patients had lower local control (64% vs. 93%, p < 0.001) and overall survival (82% vs. 95%, p = 0.02) at 24 months, respectively. For stages IB, IIA, IIB, IIIB, 24 month local control rates for NRONMC vs. Moffitt patients were (60% vs. 93%; p = 0.05), (89% vs. 100%; p = 0.35), (91% vs. 91%; p = 0.89), (53% vs. 91%; p = 0.02) and 24 month OS rates were (85% vs. 100%; p = 0.06), (100% vs. 100%; p = 0.48), (85% vs. 96%; p = 0.2), (73% vs. 91%; p = 0.24), respectively. Treatment duration > 55 days predicted poorer overall survival on multivariable analysis (MVA). Stage III disease predicted poorer local control on MVA. Conclusions: Significant differences were noted in treatment and disease characteristics between the two centers. Feasible improvements for patients treated at NRONMC include removing financial barriers to chemotherapy access, improving radiotherapy delivery capacity to reduce treatment delays, and screening programs to reduce advanced disease presentation.

Recurrence and survival after robotic-assisted radical hysterectomy (RRH) for early-stage cervical cancer (CC): Experience may matter.

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Background: The phase III LACC Trial found that minimally invasive surgery (MIS) / radical hysterectomy was inferior to open radical hysterectomy (ORH) with reduced disease-free survival (86% v 96.5%) and a higher disease-specific death rate (DSDR) (4.4% v 0.6%). We evaluated our experience with attention to the learning curve. Methods: Patients (pts) with early-stage CC (4/2007-12/2017) who underwent RRH with a uterine manipulator were evaluated in a contemporaneously maintained database. First 10 learning curve cases per surgeon (Group A) were compared to all subsequent cases (Group B). Inclusion criteria mirrored the LACC trial: > one-year follow-up, adenocarcinoma, adenosquamous, or squamous carcinoma, stage IA2 or IB1 using FIGO 2014 guidelines, and pathologic tumor size (TS) of 4 cm or less. Atypical histologies and lesions > 4 cm were excluded. Study parameters assessed included recurrence free survival (RFS), DSDR, and pattern of recurrence. Results: 144 RRH pts were identified and 90 met inclusion criteria with mean age of 45.6 ± 14.3 years. Exclusions included stage 1A1 without LVSI (n = 13), atypical histology (n = 10), lost to follow-up (n = 13), and occult stage IB2 (n = 18). 40 pts met Group A and 50 met Group B criteria. Median follow-up was 61 ± 34.3 months (A = 71.5, B = 52.5). The 5-year RFS was 92% (95 CI ± 4%) and the DSDR 5.5% (n = 5). There were 7 (7.8%) recurrences with median time to recurrence of 12 ± 8.3 mos. Recurrence in Group A (n = 6, 15%) exceeded Group B (n = 1, 2%), p = 0.025. DSDR was 10% Group A v 2% B (p = 0.184). The 4.5 yr RFS was 84.8% (95 CI ± 7%) in Group A v 98% (95 CI ± 3%) in Group B. There were no differences in risk factors for recurrence between A & B (TS > 2 cm, LN (+), adjuvant therapy (AT), and LVSI p > 0.05), except (+) vaginal margin status (A = 10% v B = 0%, p = 0.034). Three recurrences involved carcinomatosis, which may be insufflation related. All recurrent cases had TS > 2 cm and 5 received AT. Conclusions: In this study, recurrence of disease in early-stage CC clustered in the first 10 cases per surgeon and occurred in TS > 2 cm. This data suggests a possible learning curve effect and argues against a uterine manipulator cause. Carcinomatosis may be insufflation related, unique to MIS, and deserves further study.
Omission of adjuvant therapy in stage I clear cell ovarian cancer: Review of the British Columbia (BC) cancer experience.

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Background: Standard guidelines recommend adjuvant chemotherapy for stage I clear cell ovarian cancer (CCOC), despite data demonstrating excellent outcomes. Since 2012, the BC Cancer provincial treatment guidelines for surgically staged stage IA/B and IC1 (defined by intraoperative rupture only) CCOC has been to offer observation only. We reviewed the clinical outcomes of stage I CCOC patients since policy implementation. Methods: A retrospective, population-based cohort study of all stage I CCOC patients operated on between April 2012 and December 2017 was conducted. Patient, tumor, surgical and clinical outcome data were collected. Survival analysis was conducted using Kaplan-Meier methods. Results: 78 patients with stage I disease were identified (see Table). Among stage IC1 patients, 9 received adjuvant therapy despite provincial policy, 6 of which were due to sharp dissection. 40 patients with stages IA/B and IC1, who underwent post-operative observation, were included in the analysis. Median duration of follow-up was 36 months. Median age at diagnosis was 55 years and >50% patients had a Charlson Comorbidity Index of 0 (N= 26) and an Eastern Cooperative Oncology Group performance status of 0 (N=28) prior to diagnosis. Lymph node dissection was not performed in 20 patients. All 16 cases tested immunohistochemically for mismatch repair were intact, and 2 of 6 cases with tumour genomic sequencing had an AURKA aberration. There were 4 recurrences (10%), 3 of which were metastatic. 5-year disease-free survival is 90%, and 5-year overall survival is 95% for stage IA/B and 90% for stage IC1 (p=0.645). In comparison, 5-year overall survival for stage IC2 (surface involvement) and IC1 with sharp dissection (all received chemotherapy) is 82% and for stage IC3 (positive washings) is 23% (p<0.001). Conclusions: Outcomes of patients with stage I A/B and C1 CCOC remain excellent. Adjuvant therapy can be safely omitted, with low recurrence rates and survival over 90% at 5 years. Consideration of disease substage is valuable in predicting the clinical outcomes of stage I CCOC.

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB</th>
<th>IC1</th>
<th>IC2</th>
<th>IC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>2</td>
<td>22</td>
<td>9</td>
<td>20</td>
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</tbody>
</table>
A randomized, double-blind, placebo-controlled phase Ib/II study of ralimetinib, a p38 MAPK inhibitor, plus gemcitabine (G) and carboplatin (C) versus GC for women with recurrent platinum-sensitive ovarian cancer.

Ignace Vergote, Florian Heitz, Paul Buderath, Matthew A. Powell, Jalid Sehouli, Christine M. Lee, Anne L. Hamilton, James Fiorica, Kathleen N. Moore, Michael Teneriello, Lisa Golden, Wei Zhang, Celine Pitou, Daphne L. Farrington, Katherine M Bell-McGuinn, Robert Michael Wenham; BGOG and University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; AGO study group & Kliniken Essen-Mitte, Department for Gynecology and Gynecologic Oncology Essen, Germany, Essen, Germany; University Hospital of Essen, Department of Gynecology, Essen, Germany; Washington University School of Medicine in St. Louis, St. Louis, MO; AGO and Charité Campus Virchow-Klinikum, Berlin, Germany; Gyn Onc of Houston, The Woodlands, TX; Peter MacCallum Cancer Centre, Melbourne, Australia; Sarasota Memorial Hospital, Sarasota, FL; Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK; Texas Oncology, Austin, TX; Eli Lilly and Company, Indianapolis, IN; Eli Lilly, Indianapolis, IN; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: p38 mitogen-activated protein kinase (MAPK) regulates cytokine production in the tumor microenvironment and enables therapeutic resistance of cancer cells. Ralimetinib (R) is a selective small-molecule inhibitor of p38α and p38β MAPKs. Methods: Main inclusion criteria: ≥18 y; recurrent platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal, cancer after first-line treatment. Phase (Ph)1b was to determine the recommended Ph2 dose (RP2D) of R administered 12-hourly (Q12H) on Days 1-10 (21-day cycle [Q21D]) in combination with gemcitabine (G: 1000 mg/m² on Days 3 and 10) and carboplatin (C: AUC 4 on Day 3) for 6 cycles. In Ph2, patients (pts) were randomized double-blind, 1:1 to RP2D R+GC or placebo (P)+GC, for 6 cycles, followed by R 300 mg Q12H or P on Days 1-14, Q28D until disease progression. The stratified log-rank test compared progression-free survival (PFS; primary endpoint) between treatment groups in Ph2, at a 1-sided α level of 0.2. ClinicalTrials.gov, NCT01663857. Results: 118 pts received ≥1 dose of R or P (safety population); 8 in Ph1b and 110 in Ph2 (R+GC N = 58; P+GC N = 52). The RP2D for R in combination with GC was 200 mg Q12H. The study met its primary objective (median PFS: R+GC 10.3 mo vs P+GC 7.9 mo; HR = 0.773, 2-sided p = 0.246). The secondary objectives of median overall survival (R+GC 29.2 mo vs P+GC 25.1 mo; HR = 0.827, p = 0.469) or overall response rate (R+GC 46.6% vs P+GC 46.2%; p = 0.967) were not statistically significant, and 32.4% vs 25.0% of pts had normalized CA125 at the end of cycle 6. Most pts (safety population) experienced ≥1 Grade 3/4 treatment-emergent adverse event (TEAE: R+GC 63/66 [95.5%]; P+GC 48/52 [92.3%]). Decreased neutrophil count (60.6% vs 76.9%), platelet count (43.9% vs 38.5%), and white blood cell count, (30.3% vs 26.9%), anemia (22.7% vs 25.0%), and increased alanine aminotransferase (ALT) (19.7% vs 3.8%) were the Grade 3/4 TEAEs in ≥10% of pts in the R+GC and P+GC arms, respectively. Conclusions: Addition of ralimetinib to GC resulted in modest improvements in PFS. Grade 3/4 elevated ALT was more common in the ralimetinib arm. Clinical trial information: NCT01663857.
Efficacy and safety of tivozanib in recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer.

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Background: Tivozanib is a potent, selective pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with a long half-life. This study assessed its activity in patients with recurrent, platinum-resistant ovarian cancer (OC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC). Methods: This open-label phase II study used a Simon’s two-stage design. Eligible patients had recurrent, platinum-resistant OC, FTC or PPC; ECOG PS of 0-1; normal end organ function; and measurable or detectable disease. There was no limit on the number of prior regimens. Treatment consisted of tivozanib 1.5 mg orally once daily (3 weeks on/1 week off). The primary endpoint was response rate. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity assessment. If 1 partial response (PR) was observed in stage I (n = 12), enrollment proceeded to stage II. The null hypothesis was rejected for $\geq 4$ responses in 30 patients. Results: Thirty-one patients were enrolled, and 30 were treated. Twenty-three had OC [76.67%], 5 FTC [16.67%] and 2 PPC [6.67%]. Twenty-six had measurable [86.67%] and 4 detectable disease [13.37%]. The median age was 60, and median number of prior regimens was 4 [range 1-9]. Four PRs [13.33%] were recorded. Twelve patients had stable disease (SD) [40%]. The clinical benefit rate (PR + SD) was 53%. Seven patients [23.33%] survived progression-free for > 6 mos. One patient continued treatment for > 2 yrs. The median PFS was 4 mos [range 1-25] and median OS was 8 mos [range 1-39]. There were no treatment-related deaths. Grade 3-4 related toxicities were hypertension [8], fatigue [3], fistula [2], hyponatremia [2], intestinal perforation, obstruction, stroke, proteinuria, hypomagnesemia, hypoalbuminemia, portal hypertension, nausea and anemia [1 each]. Frequent grade 1-2 related toxicities included fatigue [19], hypertension [13], anorexia [12], arthralgia [11], diarrhea [11], weight loss [10], hoarseness [8], headache [8] and nausea [7]. Exploratory analyses in tumor samples are ongoing. Conclusions: Tivozanib is active in patients with recurrent OC, FTC or PPC, without substantial toxicity, supporting its further development. Clinical trial information: NCT01853644.
Adverse events (AEs) with maintenance olaparib in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Phase III SOLO1 trial.

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Background: In SOLO1 (NCT01844986), maintenance olaparib provided a substantial progression-free survival benefit vs placebo in newly diagnosed pts with advanced OC, a BRCAm and clinical complete or partial response to platinum therapy (HR 0.30; 95% CI 0.23–0.41) and was well tolerated (Moore et al. NEJM 2018). We analysed the most common AEs and hematologic AEs in SOLO1. Methods: Pts received olaparib tablets 300 mg twice daily or placebo until progression unless they had no evidence of disease at 2 years, in which case treatment stopped. AEs were graded using CTCAE v4.0. Results: Of 391 pts randomized, 390 (olaparib, 260; placebo, 130) were treated and included in the safety analysis. Median treatment duration was approximately 25 months for olaparib vs 14 for placebo. Median time to first onset of the most common AEs (nausea, vomiting, fatigue/asthenia, anemia) and neutropenia and thrombocytopenia was <3 months; the first event lasted a median of <2 months, apart from fatigue/asthenia, which lasted a median of <4 months (Table). AEs were usually managed with supportive therapy and/or dose modification; few pts discontinued. Conclusions: AEs in newly diagnosed pts with advanced OC treated with olaparib usually occurred early and were manageable, with few discontinuations. Clinical trial information: NCT01844986.

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Vomiting</th>
<th>Fatigue/asthenia</th>
<th>Anemia*</th>
<th>Neutropenia*</th>
<th>Thrombocytopenia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>P</td>
<td>O</td>
<td>P</td>
<td>O</td>
<td>O</td>
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<td>O</td>
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<tr>
<td>NPs with AE, n (%)</td>
<td>104</td>
<td>54</td>
<td>51</td>
<td>101</td>
<td>60</td>
</tr>
<tr>
<td>Median time to first event, months</td>
<td>1.46</td>
<td>1.54</td>
<td>1.94</td>
<td>1.81</td>
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<td>Median duration of first event, months</td>
<td>0.43</td>
<td>0.72</td>
<td>0.75</td>
<td>0.58</td>
<td>0.58</td>
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</table>

*Grouped term; AEs with no end date censored at end of safety follow-up or data cut-off, as applicable. O, olaparib; P, placebo
Results of the VENUS study: Bevacizumab efficacy and safety in platinum-sensitive recurrent ovarian cancer (OC)—A real-life ambispective study.

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Background: The VENUS study reports on the efficacy/safety of bevacizumab (Bev) in patients (pts) treated in the real-life setting. Methods: In this multicentric observational ambispective VENUS study, all pts were naive of any antiVEGF and received Bev +/- chemotherapy. Pts were followed until progression or death, for a maximum of 3 years since Bev initiation. De novo side effects were defined as symptoms for which patients were naive at baseline. Results: 148 OC pts were included (27 centres), 10 excluded and 8 were lost of follow-up. 52 were retrospective. Median age 64 years (55-70). 84.1% were advanced. Median duration of Bev was 8.6 months, min 1 max 36 months. Initial Bev dose was 15 mg/kg Q3W for 65.3%, 10.0 for 22.5%, 7.5 for 10.2% and 5.0 for 2%. 2 pts presented with thrombotic microangiopathy (1.4%). Before Bev, hypertension (HTN) was present in 28.9%; proteinuria in 11.3%. Incidence of de novo HTN was 25%. 43 pts (31.2%) experienced de novo Grade 1-2 Pu, for a total of 56 events, no grade 3-4 was observed. A total of 12 Grade 4 events occurred: 9 neutropenia and 3 thrombopenia. Mean overall survival (OS) and progression free survival (PFS) were 30.0 and 13.3 months, respectively. Conclusions: 1) 1/3 of pts were treated at low doses in this real-life study; 2) safety of Bev in real-life was manageable and as expected, 3) OS and PFS were consistent with those reported in the OCEANS study: PFS 12.4 and OS 33.6 months but lower than in the GOG-0213 study: PFS 13.8 and OS 42.6 months. De novo events recorded during follow-up.

<table>
<thead>
<tr>
<th>Event</th>
<th>% of pts (%</th>
<th>Grade 3 (n events)</th>
<th>Grade 4 (n events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>65.2 (90)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>39.9 (55)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>35.5 (49)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31.2 (43)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29.0 (40)</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Constipation</td>
<td>26.1 (36)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25.4 (35)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>24.6 (34)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>22.5 (31)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21.0 (29)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cephalgia</td>
<td>20.3 (28)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.6 (27)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18.8 (26)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>16.7 (23)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Edema (lower limbs)</td>
<td>13.8 (19)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13.0 (18)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10.9 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>9.4 (13)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Back pain</td>
<td>8.7 (12)</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

*NCI-CTCAE 4.03; G=Grade; de novo = pt with no event at inclusion and who presented an event during f/u; NA: Not available, not graded. Other adverse events with all grade incidence <5% are not reported in this abstract. VENUS was supported by an unrestricted educational grant from Roche France.
Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial.

Cara Amanda Mathews, Kathleen N. Moore, Nicoletta Colombo, Giovanni Scambia, Byoung-Gie Kim, Ana Oaknin, Michael Friedlander, Alla Sergeevna Lisysanskaya, Anne Floquet, Alexandra Leary, Gabe S. Sonke, Charlie Gourley, Susana N. Banerjee, Amit M. Oza, Antonio González-Martín, Carol Aghajanian, William Hampton Bradley, Elizabeth S. Lowe, Ralph Bloomfield, Paul Disilvestro; Women & Infants Hospital, Providence, RI; Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK; University of Milan-Bicocca and Istituto Europeo di Oncologia, Milan, Italy; Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Prince of Wales Clinical School, University of New South Wales, and Royal Hospital for Women, Sydney, Australia; St Petersburg City Oncology Dispensary, St Petersburg, Russia; Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, and Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, Bordeaux, France; Gustave-Roussy Cancer Campus, Villejuif, and Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, France; The Netherlands Cancer Institute, Amsterdam, Netherlands; Cancer Research UK Edinburgh Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom; The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; Princess Margaret Cancer Centre, Toronto, ON, Canada; MD Anderson Cancer Center, Madrid, Spain; Memorial Sloan Kettering Cancer Center, New York, NY; Froedtert and the Medical College of Wisconsin, Milwaukee, WI; AstraZeneca, Gaithersburg, MD; AstraZeneca, Cambridge, United Kingdom

Background: In SOLO1 (NCT01844986), maintenance olaparib significantly improved progression-free survival (PFS) vs placebo (HR 0.30; 95% CI 0.23–0.41; Moore et al. N Engl J Med 2018) in pts with newly diagnosed advanced OC and a BRCAm. This analysis evaluates olaparib efficacy by timing of surgery, presence of residual tumor following surgery and response status after completion of chemotherapy in SOLO1. Methods: Pts underwent cytoreductive surgery and were in clinical complete response (CR) or partial response (PR) after platinum-based chemotherapy. Pts were stratified by response and received olaparib tablets 300 mg twice daily or placebo. Investigator-assessed PFS and objective response were assessed using modified RECIST v1.1. Results: 260 pts were randomized to olaparib and 131 to placebo; one pt did not receive placebo. Median follow-up was 41 months in both arms. 63% and 35% of pts underwent upfront and interval surgery, 21% and 76% had residual and no residual macroscopic disease after surgery, and 74% and 26% entered the study in clinical CR and PR (based on electronic case report form [eCRF] data). PFS was significantly improved regardless of the timing of surgery, residual disease status after surgery or response after platinum-based chemotherapy (Table). In pts with baseline radiologic evidence of disease (n=80; eCRF), the objective response rate was 43% for olaparib (CR, 28%) and 23% for placebo (CR, 12%). Conclusions: Maintenance olaparib improved outcomes compared with placebo in pts with newly diagnosed advanced OC and a BRCAm, regardless of surgical or tumor status. Clinical trial information: NCT01844986.

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, months</th>
<th>HR (95% CI)</th>
<th>O vs P</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>D vs P</td>
<td></td>
</tr>
<tr>
<td>Upfront surgery</td>
<td>NR 15.3</td>
<td>0.31 (0.21-0.46)</td>
<td></td>
</tr>
<tr>
<td>Interval surgery</td>
<td>33.6 9.8</td>
<td>0.37 (0.24-0.58)</td>
<td></td>
</tr>
<tr>
<td>Residual disease</td>
<td>29.4 11.3</td>
<td>0.44 (0.25-0.77)</td>
<td></td>
</tr>
<tr>
<td>No residual disease</td>
<td>NR 15.3</td>
<td>0.33 (0.23-0.46)</td>
<td></td>
</tr>
<tr>
<td>Clinical CR†</td>
<td>NR 15.3</td>
<td>0.34 (0.24-0.47)</td>
<td></td>
</tr>
<tr>
<td>Clinical PR†</td>
<td>30.9 8.4</td>
<td>0.31 (0.18-0.52)</td>
<td></td>
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</table>

*NED and a normal CA-125 level. †≥30% decrease in tumor volume or NED after chemotherapy but an abnormal CA-125 level. ‡By eCRF, NED, no radiologic evidence of disease; NR, not reached; O, olaparib; P, placebo

Ofranergene obadenovec (VB-111) in platinum resistant ovarian cancer: with an immunotherapeutic effect.

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Background: VB-111 is a targeted anti-cancer gene therapy with a dual mechanism: anti angiogenic/vascular disruption and induction of an anti-tumor directed immune response. We report final results of a phase I/II study of VB-111 in combination with paclitaxel in patients with platinum-resistant ovarian cancer. Methods: Study NCT01711970 was a prospective, open label, dose escalating study assessing combination treatment of VB-111 Q8W and weekly Paclitaxel. In the phase I part of the study patients were treated with escalating doses of intravenous VB-111 and Paclitaxel. In phase 2 patients were treated with therapeutic doses of VB-111 1x10^13 Viral Particles and paclitaxel 80mg/m^2. Assessments included safety, overall survival (OS), PFS, tumor response (CA-125 and RECIST) and histopathology. Results: 21 patients with recurrent platinum-resistant ovarian cancer were enrolled and treated in 2 US sites. Patients received a mean of 2.3 ± 1.8 repeat doses of VB-111. 17/21 received the therapeutic dose. Median age was 65 (41-79) with a median of 3 (1-4) prior lines of therapy. Half of the subjects were Platinum refractory, and half were previously treated with antiangiogenics. No DLTs were observed. VB-111 was well tolerated and was associated with generally mild flu-like symptoms. In the therapeutic dose cohort, a 58% CA-125 GCIG response rate was seen in evaluable patients including durable responses, and responses in patients with platinum refractory disease and post anti-angiogenic failure. The median OS was 498 days in patients treated with Therapeutic Dose compared to 173 days in Sub-therapeutical dose (p = 0.028). Tumor Specimens taken after treatment demonstrated tumor infiltrated with cytotoxic CD8 T-cells and regions of apoptotic cancer cells. Conclusions: Treatment with VB-111 in combination with weekly Paclitaxel was safe and well tolerated. Favorable tumor responses and overall survival outcomes were associated with induction of an immunotherapeutic effect manifested as tumor infiltration with CD-8 T cells. Encouraging results are the basis for further exploration in the ongoing, placebo controlled, pivotal OVAL study. Clinical trial information: NCT01711970.
Background: Circulating tumor DNA (ctDNA) analysis in epithelial ovarian cancer (EOC) was previously reported, however with limited samples or limited genes. Here, we reported an analysis of ctDNA in EOC cohort using targeted sequencing with a 1021-gene panel. Methods: Patients with EOC were enrolled, and treatment-naive tumor tissues and blood samples were collected. We utilized a 1021-gene NGS panel in matched tissue DNA and ctDNA to identify somatic mutations with white blood cell DNA as a germline control. Results: Mutations were identified in all of the 65 tissues and in 53 (81.5%) ctDNA. The median ctDNA mutation allelic frequency was 2.5%, ranging from 0.1% to 36.2%. A median of 66.7% (12.5%-100.0%) of tissue derived mutations were observed in ctDNA. Besides, there were 91 ctDNA private mutations, including TP53 gene mutations. The most frequently mutated genes were TP53 (55.4%), PIK3CA (13.8%) and ARID1A (12.3%) in ctDNA analysis, which were consistent with tissue analysis (60.0%, 26.2% and 20.0% of tissues with TP53, PIK3CA and ARID1A mutations, respectively). Mutations of TP53 (37/42) in high-grade serous ovarian carcinoma (HGSOC), PIK3CA (10/11) and ARID1A (8/11) in ovarian clear cell carcinoma, BRAF (4/5) in low-grade serous ovarian carcinoma and PIK3CA (3/5), ARID1A (2/5) and PTEN (2/5) in endometrioid carcinoma were observed as the most commonly genetic aberrations in ctDNA in different sub-types of EOC, which located in different signal pathways and suggested different pathogenesis. In total, 90.5% (38/42) of HGSOC were ctDNA positive, comparing with 65.2% (15/23) of other EOC subtypes (p = 0.012). In addition, 56.5% (13/23) of stage I–II EOC were ctDNA positive, comparing with 94.7% (36/38) of stage III (p = 0.002). No association between ctDNA positivity and other clinic characteristics was observed, including pathological differentiation, CA125, lesion density (solid vs. cystic-solid and cystic). Multivariable analysis suggested FIGO stage III (p = 0.008) as an independent predictor of ctDNA detection. Conclusions: In summary, genomic characterization of EOC may offer insights into tumorigenesis and identify potential therapeutic targets in this disease.
First-in-human (FIH) phase 1 (Ph1) study of MORAb-202 in patients (pts) with advanced folate receptor alpha (FRA)-positive solid tumors.

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Background: MORAb-202 is an antibody drug conjugate consisting of farletuzumab (a humanized monoclonal antibody that binds to FRA) paired with a cathepsin B-cleavable linker to eribulin mesylate (a microtubule dynamics inhibitor). We report preliminary results from a FIH Ph1 study of MORAb-202 in pts with FRA-positive solid tumors. Methods: This open-label, ongoing, FIH study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, maximum tolerated dose, and/or the recommended dose of MORAb-202 (Part 1: Dose finding part with accelerated modified toxicity probability interval design; Part 2: Expansion part). Eligible pts had FRA-positive solid tumors who failed standard therapy and an ECOG PS of ≤1. MORAb-202 was administered by intravenous injection once every 3 weeks and dose-limiting toxicities (DLTs) were assessed during the first 21-day cycle. Efficacy endpoints were assessed with RECIST v1.1 by investigator assessment. Results: As of Nov 16, 2018, 16 pts with confirmed FRA-positive tumors were enrolled and treated with MORAb-202 across 4 dose levels in Part 1 (0.3mg/kg: n = 3 [2 endometrial and 1 ovarian], 0.45mg/kg: n = 3 [3 ovarian], 0.68mg/kg: n = 3 [1 NSCLC, 1 ovarian, and 1 TNBC], 0.9mg/kg: n = 7 [4 ovarian, 1 endometrial, 1 NSCLC, and 1 TNBC]); all completed 1 cycle. One pt in the 0.9mg/kg cohort experienced DLTs of alanine aminotransferase increased (grade 3) and gamma-glutamyl transferase increased (grade 3). Treatment-emergent adverse events (TEAEs) occurred in 15 pts (93.8%). The most common TEAEs were leukopenia and neutropenia (50% each). The objective response rate based on RECIST v1.1 was 37.5% (6/16 pts) in Part 1 with 1 complete response (ovarian) at 0.9mg/kg and 5 partial responses including 2 pts (both ovarian) at 0.9mg/kg, 1 pt (endometrial) at 0.3mg/kg, and 2 pts (1 TNBC and 1 NSCLC) at 0.68mg/kg. The disease control rate was 75% (12/16 pts). Exposure to MORAb-202 was dose proportional across the dose range investigated. Conclusions: MORAb-202 escalation to 0.9mg/kg was manageable with encouraging initial antitumor activity in pts with FRA-positive solid tumors. Clinical trial information: NCT03386942.
SOLO1 versus SOLO2: Cost-effectiveness of olaparib as maintenance therapy for newly diagnosed and platinum-sensitive recurrent ovarian carcinoma among women with germline BRCA mutations (gBRCAmut).

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Background: With the December 19, 2018 regulatory approval by the US FDA of olaparib tablets as maintenance therapy for women with deleterious or suspected deleterious germline or somatic BRCAmut advanced ovarian carcinoma, it becomes important to clarify the role of PARP inhibitors in this disease. We evaluated cost-effectiveness of olaparib in the upfront (SOLO1) versus the recurrent maintenance setting (SOLO2).

Methods: Data were obtained from SOLO1, the phase 3 placebo-controlled randomized upfront maintenance study among gBRCAmut patients [median PFS greater than 49.8 vs 13.8m: HR 0.30; 95% CI, 0.23-0.41; p < 0.001, NCT01844986] and SOLO2, the phase 3 placebo-controlled randomized maintenance study among gBRCAmut patients with platinum-sensitive recurrence and at least two prior lines of therapy [median PFS 19.1 vs 5.5m: HR 0.30; 95% CI, 0.22-0.41; p < 0.0001, NCT01874353]. Investigator-assessed median PFS and toxicity data from the trials were incorporated in a Markov model which transitioned patients through response, hematologic complications, non-hematologic complications, progression, and death. Using TreeAge Pro 2015, the costs of pre-treatment testing (eg. gBRCAmut), medications, and management of adverse effects were analyzed. Incremental cost-effectiveness ratios (ICERs) per month of life gained and individual PFS-life year saved (PFS-LYS) were also calculated and compared. Results: In SOLO1, cost prior to progression was 1.7x that of SOLO2 ($937,440 vs $564,451). With the extended, estimated median PFS of at least 49.8m for SOLO1 and 19.1m for SOLO2, upfront maintenance therapy was more cost-effective. SOLO 1 was associated with $312,480 PF-LYS per individual patient, while SOLO2 demonstrated $498,045 PF-LYS. Maintenance olaparib was found to be more cost-effective in the 1st-line setting, with an ICER of $12,149 per month of life gained when compared directly to SOLO2. Conclusions: Although the higher cost associated with olaparib in SOLO1 reflects the longer time patients stay on drug due to extended PFS, the ICER supports early use in the disease course as first-line maintenance therapy among women with gBRCAmut advanced ovarian carcinoma.
Modeled CA-125 kinetics during neoadjuvant chemotherapy for predicting the likelihood of optimal interval debulking surgery in ovarian cancer patients: Data from CHIVA trial (a GINECO study).

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Background: A pre-operative predictive biomarker of CC0 interval debulking surgery (IDS) likelihood would be helpful. The modeled CA125 elimination rate constant KELIM predicts OS in 1st line setting (You et al. Clin Cancer Res 2019). The predictive/prognostic values of KELIM regarding CC scores at IDS, and survivals during neo-adjuvant chemotherapy were assessed. Methods: The data of the CHIVA randomized phase II trial, comparing carboplatin-paclitaxel +/- nintedanib before IDS (NCT01583322), were used. A semi-mechanistic model was built to describe CA125 longitudinal kinetics during the first 100 treatment days. The relationships between KELIM and IDS CC scores, PFS & OS, were assessed with other major prognostic factors (grade, histology, GCIG CA125 response, FIGO stage, and arm) using multivariate logistic regression (logit), C-index & survival tests. Results: The longitudinal kinetics of 529 CA125 values, assessed every 3 weeks during neo-adj chemotherapy, were modeled in 133 patients (out of 188). KELIM (as a continuous covariate) was the only significant predictive factor of CC0 IDS likelihood using multivariate analyses (OR = 12.37, 95% CI [4.32-39.67]). CC0 IDS probability can be estimated with patient KELIM: $\geq 90\%$ if standardized KELIM $\geq 0.12$. Non-parametric survival models confirmed the independent predictive values of KELIM categorized by terciles regarding PFS & OS (Table). The parametric model linking KELIM (as a continuous covariate) with OS allows to predict the patient survivals (months) based on their estimated KELIM (HR = 0.20, [0.10-0.39]). Conclusions: The prognostic & predictive values of the modeled CA125 KELIM are also confirmed regarding CC0 IDS likelihood, PFS and OS with neo-adjuvant chemotherapy. Patient KELIM is calculable online, based on observed CA125 values, on http://www.biomarker-kinetics.org/. Clinical trial information: 2011-006288-23.
Recurrence of ovarian cancer in BRCAwt patients without maintenance therapy: Real-world evidence.

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Background: Development of platinum resistance is a major clinical challenge in ovarian cancer (OC) treatment. In the phase 3 ENGOT-OV16/NOVA trial of the poly(ADP-ribose) polymerase inhibitor (PARPi) niraparib, 55% of BRCA wild-type (BRCAwt) patients (pts) receiving placebo developed platinum resistance after their last platinum-based therapy (ie, progressive disease within 6 months of their last chemotherapy [CT] dose). Niraparib, a PARPi approved for the maintenance treatment of adult pts with recurrent OC following platinum-based CT, significantly prolongs progression-free survival (PFS). This real-world data analysis investigated the risk of platinum eligibility loss for BRCAwt pts who did not receive maintenance therapy after platinum treatment. Methods: This retrospective study identified 5,535 pts with OC from January 2011–October 2018 using data from Flatiron, a longitudinal, demographically and geographically diverse database derived from records of > 265 cancer clinics and > 2 million US cancer pts. BRCAwt pts who had received ≥2 lines of platinum-based CT, had disease progression ≥6 months after their previous line of therapy, and had no maintenance therapy (PARPi, bevacizumab, or CT agents) after their current treatment were included. Kaplan-Meier analysis was used to estimate the probability of pts initiating next treatment or death, whichever occurred first, within 6 months. Results: Of 5,535 pts diagnosed with OC, 147 BRCAwt pts met the inclusion/exclusion criteria of this analysis (similar to ENGOT-OV16/NOVA placebo arm). An estimated 56% of pts received the next treatment or died within 6 months after their last platinum-based therapy. Median time to next therapy or death was 5.1 months (95% confidence interval, 3.1–7.2). Conclusions: Our real-world data analysis shows that 56% of BRCAwt pts who received platinum-based treatment without maintenance therapy had recurrent OC within 6 months, classifying them as platinum resistant. Use of maintenance treatment options, such as niraparib, has been shown to significantly prolong PFS after platinum-based CT and may be beneficial in extending the platinum-free interval, enabling pts to remain eligible for further platinum therapy.
Risk factors for progression or death in ovarian cancer patients who completed first-line platinum treatment.

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Background: Limited real-world information is available in ovarian cancer (OC) regarding prognostic factors for disease progression or death after initial treatment. Here, we assessed potential prognostic risk factors in OC patients (pts) who completed first-line (1L) platinum-based chemotherapy (CT) using real-world data. Methods: This retrospective study identified 5535 pts diagnosed with OC from January 2011–October 2018 from the Flatiron database, a longitudinal, demographically and geographically diverse database derived from health records from > 265 cancer clinics and > 2 million US cancer pts. Stage III/IV OC pts who completed 1L platinum-based CT after primary debulking or interval debulking surgery were included. Pts who received a poly(ADP-ribose) polymerase inhibitor (PARPi) in 1L treatment or as maintenance therapy after 1L treatment were excluded. Cox proportional hazards model was used to assess the association between baseline factors (neoadjuvant CT, disease stage, residual disease, BRCA status, ECOG, age, platelet count, hemoglobin, and neutrophil count) and time to next treatment (TTNT; a proxy for progression-free survival) or overall survival (OS) in these pts. Results: 1064 of 5535 pts were eligible per our inclusion/exclusion criteria. Neoadjuvant treatment, stage of disease, residual disease after surgery, and BRCA mutation (BRCAmut) status were significant prognostic factors for either TTNT or OS. Neoadjuvant chemotherapy pts had a shorter TTNT (hazard ratio [HR] = 1.37; P = .001) and OS (HR = 1.64; P = .0002) than pts who underwent primary surgery after adjusting for other covariates. Stage IV pts had a shorter TTNT (HR = 1.26; P = .01) and OS (HR = 1.24; P = .09) than stage III pts. OS was also worse in pts with vs without residual disease (HR = 1.27; P = .04) and worse in BRCAwt than BRCAmut pts (HR = 1.37; P = .10). Conclusions: In this retrospective analysis of a real-world data set, BRCAwt status was associated with higher risk of death. Receipt of neoadjuvant CT, higher stage of disease at diagnosis, or presence of residual disease after surgery were also associated with a shorter TTNT or higher risk of death. These real-world data confirm previously identified prognostic factors.
How long have we got? The accuracy of physicians’ estimates and scenarios for survival time in 898 women with recurrent ovarian cancer (ROC).

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Background: Predicting, formulating, and communicating prognosis in women with ROC is difficult. Best-case, worst-case, and typical scenarios for survival time based on simple multiples of an individual’s expected survival time (EST) estimated by their oncologist have proven accurate and useful in a range of advanced cancers. We sought the accuracy and prognostic significance of such estimates in the GCIG Symptom Benefit Study: a multinational, prospective cohort study of women with ROC (platinum resistant and potentially platinum sensitive ROC who have had more than 2 lines of chemotherapy). Methods: Oncologists estimated EST at baseline for each woman they recruited to the GCIG Symptom Benefit Study in 11 countries. We hypothesised a priori that oncologists’ estimates of EST would be unbiased (equal proportions [approximately 50%] of women living longer versus shorter than their EST), imprecise (< 33% living within 0.75 to 1.33 times their EST), and provide accurate scenarios for survival time (approximately 10% dying within 1/4 of their EST, 10% living longer than 3 times their EST, and 50% living from half to double their EST). We also hypothesised that oncologists’ estimates of EST would be independently significant predictors of survival in a multivariable Cox model adjusting for prognostic factors established in previous studies. Results: Oncologists’ individualised estimates of EST in 898 women with ROC were unbiased (55% of women lived longer than their EST) and imprecise (23% lived within 0.75 to 1.33 times their EST). Scenarios for survival time based on oncologists’ estimates of EST were remarkably accurate: 7% of women died within 1/4 of their EST, 13% lived longer than 3 times their EST, and 53% lived from half to double their EST. The median EST was 12 months (range 3-70), and median observed was 12.7 months. Oncologists’ estimates of EST were independently significant predictors of overall survival (HR 0.96, CI 0.94-0.98, p < 0.0001) in Cox models accounting for previously established prognostic factors. Conclusions: Oncologists’ estimates of EST were unbiased, imprecise, and independently significant predictors of survival time. Best-case, worst-case and typical scenarios based on simple multiples of EST were remarkably accurate, and provide a useful approach for predicting, formulating, and explaining prognosis in women with recurrent ovarian cancer. Clinical trial information: ACTRN: 12607000603415.
Randomized phase III trial comparing pegylated liposomal doxorubicin (PLD) 50 mg/m$^2$ and 40 mg/m$^2$ in patients with platinum-resistant Müllerian carcinoma (JGOG3018).

Background: The standard dose of single-agent pegylated liposomal doxorubicin (PLD) is 50 mg/m$^2$ every 4 weeks, but 40 mg/m$^2$ has recently been used in clinical practice, though there is no evidence available to support its use. Methods: A Phase III, randomized, multicenter, non-inferiority study comparing progression-free survival (PFS) of patients with platinum-resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma) treated with an experimental arm (40 mg/m$^2$ PLD) versus a standard arm (50 mg/m$^2$ PLD) until 10 courses, disease progression, or unacceptable toxicity was conducted. Eligible patients had $\geq$2 prior lines. Stratification was by performance status (PS) and PFS of prior chemotherapy (<3 months versus $\geq$3 months). The primary endpoint was PFS, and secondary endpoints were overall survival (OS), toxicity profile, clinical response, and tolerability. The target total number of patients was 412. Results: The trial was closed due to accrual futility as patient recruitment was slow, with 272 patients randomized to the experimental arm (n=137) and the standard arm (n=135). The final analysis was performed with 234 deaths and 269 events for PFS. Median patient age was 62 years; 58% of patients had a treatment-free interval less than 3 months, and 81% of patients had PS 0. In the experimental versus standard arm, median PFS was 4.0 months versus 4.0 months (HR 1.065, 95.8%CI: 0.830-1.366), and median OS was 14.0 months versus 14.0 months (HR 1.078, 95%CI: 0.831-1.397). Adverse events grade 2 including oral cavity mucositis were more frequent in the standard arm than in the experimental arm (26.7% vs. 13.5%, respectively; p=0.0089), but there was no difference in grade 2 hand-foot-skin reactions (19.8% vs. 15.0%, respectively; p=0.333). Conclusions: The non-inferiority of PFS with the reduced dosing schedule was not confirmed because the trial was closed prematurely, but PFS and OS were similar. These results suggest a reduction of the standard dose of PLD because of the low rate of oral mucositis in patients with platinum-resistant ovarian cancer treated with the lower dose regimen. Clinical trial information: UMIN000003130.
Efficacy of maintenance olaparib for newly diagnosed, advanced ovarian cancer patients (pts) by BRCA1 or BRCA2 mutation in the phase III SOLO1 trial.

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Background: In SOLO1 (NCT01844986), maintenance olaparib resulted in a significant improvement in progression-free survival (PFS) for newly diagnosed, BRCA1- and/or BRCA2-mutated, advanced ovarian cancer pts compared with placebo (HR 0.30, 95% CI 0.23–0.41; median not reached vs 13.8 months; Moore et al. N Engl J Med 2018). We investigated PFS in SOLO1 for the subgroups of pts with BRCA1 mutations (BRCA1m) or BRCA2 mutations (BRCA2m).

Methods: All pts were in clinical complete or partial response to platinum-based chemotherapy and were randomized to maintenance olaparib (300 mg twice daily; tablets) or placebo. After 2 years, pts with no evidence of disease discontinued study treatment, but pts with evidence of disease could continue study treatment. PFS by BRCAm was a predefined analysis. BRCAm were identified by central germline (Myriad or BGI) or local testing; Foundation Medicine testing confirmed tumor BRCAm. Results: Median follow-up for PFS was ~41 months in the olaparib and placebo arms. Of 391 randomized pts, 282 had BRCA1m (72%), 106 had BRCA2m (27%) and three (1%) had both (Table). Two pts in the olaparib arm had somatic BRCAm (one BRCA1m, one BRCA2m); all others had germline BRCAm. At the primary data cut-off, 155 pts in the BRCA1-mutated group (55%), 43 in the BRCA2-mutated group (41%) and none in the BRCA1/2-mutated group had disease progression. The percentage of BRCA1-mutated pts who received olaparib and were progression-free at 1, 2 and 3 years was 86%, 69% and 53% (vs 52%, 36% and 26% receiving placebo) and for BRCA2-mutated pts was 92%, 85% and 80% (vs 50%, 32% and 29%, respectively). Conclusions: Significant PFS benefit with olaparib versus placebo was demonstrated for all pts, regardless of whether they had BRCA1m or BRCA2m. Statistical tests were not used to compare BRCA1- and BRCA2-mutated pts, but those with BRCA2m appeared to receive greater benefit from maintenance olaparib than those with BRCA1m. Clinical trial information: NCT01844986.
Delays from neoadjuvant chemotherapy to interval debulking surgery and survival in ovarian cancer.

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Background: Prolonged time from primary surgery to chemotherapy is associated with worse survival in ovarian cancer (OC); however, the impact of prolonged time from neoadjuvant chemotherapy (NACT) to interval debulking surgery (IDS) is unknown. Given increasing utilization of NACT, we seek to evaluate the role of delays from NACT to IDS (TIDS) on survival.

Methods: At a single center, we prospectively identified 224 women with newly diagnosed stage III/IV OC given NACT from 7/1/15 to 12/1/17. Clinical characteristics were abstracted by two independent reviewers. Delays in TIDS were defined as time from last preoperative carboplatin to IDS > 6 weeks. Fisher’s exact/Wilcoxon rank sum tests were used to compare clinical characteristics by delay in TIDS. Kaplan Meier method was used to estimate progression-free (PFS) and overall survival (OS) from date of IDS. Log-rank test/multivariate CoxPH models were used to examine differences by delay groups, adjusting for covariates.

Results: Of the 224 women, 159 underwent IDS, and 34 (21%) experienced TIDS delays. These women were older (median 68 vs. 65 years, p = 0.05) and had more preoperative NACT cycles (median 6 vs. 4, p = 0.003). Patients with delays in TIDS also had a longer interval from pathological diagnosis to start of NACT (TNACT), median 22 vs. 17 days, p = 0.01, and interval from IDS to postoperative chemotherapy (TPOC), median 37 vs. 30 days, p = 0.01; however, neither TNACT nor TPOC predicted survival, p > 0.05. On univariate analysis, delays in TIDS also had a longer interval from pathological diagnosis to start of NACT (TNACT), median 22 vs. 17 days, p = 0.01, and interval from IDS to postoperative chemotherapy (TPOC), median 37 vs. 30 days, p = 0.01; however, neither TNACT nor TPOC predicted survival, p > 0.05. On univariate analysis, delays in TIDS were significantly associated with worse OS (HR 2.4 95% CI 1.2-4.8, p = 0.01); however, this was attenuated in multivariate models (HR 1.66 95% CI 0.8-3.4, p = 0.17), adjusting for age, stage and complete gross resection (CGR). On univariate analysis, delays in TIDS were not associated with PFS (HR 1.55 95% CI 0.97-2.5, p = 0.062), and in multivariate models, increase in number of preoperative NACT cycles (p = 0.005) and lack of CGR (p < 0.001) were the only variables predictive of worse PFS.

Conclusions: Delays in TIDS are associated with OS, but not after adjustment for age, stage and CGR, suggesting a need to maximize cytoreduction regardless of delays in NACT. The role of preoperative NACT cycles on survival should be further studied.
Molecular stratification of endometrioid ovarian carcinomas.

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**Background:** Endometrioid ovarian carcinomas (EC) have been historically under-investigated. We sought to determine the molecular landscape of contemporarily defined EC using whole exome sequencing (WES).

**Methods:** Tumours diagnosed as EC between May 1980 and December 2013 were identified through the Edinburgh Ovarian Cancer Database. Pathology review was performed according to WHO 2014. Other pathologies including WT1 positive HGSOC were excluded. A selected cohort underwent WES and were analysed for single nucleotide and copy number variants across a panel of genes previously reported as mutated in endometrial, ovarian or pan cancer studies. Tissue microarrays were stained for ER, PR and AR. Multivariable analysis for disease specific survival (DSS) was performed.

**Results:** 125 tumours were included. 61 tumours of all grades underwent WES. 5 molecular groups were identified based on the presence of TP53 mutations (45.9%); or an EC-like profile (one or more mutations in ARID1A (41.0%); CTNNB1 (31.1%), PTEN (24.6%) or PIK3CA (23.0%)). Tumours with no mutations in EC-like genes were termed EC null. Each group demonstrated differential DSS (table). Some EC null: TP53mut tumours also displayed mutations in KRAS, APC and mismatch repair genes. Unsupervised clustering analysis based on the top 100 differentially mutated genes across the dataset validated these groups. Somatic copy number alterations were significantly higher in the TP53mut groups than the TP53wt groups (P < 0.0001), and were identified across EC-like genes in the ECnull groups. A PR histoscore of > 150, but not ER or AR, was more frequent in the TP53mut group compared to the TP53wt groups (P = 0.003). TP53mut status (P = 0.0182) and PR histoscore ≤ 150 (P = 0.0115) were independently associated with DSS. **Conclusions:** EC is a heterogeneous disease comprising 5 molecular subgroups each demonstrating differential clinical outcome. TP53 mutations and PR histoscore ≤ 150 are independently associated with poor prognosis.

<table>
<thead>
<tr>
<th>Group</th>
<th>5 year DSS</th>
<th>Statistics</th>
</tr>
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<tbody>
<tr>
<td>EClike:ARID1A</td>
<td>100%</td>
<td>HR=0.14[0.02-1.11], P=0.0623</td>
</tr>
<tr>
<td>EClike:TP53</td>
<td>77%</td>
<td>HR=0.24[0.08-0.67], P=0.0063</td>
</tr>
<tr>
<td>ECnull:TP53</td>
<td>60%</td>
<td>HR=0.48[0.14-1.69], P=0.2551</td>
</tr>
<tr>
<td>ECnull:TP53</td>
<td>80%</td>
<td>HR=0.38[0.09-1.66], P=0.1977</td>
</tr>
<tr>
<td>ECnull:TP53</td>
<td>30%</td>
<td>reference</td>
</tr>
</tbody>
</table>
Olaparib maintenance therapy in patients (pts) with a BRCA1 and/or BRCA2 mutation (BRCAm) and newly diagnosed advanced ovarian cancer (OC): SOLO1 China cohort.

Lingying Wu, Jianqing Zhu, Rutie Yin, Xiaohua Wu, Ge Lou, Jing Wang, Yunong Gao, Beihua Kong, Xin Lu, Qi Zhou, Yueling Wang, Youguo Chen, Weigu Lu, Wei Li, Ying Cheng, Jihong Liu, Xin Ma, Ji Hong; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; Department of Gynecologic Oncology, Zhejiang Cancer Hospital, Hangzhou, China; Department of Gynecology and Obstetrics, West China Second University Hospital, & Key Laboratory of Obstetrics and Gynecologic and Pediatric Diseases and Birth Defects of the Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China; Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China; Department of Gynecology and Oncology, Harbin Medical University Cancer Hospital, Harbin, China; Department of Gynecologic Oncology, Hunan Cancer Hospital, Changsha, China; Beijing Cancer Hospital, Beijing, China; Qilu Hospital of Shandong University, Jinan, China; Department of Gynecologic Oncology, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China; Chongqing Cancer Hospital, Chongqing, China; No. 1 Affiliated Hospital of Medical School, Xi’an Jiaotong University, Xi’an, China; The First Affiliated Hospital of Soochow University, Suzhou, China; Women’s Hospital, Zhejiang University School of Medicine, Hangzhou, China; Oncology Center, The First Hospital of Jilin University, Changchun, China; Jilin Cancer Hospital, Changchun, China; State Key Laboratory of Oncology in South China and Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; AstraZeneca, Shanghai, China

Background: SOLO1 (NCT01844986) is a randomized, double-blind, Phase III trial evaluating the efficacy and safety of the PARP inhibitor, olaparib, as maintenance monotherapy in newly diagnosed advanced OC pts with a BRCAm. A separate pt cohort evaluated the efficacy and safety of olaparib in Chinese pts in this setting. Methods: The China cohort of SOLO1 planned to enroll ~53 newly diagnosed OC pts who had completed first-line platinum-based chemotherapy and were in clinical complete or partial response. This sample size provided around a 90% chance to observe an HR < 1, assuming a true HR = 0.62. Pts were randomized 2:1 to olaparib (300 mg bid; tablet) vs placebo. The primary endpoint was investigator-assessed progression-free survival (PFS; modified RECIST v1.1). Sensitivity analysis of PFS was performed by blinded independent central review (BICR). Results: All 64 randomized pts received study treatment (olaparib, n = 44; placebo n = 20). Median follow-up was ~30 months in both arms. Median PFS was not reached in the olaparib arm and was 9.3 months in the placebo arm (Table). The most common AEs in the olaparib group were nausea (n = 28, 63.6%), anemia (n = 25, 56.8%) and vomiting (n = 18, 40.9%). Grade ≥3 AEs occurred in 56.8% of olaparib pts vs 30.0% of placebo pts; the most common grade ≥3 AE was anemia (n = 16, 36.4%). Olaparib dose interruptions, reductions and discontinuations occurred in 56.8%, 27.3% and 6.8% of pts, respectively (vs in 30.0%, 10% and 0% of pts in the placebo arm). Conclusions: In the China cohort of SOLO1, a clinically relevant improvement in investigator-assessed PFS was observed in newly diagnosed OC pts receiving olaparib maintenance therapy. Olaparib treatment led to a 54% reduction in risk of progression or death vs placebo. The safety results were consistent with the known profile of olaparib in Chinese pts. Clinical trial information: NCT01844986.

<table>
<thead>
<tr>
<th>PFS events, n</th>
<th>Median PFS, months</th>
<th>HR (95% CI; P value)</th>
<th>Full analysis set (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib Placebo (n = 44)</td>
<td>18 13 NR</td>
<td>9.3</td>
<td>0.46 (0.23, 0.97; 0.0320)</td>
</tr>
<tr>
<td>Olaparib Placebo (n = 20)</td>
<td>13 13 NR</td>
<td>9.3</td>
<td>0.39 (0.17, 0.86; 0.0168)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NR, not reached.
Menopausal symptoms in epithelial ovarian cancer survivors: The GINECO VIVROVAIRE2 study.

Florence Joly, Patricia Pautier, Elsa Kalbacher, François Gernier, Raffaele Fauvet, Anne Floquet, Dominique Berton-Rigaud, Olivier Tredan, Philippe Follana, Jerome Alexandre, Alain Zannetti, Nadine Dohollou, Stephanie Trager, Idlir Licaj, Jean-Michel Grelard, Bénédicte Clarisse, Djihane Ahmed-Lecheheb, Christine Rousset-Jablonski, Anne Gompel; Centre François Baclesse, CHU Côte de Nacre, Univ. UniCaen, Caen, France; GINECO and Gustave Roussy Cancer Center, Villejuif, France; CHU Jean Minjoz, Besançon, France; INSERM U1086, Clinical Research Department, Centre Françoïs Baclesse, Caen, France; Department of Oncology, CHU de Caen., Caen, France; Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, and Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, Bordeaux, France; GINECO and Institut de Cancérologie de l’Ouest (ICO) René Gauducheau, Saint-Herblain, France; Département d’Oncologie Médicale, Centre Léon Bérard, Lyon, France; GINECO and Department of Medical Oncology, Centre Antoine-Lacassagne, Nice, France; Department of Medical Oncology, Hopital Cochin, Université Paris Descartes, CARPEM, APHP, Paris, France; Centre Hospitalier de Cholet, Cholet, France; Polyclinique Bordeaux Nord, Bordeaux, France; GHPSO Site de Sentes, Senlis, France; Centre François Baclesse, Clinical Research Department, Caen, France; UNICANCER, Centre François Baclesse, Clinical Research Department, av général Harris, Caen, France; Centre Léon-Bérard, Lyon, France; Hôpitaux Universitaires Cochin Hôtel-Dieu Broca, Paris, France

Background: We have previously shown that Epithelial Ovarian Cancer and its treatments have significant negative effects on Quality of Life (QoL) and long term fatigue. The aim of the present multicentric VIVROVAIRE2 study was to report the main menopausal, Vasomotor Symptoms (VMS) of Epithelial Ovarian Cancer survivors (EOCS).

Methods: 166 patients of the 322 EOCS without relapse $\geq$3 years after first line of treatment accepted to participate to a gynecological consultation carried out by a gynecologist, including a questionnaire related to menopausal symptoms, a clinical examination, and an osteodensitometry. VMS (hot flashes and/or night sweats) were described according to natural menopause (NM) or surgically induced menopause (SIM). QoL and Fatigue were measured with the validated questionnaires FACT-G and FACT Fatigue.

Results: Median age was 62 years [20-83], FIGO stage III/IV (48%) and $<10\%$ BRCA1&2 mutated. Histological subtypes were: high grade serous 31%, low grade serous 23%, endometrioid G2-3 (14%) endometrioid G1( 4%), clear-cell 21%, mucinous 5%. All EOCS had surgery, 97% of patients received platinum and taxane chemotherapy, median delay from treatment was 5 years [3-24] and 59 (36%) had SIM. 14% of EOCS had osteoporosis; this rate was similar to the general population. 52% of patients (85) reported either hot flashes (47%) or night sweats (32%). 72% with SIM had VMS compared to 41% with NM (p $< 0.001$). VMS were not associated with poor global QoL or fatigue. At the time of the survey, only 8 (5 SIM & 3 NM) EOCS received hormone replacement therapy (HRT). Among the 85 EOCS with VMS, 80 (94%) (38 SIM (93%) 42 NM (95%)) did not benefit from HRT after cancer treatment. Among 80 EOCS with VMS and no HRT, 25 (66%) with SIM and 34 (81%) of NM had high grade serous, endometrioid G2-3, clear cell and mucinous histology.

Conclusions: Vasomotor symptoms are frequently reported by EOCS, particularly among surgically induced menopause patients. A majority of EOCS with these symptoms might have benefited from hormone replacement therapy.
Cost-effectiveness analysis of laparoscopic disease assessment in ovarian cancer.

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Background: Laparoscopic assessment of disease resectability can be useful for treatment planning for patients [pts] with advanced ovarian cancer [OC] but may be associated with added cost. Methods: We performed a cost-effectiveness analysis from a payer perspective to compare (1) a conventional strategy, where standard new pt evaluation was used to assign pts to either primary cytoreduction [PCS] or neoadjuvant chemotherapy with interval cytoreduction [NACT], and (2) an alternative approach, where pts considered candidates for PCS would undergo laparoscopy to evaluate disease resectability using a validated scoring system, who were then triaged to either PCS or NACT based on this evaluation. Diagnostic work-up, surgical and adjuvant treatment, perioperative complications, and progression-free survival [PFS] were included in the model. We derived model parameters from the literature and our institution’s experience with laparoscopic triage. Utility estimates for health states related to primary treatment were assessed prospectively and taken from the literature. Costs were estimated using Medicare reimbursement. Effectiveness was defined in quality-adjusted progression-free life years [QPFLYs]. We performed multiple sensitivity analyses. Results: Under baseline model parameters, the expected cost of treating one pt under the conventional and alternative strategies was $26,539 and $26,653, respectively. The expected quality-adjusted progression-free survival for pts in the conventional and alternative strategies was 0.70 and 0.94 QPFLYs, respectively. The calculated incremental cost-effectiveness was $473.97 per QPFLY saved. The alternative strategy became cost saving if pts found to have resectable disease by laparoscopy underwent cytoreduction during the same procedure. The conventional strategy may be preferred if PCS increased PFS over NACT by ≥5 months. Conclusions: For newly-diagnosed advanced stage OC pts, laparoscopic assessment of disease resectability prior to PCS was a cost-effective strategy. A conventional strategy may be preferred if PCS produced substantially longer PFS. Sensitivity analysis suggests the benefit of utilizing laparoscopic triage is influenced by mitigation of serious perioperative morbidity and associated costs.
Bevacizumab beyond progression: Impact of subsequent bevacizumab retreatment in patients with ovarian, fallopian tube, and peritoneal cancer after progression.

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Background: The Food and Drug Administration approved the use of bevacizumab for treatment of recurrent epithelial ovarian, fallopian tube, and primary peritoneal carcinoma (OC) in combination with chemotherapy. This study evaluates whether patients immediately retreated with bevacizumab derive benefit after progressing on a bevacizumab-containing regimen. Methods: This multi-institutional, retrospective study compared patients with high grade non-mucinous epithelial OC who received bevacizumab followed directly by another bevacizumab-containing treatment regimen to patients who received bevacizumab followed by a regimen that did not contain bevacizumab (or received no further treatment). All patient retreated with bevacizumab had stable or progressive disease on prior bevacizumab-containing regimen. Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan and Meier product-limit estimator and modeled via Cox proportional hazards regression. PFS was measured from the date of first bevacizumab treatment to the date of first progression, date of death or date of last clinic visit. OS was measured from the date of first bevacizumab treatment after progression to the date of death or date of last contact/clinic visit. Statistical significance was defined at the 0.05 level. Results: 275 patients received bevacizumab, of which 226 were evaluable; 102 received sequential treatment with bevacizumab and 124 received a bevacizumab containing regimen followed by a non-bevacizumab containing regimen at the time of progression. There was no significant difference between tumor grade, stage, or BRCA mutation. Median follow-up for all subjects was 17 months (range: 1.2-138.2 months). Median PFS was 10.21 months (95%CI: 8.05 - 11.79) and median OS was 22.14 months (95%CI: 17.1 – 27.4). Median PFS for patients who received bevacizumab without retreatment was 5.1 months (95%CI: 4.3 – 6.3) and 17.6 months (95%CI: 14.3 – 21.3) for patients who received sequential bevacizumab retreatment (p < 0.001). Median OS for patients who received bevacizumab without retreatment was 12.9 months (95%CI: 9.3 – 16.7) and 30.1 months (95%CI: 26.1 – 35.4) for patients who received sequential bevacizumab retreatment (p < 0.001). Conclusions: Our study shows OC patients treated with bevacizumab-containing regimens sequentially at the time of progression have significantly prolonged survival outcomes compared to those patients who received no re-treatment with bevacizumab.
Patient preferences for maintenance PARP therapy in ovarian cancer treatment.

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Background: Maintenance therapy with PARP inhibitors has become prevalent in treating ovarian cancer. However, the preferences of women with ovarian cancer regarding the risks, side effects and benefits afforded by maintenance therapies are largely unstudied. Methods: A discrete choice experiment was designed to elicit the preferences of women with ovarian cancer regarding 6 attributes (levels presented in parentheses) relevant to the decision for maintenance PARP inhibitor therapy versus surveillance: (1) overall survival (36, 38, 42 months); (2) progression-free survival (15, 17, 21 months); (3) nausea (none, mild, moderate); (4) fatigue (none, mild, moderate); (5) probability of death from myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML) (0%, 1%, 5%, 10%); and (6) monthly out-of-pocket cost ($0, $50, $500, $1,000). Educational material was provided, with embedded questions to test respondents' understanding. Participants chose between 2 variable clinical scenarios and a constant scenario representing a treatment break, with multiple iterations. Random-parameters logit regression was applied to model participants' choices as a function of attribute levels. Results: Of 150 women with ovarian cancer recruited, 95 were eligible and completed the survey. The mean age was 62, 48% had recurrent ovarian cancer, and 13% were currently taking a PARP. Participants always significantly preferred better clinical outcomes to worse (except between 0% and 1% risk of MDS/AML), preferred low out-of-pocket cost, and disliked the idea of a treatment break. Participants valued overall survival most (average importance weight 25 out of 100 total), followed by monthly out-of-pocket cost (24), risk of death from MDS/AML (18), nausea (15), PFS (10) and fatigue (8). On average, participants would tolerate a 2% additional risk of MDS/AML in exchange for 2 additional months of PFS and 7% additional risk of MDS/AML in exchange for 6 additional months of PFS. Conclusions: Women with ovarian cancer are willing to accept the side effects of PARP maintenance therapy and a higher than clinically observed risk of MDS/AML in exchange for clinically observed levels of improvement in PFS.
Survival and clinical outcomes of ovarian cancer patients enrolled in phase I clinical trials.

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Background: Ovarian cancer patients who enroll in Phase I clinical trials are typically platinum resistant, heavily pretreated patients with a poor prognosis. Historically, clinical benefit of Phase I trials in this patient population has been uncertain. We assessed prognostic factors and survival in women with recurrent, previously treated ovarian cancer who enrolled in Phase I clinical trials. Methods: We performed a retrospective analysis of all ovarian cancer patients who were treated on Phase I clinical trials from 2008 through 2018 at the University of Colorado Cancer Center. Patient characteristics, treatment-related toxicities and survival data were assessed. Descriptive statistics and Cox proportional hazards models were utilized to identify risk factors associated with survival time. Results: A total of 132 individual patients were treated on Phase I clinical trials. Patients had a median age of 59 years (range 33-88) with a median of 5.5 (range 1-13) previous chemotherapy lines. 53/132 (40%) of patients were treated on multiple Phase I trials with a median of 1 (range 0-5) prior Phase 1 clinical trial enrollments. All patients had an ECOG performance status of 0 or 1. Overall response rate (defined as complete or partial response) was 9% and disease control rate (defined as complete or partial response or stable disease as best response) was 33%. Median overall survival (OS) was 11.5 months (95% CI: 9.3-13.7). Two patients died on trial due to progression of disease while no patients died due to treatment-related toxicity. In multivariate analysis, independent risk factors predicting shorter survival were elevated CA-125 (HR 2.8; 95% CI: 1.6-5.2) and albumin < 3.5 g/dL (HR 2.5; 95% CI: 1.65-3.79). BMI > 25 predicted longer survival (HR 0.65; 95% CI: 0.44-0.96). Conclusions: Phase I clinical trials for heavily pretreated ovarian cancer patients are safe by a standard of no patients experiencing toxicity-related deaths in our study. They are clinically efficacious with patients experiencing OS of 11.5 months, which is comparable to existing approved therapies. Elevated CA-125 and low albumin levels predict shorter survival, while BMI > 25 predicts longer survival. Phase I clinical trial options should be considered for all heavily pretreated ovarian cancer patients if available to them.
Effect of estrogen and progesterone receptor expression on progression-free and overall survival outcomes in low-grade serous ovarian cancer.

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Background: Research on ER/PR receptor function in low-grade serous ovarian cancer (LGSC) and the determinants of response to treatment are lacking. A recent study (Sehouli et al., 2018) described ER/PR immunohistochemistry (IHC) cut-points that distinguished PFS. Thus, we report on a group of patients with ER/PR expression by IHC in tumor samples of patients with LGSC and used this information to evaluate survival outcomes. Methods: Clinical information and FFPE sections were obtained from the Canadian Ovarian Experimental Unified Resource (COEUR). Tissue microarray (TMA) sections were stained for ER/PR using standard IHC techniques (MK). 50 stage 3 and 5 stage 4 patients were analyzed. ER/PR expression was scored using a simple scoring system (1% cells staining, 1-50%, and ≥50%) and Allred scoring. We compared Kaplan-Meier (KM) survival (PFS and OS) curves using Log rank testing and Cox regression was used to model predictive/prognostic factors. A p-value of 0.05 was considered significant. Results: The mean age of the population was 49.5 years (SD:13.7). Ninety percent of patients were treated by surgery followed by platinum-based chemotherapy (PBC). Simple scoring did not discriminate outcomes as well for ER levels. PR Allred score (2 vs 6) clearly discriminated KM curves for PFS (p = 0.036) and OS (p = 0.01). For Allred ER score (7 vs 8) did not distinguish PFS (p = 0.4) but notably most patients received PBC after surgery. ER Allred score significantly distinguished OS (p = 0.008). Significant factors on Cox regression for PFS were residuum (p = 0.008;95%CI:1.2-3.1) and PR (p = 0.05;95%CI:0.39-0.99), whereas for OS ER(p = 0.01;95%CI:0.2-0.8) and residuum (p = 0.04;95%CI:1-2.8). Conclusions: ER/PR expression by Allred scoring was associated with PFS and OS. Patients will benefit from much needed research on ER/PR prediction/prognosis in LGSC. This work can inform clinical trials selection/stratification and patient selection for endocrine treatment.
Impact of BRCA mutation status and time to platinum resistance on patients with advanced ovarian cancer.

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Background: The influence of germline BRCA1/2 mutations (gBRCAmt) on ovarian cancer patients (pts) long-term survival remains controversial. Methods: 228 pts with serous and endometrial ovarian cancer stage Ic-IV were enrolled in the retrospective study. Next-generation sequencing testing of BRCA1/2 in blood was employed. Progression-free survival (PFS), overall survival (OS) and time to platinum resistance (TPR) were analyzed. TPR was defined as time from first line chemotherapy to registration of platinum resistance relapse. Results: The rate of pathogenic gBRCAmt was defined in 29.4% (67/228) pts. There was no any significant difference between BRCA1/2 mutation carries and non-carries in both PFS (18.3 and 16.7 months, p = 0.27, HR 0.79, 95%CI 0.52-1.20) and OS (71.9 and 79.1 months, p = 0.69, HR 0.88, 95%CI 0.46-1.68). However, TPR was significantly longer in pts with gBRCAmt than in germline BRCA wild type (gBRCAwt) pts (51.4 and 34.4 months, p = 0.05, HR 0.60, 95% CI 0.36-0.98). Pts with gBRCAmt had poor prognosis after registration of platinum resistance. gBRCAwt pts had longer survival than gBRCAmt after platinum-resistance relapse: 33.7 and 16.9 months respectively (p = 0.05; HR 1.85, 95%CI 1.02-4.08). Conclusions: Our finding provided possible explanation of equal survival of pts with or without BRCA1/2 mutations. Long-term sensitivity to platinum-based chemotherapy allowed pts with gBRCA1/2mt to control the disease for a long period of time. However the non-platinum regimens had less efficacy in pts with gBRCAmt than gBRCAwt after platinum resistance.
Real life efficacy and safety data of bevacizumab-based front line treatment in advance or metastatic ovarian cancer patients: Focus on patients with malignant ascites—A phase IV study.


Background: The standard of care for Epithelial Ovarian cancer (EOC) is the combination of a taxane plus a platinum compound (TC) whereas the addition of bevacizumab (bev) to this regimen (TC-bev) has been shown to improve the PFS. Patients (pts) with ascites have more aggressive disease and less overall survival. The aim of the study was to evaluate the safety of the TC/bev regimen in the real life clinical practice. Methods: A multi-center observational study, approved by the ethics committees of the participating centers, including 314 pts with stage III/IV EOC, was conducted (11.2011-06.2014) in Greece. Two independent cohorts, with similar clinico-pathologic characteristics, were treated with front-line TC (n = 109) or TC/bev (n = 205) according to the physician’s choice. 83 (40.5%) and 40 (36.7%) in the TC/bev and TC groups presented with ascites. Results: Disease control was achieved in 90.7% and in 78.9% of patients treated with TC/bev and TC, respectively (p = 0.003). Pts with ascites treated with TC/bev experienced a better overall response rate (ORR) (68.7% Vs 55%) and less progression disease (PD) compared to patients receiving TC (13.2% Vs 30.8%). The median PFS in all pts was 21.5mo and 12.4mo (p < 0.001) and median PFS in ascites pts was 18.1mo and 10.3mo in the TC/bev and TC cohort, respectively (p < 0.001). The median OS was not reached in the TC/bev group and it was 36.9mo in the TC group, (p = 0.059) while in the ascites pts also has not reached and it is 22.5m, respectively (p = 0.023). The 3 year survival rate in all pts was 59.4% and 50.4% and in ascites pts was 55.3% and 30% in the TC/bev and TC respectively. Neutropenia was the most common grade 3/4 adverse event in 16.6% and 9.1% in TC/bev- and TC- treated patients (p = 0.072) with no other adverse events > 5%. Conclusions: These real life data demonstrate that the combination of TC/bev represents an active and well tolerated regimen offering survival benefit in patients with stage III/IV EOC and especially in patients with ascites. Additional larger prospective studies are required to confirm these observations. Clinical trial information: NCT01982500.
Impact of the Affordable Care Act on early-stage diagnosis and treatment for women with ovarian cancer.

Anna Jo Smith, Amanda Nickels; Johns Hopkins Department of Gynecology and Obstetrics, Baltimore, MD

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 1. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.
Bevacizumab or PARP-inhibitors maintenance therapy for platinum-sensitive (PS) recurrent ovarian cancer (rOC)? A network meta-analysis (NMA).

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Background: Patients (pts) experiencing a PS rOC are generally re-exposed to a platinum based-chemotherapy (CT). In this setting, the addition of a targeted agent like bevacizumab (BEV) or PARP inhibitors (PARPi) as concomitant and/or maintenance therapy has shown to improve progression free survival (PFS). In the absence of direct comparison in randomized trials (RCTs), we have performed a NMA to evaluate differences in terms of efficacy between BEV and PARPi in pts with PS rOC, according to BRCA status. Methods: We searched PubMed, Embase and Medline for RCTs involving pts with PS rOC treated with BEV (n = 3, 1563 pts) or PARPi (n = 5, 1839 pts). Only trials with PFS as primary endpoint were included. Trials in first line setting were excluded. Analyses have been done pooling pts who had received PARPi in three groups, according to the available data on BRCA genes status: all comers (AC), BRCA mutated pts (BRCAm) and BRCA wild-type pts (BRCAwt). A frequentist approach has been used with R statistical software. To rank the effect size of treatments, surface under the cumulative ranking value (SUCRA) has been applied. Results: In AC pts, PARPi improved PFS compared to BEV (hazard ratio [HR] = 0.70, 95% CI 0.54-0.91, test of heterogeneity [I^2] = 40.5%). In BRCAm pts the gain in PFS for PARPi was even higher compared to BEV (HR = 0.46, 95% CI 0.36-0.59, I^2= 17.2%). In BRCAwt pts the benefit of PARPi over BEV was not statistically significant (HR = 0.87, 95% CI 0.63-1.20, I^2 = 35.7%) but PARPi had the highest likelihood of being ranked as the best treatment in terms of efficacy according to SUCRA (90% and 60%, respectively for PARPi and BEV). Hazard ratio for PFS between PARPi, BEV and CT in the three cohorts are reported in the table. Conclusions: According to indirect comparisons, PARPi performed the best for the treatment of PS rOC, especially in BRCAm pts who had not previously received PARPi. BEV could be still an option in BRCAwt pts.

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<tr>
<th>Treatments</th>
<th>AC</th>
<th>BRCAm</th>
<th>BRCAwt</th>
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<tr>
<td>PARPi vs BEV</td>
<td>0.70 (0.54-0.91)</td>
<td>0.46 (0.36-0.59)</td>
<td>0.87 (0.63-1.20)</td>
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<td>PARPi vs CT</td>
<td>0.38 (0.31-0.47)</td>
<td>0.25 (0.21-0.31)</td>
<td>0.48 (0.36-0.63)</td>
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<tr>
<td>BEV vs CT</td>
<td>0.55 (0.31-0.47)</td>
<td>0.55 (0.48-0.63)</td>
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Rethinking breast cancer surveillance in women with BRCA-associated ovarian cancer in the post-solo trial era.

Catherine S. John, Farin F. Amersi, Abigail Fong, Jessica Gillen, Kathleen N. Moore, Christine S. Walsh, Andrew John Li, Bj Rimel, Ilana Cass; Cedars Sinai Medical Center, Los Angeles, CA; 8215-NT, Los Angeles, CA; Oklahoma University Medical Center, Oklahoma City, OK; Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK; Cedars-Sinai Medical Center, Los Angeles, CA; Cedars Sinai Medcl Ctr, Los Angeles, CA; Cedars Sinai Medical Center, Los Angeles, CA

Background: Patients with BRCA mutations are at increased risk of developing both breast (BC) and epithelial ovarian cancer (EOC). Optimal breast cancer surveillance guidelines for BRCA mutation carriers following EOC has not been defined due to high risk of EOC recurrence. The recent SOLO-1 trial demonstrated a survival benefit of olaparib maintenance therapy for newly diagnosed women with advanced stage EOC. Olaparib reduced the risk of disease-progression or death by 70% compared to placebo with a median progression-free survival (PFS) of 36 months. Methods: An IRB-approved, multi-institutional study retrospective chart review was performed. Patients had BRCA-associated EOC diagnosed between 1990-2015 without a history of prior BC or mastectomy. All women received combination chemotherapy for EOC. The observed breast cancer free survival was adjusted to reflect the enhanced 3-year PFS observed in olaparib-treated women from the SOLO-1 trial. Kaplan-Meier survival curves were performed. Results: 191 patients with BRCA-associated EOC were included (135 BRCA1, 55 BRCA2, 1 BRCA1 and BRCA2). Median age was 53 years. Most women had advanced stage, high-grade serous EOC (75%). The median overall survival was 7.7 years for BRCA 1, and 9.7 years for BRCA2 mutation carriers. Annual mammography and MRI were performed in 43% and 34% of women, respectively, with a median of 4 mammograms and 3 MRI per patient. 16 women (8.3%) were diagnosed with BC over a median follow up of 80 months: 7 (44%) DCIS and 9 (56%) invasive ductal carcinoma. 14 (88%) women had early stage (0-2) BC. 28 (15%) of women had risk-reducing mastectomy performed an average of 2.1 years following their EOC diagnosis. The incidence of BC increased from 5.6% to 11% at 5- and 10-years post EOC, and in the predicted model with olaparib, from 10% to 17% at 5- and 10-years, assuming olaparib does not impact breast cancer incidence. Conclusions: The risk of metachronous BC following BRCA-associated EOC increases over time. In the post SOLO trial era, BC surveillance strategies in women with EOC should be optimized to reflect improved outcome.

<table>
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<tr>
<th>Time since EOC Diagnosis</th>
<th>Incidence of Breast Cancer</th>
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<tr>
<td></td>
<td>PRIOR to SOLO-1</td>
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<tr>
<td>2-year</td>
<td>2%</td>
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<tr>
<td>5-year</td>
<td>5.6%</td>
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<tr>
<td>10-year</td>
<td>11%</td>
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Real-life data: Women with recurrent platinum-sensitive ovarian cancer and BCARGEM treatment.

Frederique C. van der Scheun, Cheryl P. Bruijn, Petronella Witteveen, Britt B.M. Suelmann; Department of Medical Oncology, Cancer Center University Medical Center Utrecht, University of Utrecht, Utrecht, Netherlands

Background: Ovarian cancer is still the most mortal gynaecological cancer in the world. Even after achieving a good clinical response after initial treatment, the cancer will relapse in 80% of the patients. Treatments that improves progression-free survival (PFS) are necessary. In 2012, the OCEANS trial showed an improved PFS (12.4 months) for patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian cancer (ROC) treated with carboplatin, gemcitabine plus the monoclonal antibody bevacuzimab followed by maintenance therapy of bevacuzimab (BV) till progression (BCARGEM). Based on this trial, bevacuzimab was incorporated in the second line treatment protocol of various European countries for patients with platinum-sensitive ROC. However, there is no real life information yet available on the effectivity and tolerance of this one randomized clinical trial (RCT) in clinical practise. Therefore, the aim of this study was to assess what the real time efficacy and tolerance of treatment with BCARGEM was in patients with platinum-sensitive ROC.

Methods: All patients with platinum-sensitive ROC and treated with BCARGEM in the UMC Utrecht Cancer Center were retrospectively selected for analysis. All data such as baseline information, assessments and adverse events during cycles were obtained from medical records. The primary outcome was PFS; secondary outcomes were relative dose intensity (RDI), adverse events (AE) leading to dose modifications, and overall survival (OS).

Results: Overall, the median PFS of the 39 patients with platinum-sensitive ROC and treated with BCARGEM was 9.4 months (95% CI 4.6 - 14.2). The median OS was 20.9 months (95% CI 15.0-26.7). The average RDI for BCARGEM was 67%. None of the patients reached a RDI of 100%. In most patients (69%) neutropenia grade 3 led to dose modifications or discontinuance of BCARGEM. After treatment with BCARGEM, 34 patients started treatment with BV till progression. The median number of cycles of BV was 5. In 26 of the cases the BV was ended due to progression.

Conclusions: In our retrospective study, the PFS of real life patients treated with BCARGEM is lower compared to the study patients in the OCEANS trial; 9.4 versus 12.4 months. In addition, the RDI of BCARGEM is very low reflecting the many AEs leading to dose modifications or discontinuation. Therefore, this study underlines the fact that results of RCTs with strict in- and exclusion criteria do not represent actual outcomes in clinical care, because the selected study patient does not match the patient we face in real time.
Everolimus plus letrozole treatment of recurrent gynecologic cancers.

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**Background:** Hormonal therapy has limited activity in gynecologic (Gyn) cancer treatment. mTOR inhibitors plus aromatase inhibitors (AIs) improve the response rate and response duration in breast cancer patients. We studied this combination in heavily pre-treated women having estrogen receptor positive (ER+) Gyn cancers. **Methods:** This phase II study combines everolimus and letrozole for ER+ Gyn cancers with disease progression following primary and salvage chemotherapy. 19 patients participated (Ovary-10, Endometrium-7, and Primary Peritoneal Cancer-2). The mean age was 64, prior lines of therapy ranged from 2-7, and median time from diagnosis to study entry was 67 months (m) (range 10-348m). **Results:** There were no complete responders, but 7 of 19 (37%) patients treated had clinical benefit, with 1 PR and 6 with stable disease. In responding patients, the earliest time to best response was 2m and the median time to progression was 5m (range 5-40+m). The mean number of treatment cycles was 11. Toxicities: The most common adverse events were: hyperglycemia, rash, stomatitis, fatigue, and anemia. 7 patients required dose reductions, and 2 discontinued study drugs due to pneumonitis. The therapy was generally well tolerated in both women < 65 and ≥ 65 years old. Toxicities were less common with reduced everolimus doses. **Conclusions:** Recurrent Gyn cancers become refractory to chemotherapy. We tested the combination of everolimus plus letrozole in heavily pretreated patients with ER+ recurrent disease. 1 patient had a PR and 6 had stable disease with a range of 5-40+m. This oral regimen was generally well tolerated and allowed time without IV chemotherapy, while providing clinical benefit to patients with refractory ER+ Gyn cancers.
Elucidation of PARP inhibitor activity in BRCAwt recurrent ovarian cancer by hrr mutational gene profile analysis.

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Background: Niraparib is an oral, selective poly(ADP-ribose) polymerase inhibitor (PARPi) approved for maintenance treatment of BRCA mutated (BRCAmut) and BRCA wild-type (BRCAwt) recurrent ovarian cancer patients (pts) who are in response to platinum-based chemotherapy. In the non-germline BRCA mutated (non-gBRCAmut) cohort of the ENGOT-OV16/NOVA trial, clinical benefit with niraparib vs placebo was seen in pts regardless of their Myriad myChoice HRD test status (BRCAmut and homologous recombination deficiency [HRD] score), with a hazard ratio (HR) of 0.38 in HRD-positive (HRDpos) and 0.58 in HRD-negative (HRDneg) pts. To determine if treatment benefit in HRDneg pts may result from mutations in other homologous recombination repair (HRR) genes, we examined the relationship between progression-free survival and other HRR gene mutations in the NOVA non-gBRCAmut cohort. Methods: A retrospective, exploratory biomarker analysis was conducted using all available tumor samples from 331 pts enrolled in the NOVA non-gBRCAmut cohort. Mutation status of HRR genes was evaluated using a 43-gene NGS assay (Myriad Genetics), including BRCA1/2 and 16 additional HRR genes. Results: In this exploratory analysis of the NOVA non-gBRCAmut cohort, niraparib demonstrated clinical benefit in pts with somatic BRCA mutation (HR, 0.27) and in BRCAwt pts (HR, 0.47). In addition, BRCAwt pts with other HRR gene mutations also derived benefit from niraparib (HR, 0.49). When BRCAwt/HRRwt pts were categorized by HRD score, clinical benefit was also observed in both HRDpos and HRDneg pts, with HRs of 0.33 and 0.60, respectively. These results suggest that, although these biomarkers have good positive predictive value, they are not good negative predictors for niraparib benefit in this indication. Conclusions: This retrospective, exploratory analysis of the ENGOT-OV16/NOVA non-gBRCAmut cohort suggests that although pts with somatic BRCA mutation and other HRR mutations benefit from niraparib treatment, clinical benefit is also seen in HRDneg pts without HRR mutations, perhaps related to other genomic, epigenetic, or functional alterations within ovarian tumors yet to be defined.
Multi-parametric FDG PET/MRI as an early predictor of response to neoadjuvant chemotherapy in patients with epithelial ovarian cancer.

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Background: For patients with ovarian cancer undergoing neoadjuvant chemotherapy, the effectiveness of treatment is not evaluable by conventional methods until all or much of the treatment has been given. The purpose of this study is to investigate the performance of FDG PET, dynamic contrast-enhanced (DCE) and intra-voxel incoherent motion (IVIM) MR as early predictors of treatment response. Methods: Subjects with a new diagnosis of epithelial ovarian cancer underwent 3 cycles of standardized chemotherapy followed by cytoreduction. FDG PET/MR including DCE and IVIM was performed at baseline (T0), after cycle 1 (T1) and after cycle 3 (T2) of chemotherapy. Final responses were categorized at T2 by RECIST 1.1. Image volumes at T1 were analyzed as predictors of final response. Parametric images of molecular diffusion restriction (D), tissue perfusion (D*), vascular volume fraction (F), blood–interstitium constant of transfer (Ktrans), interstitium–plasma constant of transfer (Kep), extravascular/extracellular volume % (Ve) and plasma volume % (Vp) were investigated along with routine measures of SUV and ADC.

Results: Nine subjects were enrolled, 8 were responders by RECIST at T2 and one had stable disease. At T0 the mean, min, and max SUVmax of dominant tumor deposits was 11.5, 6.3, 19.0, respectively. Mean, min, and max values were 1.0, 0.75 and 1.63 for ADCmean and 0.62, 0.30, 0.96 for ADCmin. At T1, ADCmean increased in 8 subjects by +0.22% (s.d. +/- 13%) and decreased by -3% in one subject. ADCmin increased in 8 subjects by +21% (s.d. +/-11%) and decreased by -23% in one subject. D increased for 8 subjects (average +29% s.d. +/- 13%) and decreased by -10% in one. D*, F, Kep, Ktrans, Ve and Vp had no recognizable pattern. At T2, SUVmax, SUVmin, and ADCmean maintained their change direction across all subjects with measurable lesions. The only subject with a complete response at T2 had the highest ADCmin and ADCmean change at +45% after one cycle of chemotherapy (T1). The subject with stable disease at T2 had no significant difference in changes amongst all metrics.

Conclusions: FDG PET/MR SUVmax and ADCmean values obtained after one cycle of neoadjuvant chemotherapy were consistently associated with partial anatomical treatment responses after three cycles. Molecular diffusion restriction also was reliably associated with treatment response. Future studies evaluating FDG PET/MR in platinum-resistant patients may allow for early discontinuation of ineffective and toxic treatment.
Correlation of surgeon radiology assessment with laparoscopic scoring in patients with advanced-stage ovarian cancer.

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Background: To determine the correlation between surgeon radiology assessment and laparoscopic scoring in patients with newly diagnosed advanced stage ovarian cancer. Methods: Following IRB approval, 14 gynecologic oncologists from a single institution performed a blinded review of radiology imaging from 20 patients with advanced stage ovarian cancer. All patients previously underwent laparoscopic scoring assessment to determine primary resectability at tumor reductive surgery (TRS) using a validated scoring method from April 2013 to December 2017. The patients with predictive index value (PIV) scores $\leq$ 8 were offered primary surgery and those with a score $\geq$ 8 received neoadjuvant chemotherapy (NACT). Surgeons viewed contrasted CT imaging reports and images from all patients in a blinded fashion and recorded PIV scores using the same validated scoring method. Linear mixed models were conducted to calculate the correlation between radiology and laparoscopic score for each surgeon and as a group. Once the model was fit, the inter-class correlation (ICC) and 95% confidence interval was calculated. Results: Radiology review was performed on 20 patients with advanced stage ovarian cancer who underwent laparoscopic scoring assessment. Most patients had stage IIIC disease (85%) and median laparoscopic score was 9 (range 0-14). Surgeon faculty rank included Assistant Professor (n = 5), Associate Professor (n = 4), and Professor (n = 5). Median surgeon experience during the study period with laparoscopic assessment was 13 cases (range 1-28) and TRS was 22.5 cases (range 2-48). The kappa inter-rater agreement was -0.017 (95% CI 0.023 to -0.005) indicating low inter-rater agreement between radiology review and actual laparoscopic score. The ICC in this model was 0.06 (0.02-0.21) indicating that surgeons do not score the same across all the images. When using a clinical cutoff of PIV of 8, the probability of agreement between radiology and actual laparoscopic score was 0.56 (95% CI: 0.49-0.73). Number of laparoscopic cases, TRS cases, or faculty rank was not significantly associated with agreement. Conclusions: Surgeon radiology review did not correlate highly with actual laparoscopic scoring assessment findings in patients with advanced stage ovarian cancer. 44% of patients in our study may have been inadequately triaged by radiology review alone, which may have led to suboptimal TRS. Our study highlights the utility of laparoscopic scoring assessment to determine resectability over radiology assessment alone in ovarian cancer.
Comprehensive genomic analysis of mucinous ovarian cancer reveals unique therapeutic vulnerabilities.

Dane Anthony Cheasley; Peter MacCallum Cancer Centre, North Melbourne, Australia

**Background:** Mucinous ovarian carcinoma (MOC) is a rare subtype of epithelial ovarian cancer that responds poorly to ovarian chemotherapies and has an unknown etiology. It is diagnostically challenging and can be confused with metastases from gastro-intestinal tract primaries. The GAMuT study is a multinational effort to understand molecular drivers and cell of origin of this rare tumour, including identification of a genetic progression model and novel therapeutic options. **Methods:** We performed RNAseq (n = 67), exome sequencing (n = 61), SNP arrays (n = 67) and whole genome sequencing (n = 5) on MOC and precursor lesions. A subset of ~500 genes was further evaluated by targeted sequencing, including 129 MOC, 23 borderline mucinous tumours (non-invasive) and 23 extra-ovarian mucinous metastases. Immunohistochemistry data was collected for CK7, CK20, ER, PAX8, p53 and HER2 (n = 162-256). Extensive pathology review was performed and associated clinical data obtained. **Results:** Comparison with TCGA and other data sets showed that MOC are distinct from mucinous tumours from other organs, including colorectal, appendiceal and gastric cancers. Our data supports a clear genetic progression model from benign and borderline precursors to both low- and high-grade MOC. TP53 mutation, ERBB2 amplification and increasing copy number changes were key events associated with progression to invasive disease, including a novel amplicon on 9p13. Copy number aberration burden was significantly associated with poor survival. We identified several recurrent mutational events suggesting utility of an existing targeted therapy, including ERBB2 amplification (26%), ERBB3 mutation (4%) and BRAF mutation (9%). MOC could be included in clinical trials for novel agents targeting TP53 missense mutation (46%), RNF43 mutation (12%), PIK3CA mutation (8%) and KRAS/NRAS mutations (66%). Other frequent events included CDKN2A inactivation (57%), ARID1A mutation (9%) and TP53 inactivating mutations (15%). **Conclusions:** MOC of any grade can derive from a primary ovarian tumour precursor, and is distinct from extra-ovarian metastases. MOC is genetically diverse and advanced disease should be assessed for targetable mutations which may provide novel therapeutic options.
BRCA tumor test in ovarian cancers: The changing role of molecular pathology in the era of PARP inhibitor (PARPi) therapy.

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Background: The PARPi Olaparib has been approved in maintenance setting of recurrent platinum-sensitive and BRCA mutated, ovarian cancer (OC) patients. However, according to the striking results of SOLO 1 trial, it could be shortly proposed even to newly diagnosed BRCA mutated OC women. We report the results of the implementation of tumor BRCA test in diagnostic setting within the frame of institutional workflow for the management of OC patients. Methods: 223 women with OC were consecutively referred over 25 months to tumor BRCA test. The test was requested by gynecologic oncologist at the diagnosis of non-mucinous and non-borderline OC, upon discussion on the implications of the test result and written consent collected for each patient. Formalin-fixed paraffin embedded (FFPE) specimens of OC were tested using the automatized "Oncomine BRCA Research Assay" Next Generation Sequencing (NGS) panel. The tumor BRCA test was also performed on 5 archetypal cytological samples from ascites. Results: All the cases were considered adequate for the NGS analysis according to the tumor cell content (more than 10%) and the DNA yield extracted (more than 10 ng). The tumor BRCA test had a successful rate of 99.1%. The median Turn-Around Time (TAT) was 17 calendar days, from 33 days of the first trimester to 14 days of the last trimester of this analysis. Overall BRCA1 or BRCA2 pathogenic (P)/likely pathogenic (LP) mutations were found in 62 (28.1%) cases and variants of uncertain significance (VUS) in 25 (11.3%) cases, including 3 cases with a BRCA1 P variant and a concurrent BRCA2 VUS alteration. In detail, 47 P/LP variants and 16 VUS were identified in BRCA1 whereas 15 P/LP mutations and 9 VUS occurred in BRCA2. Complete concordance in tumor BRCA test results were seen between ascites cytological samples and matched tumors. Conclusions: The tumor BRCA test could be implemented in routine diagnostic setting, at diagnosis of non-mucinous and non-borderline OC. The test could be performed on FFPE specimens, had an high successful rate and a TAT compatible with clinical needs. The promising data on cytological samples will be confirmed in larger series.
Background: Ovarian cancer is associated with high mortality due to detection at late stages with widespread peritoneal metastases at diagnosis in a majority of patients. Ovarian cancer recurrences are primarily found in the peritoneal cavity, and peritoneal disease is the primary cause of morbidity and mortality in this disease. This pattern of tumor engraftment and recurrence indicates that the peritoneal tumor environment is distinct from other niches. Our data indicate that selective peritoneal dissemination is immunologically mediated, based on functional differences in peritoneal and systemic T cells during ovarian cancer progression. This is consistent with data in other solid tumors demonstrating that tumor immunity is driven by regional lymphocyte populations. However, less is known about the mechanisms that establish a permissive immune environment in the peritoneal cavity. We hypothesize that pathways regulating T cell recruitment and retention in the peritoneal cavity (PC) are co-opted by ovarian cancer cells to enable intraperitoneal cancer dissemination and recurrence. Methods: We have developed a novel model that uses direct in vivo labeling of peritoneal cells in an established immune-competent high grade serous murine cancer model. This functional approach enables us to identify T cell subsets retained in the PC with tumor engraftment and progression. Results: We identified high expression of CD49d (a4 integrin) as the most prevalent cell surface marker on T cells retained in the peritoneal cavity, consistent with prior published data in healthy mice and people. We demonstrated a functional role for CD49dhi in T cell retention by showing preferential binding to VCAM. A role for tumor cells mediating this interaction was observed based on enhanced binding affinity in vitro with tumor monolayers. The importance of this mechanism is supported by high VCAM expression in multiple murine and human ovarian cancer cell lines, and T cell localization to VCAM rich areas within ovarian cancer tumors in vivo. Conclusions: CD49d not only defines a lymphocyte subset with a significant role in tumor immunity but presents itself as an important potential therapeutic target to modulate T cell trafficking.
The Circulating Cell-free Genome Atlas (CCGA) Study: Follow-up (F/U) on non-cancer participants with cancer-like cell-free DNA signals.

Allen Lee Cohn, Michael Seiden, Kathryn N. Kurtzman, Earl Hubbell, Samuel Gross, Oliver Venn, Eric T. Fung, Minetta C. Liu, Eric A. Klein, Geoffrey R. Oxnard, Anne-Renee Hartman, David Michael Waterhouse; Rocky Mountain Cancer Center, US Oncology, Denver, CO; McKesson Specialty Health, The Woodlands, TX; GRAIL, Inc., Menlo Park, CA; Mayo Clinic, Rochester, MN; Cleveland Clinic Foundation, Cleveland, OH; Dana-Farber Cancer Institute, Boston, MA; Oncology Hematology Care, Inc., Cincinnati, OH

Background: A noninvasive cell-free DNA (cfDNA)-based cancer detection assay offers the hope of a blood test that might reduce morbidity and mortality of cancers, particularly those without recommended screening tests (e.g., some gynecologic cancers). CCGA (NCT02889978) is a prospective, multi-center, longitudinal, case-control study evaluating models for discriminating cancer versus non-cancer. Here, we report F/U of control participants (pts) who demonstrated a cancer-signal in CCGA. Methods: Clinically evaluable samples (N = 2508) from pts enrolled without a cancer diagnosis (dx; NC) and treatment-naive pts with newly diagnosed cancer (C) were divided into training (n = 1564; 580 NC, 984 C) and test (n = 944; 368 NC, 576 C) sets. Classification performance (cancer/non-cancer) was assessed via 3 prototype assays: whole-genome bisulfite (WGBS), whole-genome (WGS), and targeted (507 gene) sequencing. Notable outlier NC pts were identified with cancer-like scores in either ≥2 assay classification results or by the presence of known cancer drivers with ≥1 assay classification result suggesting cancer. All pts are currently in F/U in accordance with study protocol (to date: 80% with > 10 mo and 15% with > 22 mo F/U).

Results: Among training and test sets, 8 ( < 1%) NC pts were identified with a cancer-like signal. To-date, 2 have been diagnosed with a gynecologic malignancy: 1 stage IIIC clear cell endometrial carcinoma and 1 stage IIIC ovarian cancer, 3 and 2 months (mo) post-enrollment (PE), respectively. Among C pts in the study, sensitivity (at 98% specificity; WGBS) in these cancer types was: uterine/endometrial: 11% (n = 27 train) and 22% (n = 9 test); ovarian: 82% (n = 17) and 71% (n = 7). In addition, a third NC pt was diagnosed with a stage IV lung cancer 15 mo PE. Conclusions: This cfDNA-based assay detected a cancer-like signal that anticipated a clinical presentation of cancer in undiagnosed pts as early as 15 months prior to the actual dx. High specificity ( > 99%) requires accounting for undiagnosed cancers in study design and analysis. Together, these data suggest that this prototype assay may have high performance detecting a variety of gynecological and other cancers.

Clinical trial information: NCT02889978.
DPX-Survivac and intermittent low-dose cyclophosphamide (CPA) with or without epacadostat (E) in the treatment of subjects with advanced recurrent epithelial ovarian cancer (DeCidE\textsuperscript{1} trial): T cell responses and tumor infiltration correlate with tumor regression.

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Background: DPX-Survivac is a novel T cell activating therapy designed to elicit an effective immune response against recurrent ovarian cancers that express the survivin protein. The survivin specific T cells induced by DPX-Survivac can infiltrate the tumors and are associated with clinical responses. It is likely that achieving an anti-tumor effect requires a favorable ratio of T cells to tumor cells. Epacadostat (E) is an IDO1 enzyme inhibitor that may enhance effector T cell proliferation, shifting the tumor microenvironment (TME) away from an immunosuppressive state toward one supporting productive immune response.

Methods: Recurrent ovarian cancer patients with advanced and metastatic progressive disease were treated with DPX-Survivac, intermittent low dose CPA with or without E. In the Phase 1b, 53 subjects were enrolled to receive DPX-Survivac, low dose CPA and E BID. In the Phase 2, 12 subjects were randomized to receive DPX-Survivac and low dose CPA with or without E. The data on immunological responses, biomarkers, and clinical responses were analyzed in relation to the baseline sum of target lesions per RECIST 1.1. Results: The study showed that DPX-Survivac and intermittent low dose CPA with or without E can generate strong T cell responses. The infiltration of tumors with survivin-specific T cells correlates with the observed tumor regression. The sum of target tumor measurements at baseline by RECIST 1.1 correlated with observed clinical benefits. In the group of 15 patients with the baseline sum of target lesions less than 5 cm, all subjects have shown clinical benefits. Four of these subjects reached partial response and remained without progression over a prolonged period. Conclusions: The treatment studied leads to strong survivin-specific T cell responses. Infiltration of tumors by survivin-specific T cells correlated with clinical benefit in treated subjects. A predictive model based on tumor size to improve response to DPX-Survivac in recurrent ovarian cancer is being prospectively explored. Clinical trial information: NCT02785250.
Association of Ki67 expression levels and therapy outcome in low-grade serous ovarian cancer.

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**Background:** Low-grade serous ovarian cancers (LGSOC) characterize different clinical pattern and lower chemotherapy responsiveness. The expression level of Ki67 is associated with prognosis differences in this patient group. However, Ki67 has not been evaluated as prognostic marker and a predictor of therapy outcome until now. **Methods:** Patients with LGSOC and Ki67 expression results were identified in institutional database. Receiver-operator characteristics (ROC) curve analysis was performed to find cut off values of Ki67% to discriminate patients with residual tumor mass after surgery from maximal debulked patients, and platinum sensitive patients from platinum resistant patients. Odd ratios (OR) and 95% confidence intervals (95% CI) were calculated using univariate and multivariate logistic regression analysis. Two-sided tests $p < 0.05$ and are considered statistically significant at a 95% confidence interval. The statistical analysis was performed with the IBM SPSS Statistics 25.0. **Results:** A total of 68 patients with LGSOC were included. All patients underwent surgery and 15 (22.1%) patients had residual mass ($>0$ mm) after cytoreduction. Sixty-one (89.7%) patients received platinum based first-line chemotherapy. Forty-three patients revealed a recurrence $\geq 6$ months and eleven $<6$ months. Patients with Ki67 $<3.6\%$ had significantly higher therapy-free interval (TFI=6 months), (OR = 13.9, 95%CI 1.62-118.40, $p = 0.016$). In the multivariate analysis of TFI over 6 months including CA 125, age at diagnosis, peritoneal carcinomatosis and ascites ($>500$ml) Ki67 $<3.6\%$ remained significant (OR = 17.6, 95%CI 1.56-197.52, $p = 0.020$). Moreover, Ki67% $>3.6\%$ were associated with higher risk of residual mass after surgery (OR = 6.75, 95%CI 1.39-32.87, $p = 0.018$). **Conclusions:** It is the first study showing association between Ki67% expression and duration of TFI to platinum-based chemotherapy as well as outcome of the surgery in LGSOC. Further prospective trials should be planned to develop predictive models in this patients.
Real-world bevacizumab utilization and outcomes in first-line ovarian cancer.

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Background: Bevacizumab (B) is approved in combination with carboplatin and paclitaxel, followed by B monotherapy, for the treatment of advanced ovarian cancer (OC) following surgery. We sought to describe B utilization and outcomes of B in first-line (1L) OC within the US and EU. Methods: This cross-sectional study included patients who were actively receiving treatment for OC. Data were collected at a single time point from 2496 patient forms between December 2017 and March 2018 from 340 oncologists/gynecologists across the US, France, Germany, Italy, Spain, and the UK. Patients were platinum sensitive if progression was noted > 6 months after frontline platinum therapy and resistant if the interval was 0-6 months. This analysis included patients who received 1L chemotherapy (chemo) with no maintenance or 1L chemo with bevacizumab maintenance. Results: B was used in combination with chemo at 1L and as 1L maintenance monotherapy in 11% total study patients. Those receiving 1L + B were more likely to have Stage IV disease, have good performance status (PS) at diagnosis, and receive BRCA testing than patients receiving chemo only. Treatment response, platinum sensitivity, and activities of daily living are shown in the Table. Results did not vary by BRCA status. Conclusions: This study highlights differences in patient characteristics and outcomes between patients receiving/who received 1L chemo only and those receiving/who received B, however, this study was not designed to formally compare 1L treatment options.

<table>
<thead>
<tr>
<th>N who initiated 1L</th>
<th>1L Chemo Only Treatment</th>
<th>1L Chemo + B + B Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1498</td>
<td>1232</td>
</tr>
<tr>
<td>Mean age, yrs</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Stage IV, %</td>
<td>65</td>
<td>63</td>
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<tr>
<td>ECOG PS 0-1 at diagnosis, %</td>
<td>81</td>
<td>78</td>
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<tr>
<td>BRCA tested, %</td>
<td>52</td>
<td>47</td>
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<tr>
<td>BRCA positive of those screened, %</td>
<td>24</td>
<td>25</td>
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<tr>
<td>Some decrease in activities of daily living, %</td>
<td>73</td>
<td>73</td>
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<tr>
<td>N who completed 1L</td>
<td>940</td>
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<tr>
<td>Complete response, partial response or stable disease at completion of 1L, %</td>
<td>83</td>
<td>79</td>
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<tr>
<td>Platinum sensitive, %</td>
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<td>Platinum resistant, %</td>
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<td>Platinum refractory, %</td>
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<tr>
<td>Received 2L platinum, %</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Received 2L nonplatinum, %</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Mean 1L completed treatment duration, months (N)</td>
<td>4.9 (634)</td>
<td>5.1 (434)</td>
</tr>
<tr>
<td>Mean 1L completed maintenance duration, months (N)</td>
<td>8.3 (149)</td>
<td>NA (NA)</td>
</tr>
<tr>
<td>Mean time off treatment between 1-2 years of diagnosis, months (N)</td>
<td>6.3 (221)</td>
<td>8.4 (142)</td>
</tr>
</tbody>
</table>

Real-world data analysis of ovarian cancer (OC) maintenance utilization among maintenance eligible patients.

David Garofalo, Ebru Aydin, Monica Labrador, Jennifer Webster, Greg Brown, Joseph Donaldson, Hinco Jasper Gierman, Prateesh Varughese, Ash Malik, Jeffrey A. Scott; Integra Connect, West Palm Beach, FL; TESARO, Inc., Waltham, MA

Background: Approximately 1% of US women will be diagnosed with epithelial OC during their lifetime. OC patients who achieve a response to platinum-based chemotherapy may benefit from maintenance therapy, with the goal of inducing a lasting remission or extending the time interval before progression without any deleterious impact on quality of life. This analysis, based on real world data sourced from US community oncology practices, was designed to assess the current utilization of maintenance therapy among maintenance eligible patients. Methods: This analysis utilized the Integra Data Exchange (DTX) database, a deidentified data source from community oncology practice systems (EMR, practice management, paid claims). This retrospective study included 3,629 OC patients with at least two visits between 7/16/16 and 4/16/18. 398 patients who completed 2nd line or later platinum-based chemotherapy for 4-9 cycles and/or had a complete/partial response between 1/1/17 and 7/31/18 were included. Potential maintenance therapy options were monotherapy of PARP inhibitors, bevacizumab, and non-platinum-chemotherapy agents. Rate of maintenance therapy after platinum-based treatment was assessed. Results: Our real-world analysis found that 49% of 398 maintenance eligible patients received maintenance therapy at least once following response to 2nd line or later platinum chemotherapy. Among those that received maintenance, 46% received PARPi, 28% bevacizumab, and 26% non-platinum chemotherapy. Further, 56% of women with BRCA mutations received maintenance treatment, compared with 49% of women without BRCA mutations. Conclusions: Though there are several options available, 51% of OC women studied who could potentially benefit from maintenance treatment did not receive maintenance. Only 56% of BRCA mutation carriers were targeted for maintenance in the real world. Among patients that receive maintenance therapy following 2nd line or later platinum chemotherapy 46% received a PARPi based regimen. 1) Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomized controlled trial. Lancet Oncol. 2018 Aug;19(8).
Clinical outcome of sequential chemotherapy after immune checkpoint inhibitors in advanced ovarian cancer.

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Background: Immunomodulation through check point inhibition is an important treatment strategy in many cancers. In ovarian cancer (OC) response rates with immune checkpoint inhibitors (ICI) alone are around 10%. Chemotherapy antitumoural effect is driven by cytotoxicity and immunomodulatory effect. ICI treatment reduces tumour induced immune-tolerance improving immunocompetence, essential for chemotherapy effect. We chose to investigate clinical outcomes of chemotherapy post ICI in women with OC.

Methods: The Tumor Immunotherapy Program (TIP) database at the Princess Margaret Cancer Centre identified patients with OC treated with chemotherapy after ICI from 2011 to 2018. Evaluation of clinical outcomes including response rate (RR), progression free survival (PFS) and overall survival (OS) was assessed for pre ICI, ICI and post ICI.

Results: 40 women with OC were treated with chemotherapy after ICI. 90% had high grade serous histology, 7.5% carcinosarcoma and 2.5% low grade serous. Median number of pre ICI treatment lines was 3 (1-8) and 2 (1-6) in the post ICI setting. Median time of ICI initiation from diagnosis was 3 years. At ICI all patients had PS 0-1 and treated in clinical trials. 2% of the patients had platinum refractory disease, 88% had platinum resistant disease and 10% platinum sensitive disease. 50% were treated with ICI single agent, 16% were treated with ICI combined with chemotherapy, 14% ICI combo and 17% ICI in combination with other agents. Patients were treated for a median of 3 cycles (1-26). 8% experienced PR, 18% SD, no CR were seen. 67% of the patients discontinued treatment due to PD, 25% due to toxicity. Last treatment in pre ICI RR was 35%. First treatment in post ICI RR was 30%. RR for each treatment used in post ICI was 9% for liposomal doxorubicin, 25% for single agent platinum, 29% for weekly paclitaxel and 67% for chemotherapy with bevacizumab. Median PFS in the last pre ICI treatment was 6.5m and 5m in the first post ICI treatment. Median PFS and OS for all the population was 53m and 54m respectively.

Conclusions: ICI are associated with modest activity in OC, planned clinical trials exploring systematic sequential therapy integrating ICI, targeted agents and chemotherapy are needed.
Tumor stroma proportion to predict platinum chemoresistance in primary ovarian carcinomas: A prospective study.

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Background: Platinum chemotherapy resistance occurs in approximately 25% of patients with ovarian carcinoma and represents a major barrier to effective care of this patient population. To date there are no effective nor validate predictive biomarkers of chemoresistance of ovarian carcinomas. We performed a prospective trial designed to enroll patients with ovarian masses suspicious for ovarian cancer, with the goal of identifying tumor-based predictive biomarkers of platinum resistance. Methods: 60 women were enrolled on the study. Tumor specimens were collected from 49 of these women with newly diagnosed pelvic masses, of which 29 were found to have histopathologically proven primary ovarian carcinoma. Of these primary malignant cases, 24 had specimens accessible for assessment of tumor-stroma proportion and data available regarding chemosensitive vs chemoresistance status via review of the medical record using a UMN IRB-approved protocol. Tumor slices were stained with H&E and also for antibodies against two microRNAs (29b and 199a) differentially expressed in ovarian cancer cell lines. Tumor-stroma proportions were assessed by two experienced pathologists blinded to chemoresistance status, with <50% stroma scored as low proportion, >50% scored as high proportion. Results: The average age of assessed patients with malignant tumors was 62. 87.5% had high-grade epithelial carcinomas. Baseline median CA-125 was 416 (range 32-2782). 80% of ovarian cancer patients with chemoresistance had tumor stroma proportions >50%; 73.7% of cancer patients with chemosensitive tumors had proportions <50% (p-value: 0.047). Expression of miR29b or 199a did not significantly correlate with chemoresistance. Conclusions: Tumor-stroma proportion is a useful predictive biomarker of platinum chemoresistance. If validated in larger datasets, it would be a relatively inexpensive and helpful tool for tailoring treatment strategies and clinical decision-making in women with ovarian cancer.
A phase II trial of durvalumab with or without tremelimumab in patients with persistent or recurrent endometrial carcinoma and endometrial carcinosarcoma.

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Background: Monoclonal antibodies Durvalumab (D) and Tremelimumab (T) inhibit binding of programmed cell death ligand 1 (PDL1) to PD1 and inhibit activation of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), respectively, resulting in improved tumor immunosurveillance. There is rationale to study D and DT based on recent genomic and tumor microenvironment evaluation of endometrial cancer (EC).

Methods: Eligible patients (pts) were randomized to D or DT. Pts received D 1500 mg intravenously (IV) every 4 weeks (wks). DT therapy pts received D 1500 mg IV every 4 wks and T 75 mg IV every 4 wks for 4 cycles, followed by D 1500 mg IV every 4 wks until progression or unacceptable toxicities. Pts were stratified by histology with 10 carcinosarcoma or MSI-H EC pts per arm. Efficacy assessments were every 8 wks and treatment related adverse events (TRAEs) were assessed per CTCAE v.4.03. The primary endpoint was overall response rate (ORR) by RECIST v1.1. Descriptive statistics and 90% one sided CI are reported. Progression free survival (PFS) rate at 24 wks (PFS24wks) was estimated by Kaplan Meier method. Results: At planned interim analysis, 56 pts were enrolled (28 per arm). 15 pts: carcinosarcoma, 15 pts: endometrioid (3: Gr1), 14 pts: serous, and 12 pts: other histology. 5(9%) pts: MSI-H, 48(86%) pts: microsatellite stable (MSS), 3(5%): unknown. 2 pts were excluded due to early death. 27 pts per arm were evaluable for efficacy. In the D arm: 1 pt had complete response (CR)(MSS) and 3 pts had a partial response (PR) (2:MSS, 1:MSI-H) with an ORR of 14.8% (CI: 6.6-100%). The median PFS was 7.6 wks and PFS24wks was 13.3% (CI 6.1-100%). Median duration of response (DOR) was 16 wks in the D arm. In the DT arm, 2 pts achieved CR (1:MSI-H, 1:MSS) and 1 had PR (MSS). The ORR was 11.1% (CI: 4.2-100%). Median PFS was 8.1 wks, PFS24wks was 18.5% (CI 10.1-100%) and DOR was 8 wks. Grade 3 TRAEs occurred in 2 (7%) pts in D and 9 (32%) pts in DT. Grade 4 TRAEs occurred 1 (4%) pt in D and 3 (11%) pts in DT. 2 pts discontinued due to a TRAE. Most common TRAEs in total were fatigue (23%), diarrhea (20%), nausea (14%), vomiting (13%) and pruritis (11%). Conclusions: D and DT show modest activity in EC. No new safety signals were identified. Second stage accrual is ongoing. Clinical trial information: NCT03015129.
Association of total hysterectomy with survival among newly diagnosed uterine cancer patients with distant organ metastasis.

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Background: There is growing evidence that definitive local therapies (surgery or radiotherapy) may increase patient's survival for some types of metastatic cancers. However, the role of total abdominal hysterectomy (TAH) for newly diagnosed uterine cancer with distant organ metastasis has not been established. The objective of this study is to determine the potential overall survival (OS) benefit associated with TAH for distant metastatic uterine cancer. Methods: The National Cancer Database was analyzed to evaluate OS for newly diagnosed uterine cancer patients with metastasis to brain, lung, liver, bone or distant lymph node, treated with chemotherapy with or without TAH. Those without treatment, treated with definitive pelvic radiotherapy, or without baseline variables were excluded. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, and propensity score-matched analyses. In order to control the selection biases, we performed Landmark analysis, and survival analysis by the sequence of chemotherapy and TAH. Separate survival analysis was performed for patients who received chemotherapy plus definitive pelvic radiotherapy (RT) or chemotherapy plus TAH and definitive pelvic RT. Results: From 2010 to 2014, 1,809 uterine cancer patients with distant organ metastasis received chemotherapy alone and 1,388 patients received chemotherapy plus TAH. At a median follow-up of 13.4 months, addition of TAH to chemotherapy was associated with improved survival on univariate (HR 0.57; P < 0.001) and multivariate analysis (HR 0.59; P < 0.001) compared to chemotherapy alone. Propensity score-matched analysis demonstrated superior median survival (19.8 vs 11.0 months) and 2-year OS (44% vs 28%) with TAH (multivariate HR 0.59; P < 0.001). Landmark analyses limited to long-term survivors of ≥0.5, ≥1, and ≥2 years showed improved OS with TAH in all subsets (all P < 0.05). The benefit of TAH was present among not only those involving one metastatic site (HR 0.59; P < 0.001), but also those involving multiple metastatic sites (HR 0.60; P < 0.001). Separate survival analyses showed chemotherapy plus definitive pelvic RT or chemotherapy plus TAH and RT were both superior to chemotherapy alone. Conclusions: In this large contemporary analysis, uterine cancer patients with distant organ metastasis receiving TAH and chemotherapy had substantial longer survival than patients treated with chemotherapy alone. Prospective trials evaluating TAH for metastatic uterine cancer are warranted.
A phase II, open labeled, single-arm study of dose-dense paclitaxel plus carboplatin in advanced or recurrent uterine corpus cancer: KC0GG1303 study.

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**Background:** We studied the effectiveness and safety of dose-dense paclitaxel plus carboplatin in advanced or recurrent uterine corpus cancer. **Methods:** The patient eligibility criteria were women aged 20–75 years with histologically confirmed uterine corpus; FIGO stage III who had residual tumors, FIGO stage IV, and recurrence after first-line radical treatment, or second-line chemotherapy or radiotherapy. They received paclitaxel (80 mg/m^2, days 1, 8, 15) + carboplatin (area under the curve 5, day 1 every 3 weeks). The primary endpoint was the response rate (RR). The secondary endpoints were feasibility, progression-free survival, overall survival, and adverse effects. The threshold RR was set to 40%. The expected RR of this treatment was set to 60%; the number of necessary cases calculated with a type I error of 5% and power of 80% was 44. Considering the existence of dropped cases, we set the target number of cases in this study to 48. **Results:** Forty-eight patients were registered, and 45 were eligible to receive the treatment. The median age of the patients was 61 years (43–76). Twenty-two patients had recurrence; the others had primary advanced corpus cancer. On histology, there were 10 cases of serous carcinoma, 3 cases of endometrioid carcinoma G3, 2 cases of carcinosarcoma, and 2 cases of clear cell carcinoma. Twenty-eight patients (62%) could receive 6 or more cycles of chemotherapy. The RR (complete, 13 cases; partial, 20 cases) was 73.3% (60.7–86.0 95% confidence interval). **Conclusions:** Dose-dense paclitaxel plus carboplatin was safe and effective for advanced or recurrent uterine corpus cancer. Clinical trial information: R000019874 UMIN000017138.
Lynch-like syndrome in endometrial cancer: Features of a growing population.

Sushmita Gordhandas, Ryan Kahn, Brandon Paul Maddy, Becky Baltich Nelson, Gulce Askin, Paul J. Christos, Kevin Holcomb, Thomas A. Caputo, Eloise Chapman-Davis, Melissa Kristen Frey; NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY; Weill Cornell Medical College, New York, NY; Department of Biostatistics and Epidemiology, Weill Cornell Medical College, New York, NY; New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY; Advocate Christ Medical Center, Brookline, MA

Background: Current guidelines recommend screening all endometrial cancers (EC) and colorectal cancers (CRC) for defects in DNA mismatch repair (MMR). Tumor screening combined with germline genetic testing can categorize patients into three groups: intact-MMR, Lynch syndrome (LS), and Lynch-like syndrome (LLS). Our objective was to describe features of the growing population of patients with LLS in EC and compare to existing CRC literature. Methods: A systematic search of databases between 1990-2018 identified studies of EC patients with tumor testing (MMR immunohistochemistry or microsatellite instability) and germline assessment for LS. Data on clinicopathologic features was abstracted when available. Associations between LS, LLS, and intact-MMR were analyzed using descriptive statistics.

Results: The comprehensive search produced 3,427 publications; 29 met inclusion criteria. Abstracted data and features of each group are presented in the table. Conclusions: In EC, LLS closely resembles LS with younger age at diagnosis, more advanced stage and higher grade as compared to patients with intact-MMR. LLS in EC is similar to intact-MMR in regard to histology, and family history of LS-associated cancer. The CRC literature is limited, but reports LS and LLS have similar stage, grade and histology. In CRC, LS and LLS are diagnosed at a younger age, and are more likely to have family history of LS-associated cancers than intact-MMR. Features of EC with intact-MMR, LLS, and LS.

<table>
<thead>
<tr>
<th></th>
<th>Intact-MMR (N=4608)</th>
<th>MMR-deficient (N=1047)</th>
<th>LLS (N=688)</th>
<th>LS (N=212)</th>
<th>P</th>
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<tr>
<td>Mean age- years (range)</td>
<td>62 (39-65)</td>
<td>53 (34-65)</td>
<td>51 (44-58)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean BMI- kg/m² (range)</td>
<td>36 (34-37)</td>
<td>35 (33-35)</td>
<td>28 (24-32)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stage- n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>I</td>
<td>608 (81)</td>
<td>130 (70)</td>
<td>56 (67)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>45 (7)</td>
<td>19 (10)</td>
<td>10 (12)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>69 (9)</td>
<td>36 (19)</td>
<td>17 (21)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>22 (3)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Family History* n (%)</td>
<td>28 (13)</td>
<td>19 (13)</td>
<td>88 (54)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>118 (51)</td>
<td>129 (87)</td>
<td>74 (46)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Defined as Amsterdam and/or Bethesda criteria, per study
Mismatch repair deficiency as a predictor of adjuvant radiotherapy response in endometrioid endometrial carcinoma.

Stefan Kommoss, Casper Reijnen, Heidi V.N. Küsters-Vandevelde, Clemens Prinsen, Massuger Leon, Marc P.M.L. Snijders, Sara Brucker, Diethelm Wallwiener, Janice S Kwon, Jessica N. McAlpine, Johanna M.A. Pijnenborg; Department of Women’s Health, Tuebingen University Hospital, Tuebingen, Germany; Department of Obstetrics and Gynaecology, Canisius-Wilhelmina Hospital, Nijmegen, Netherlands; Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, Netherlands; Radboud University Medical Center, Nijmegen, Netherlands; University of British Columbia, Vancouver, BC, Canada; University of British Columbia and BC Cancer Agency, Vancouver, BC, Canada; Department Obstetrics and Gynaecology, Radboud University Medical Center, Nijmegen, Netherlands

Background: Adjuvant radiotherapy improves progression-free survival in intermediate and high-risk endometrial cancer. However, so far there is no evidence of improved overall or disease-specific survival after adjuvant radiotherapy. There is accumulating evidence that MMR proteins are involved in DNA repair following radiotherapy. We investigated the predictive value of MMR status in terms of survival benefit after adjuvant radiotherapy in patients with stage IB/II, grade 3 endometrioid endometrial cancer (EEC).

Methods: A retrospective multicenter cohort study was performed to compare patients with histopathologically confirmed stage IB/II grade 3 EEC with and without adjuvant radiotherapy. Patients were classified according to the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) identifying ECs as either MMR-deficient, POLE, p53abn or p53wt. Multivariable Cox regression analysis explored associations between patient characteristics, adjuvant treatment and outcome.

Results: A total of 128 patients were analyzed, including 57 patients (43.0%) with MMR-deficient EECs. Baseline characteristics were comparable, except a higher proportion of MMR-deficient EECs were stage II (36.8% vs. 15.5%, p = 0.006). Eighty-two patients (64.1%) received adjuvant radiotherapy (external beam [n = 55], vaginal brachytherapy [n = 27]). In multivariate analysis, adjuvant radiotherapy was independently associated with improved disease-specific survival in patients with MMR-deficient EECs (hazard ratio 0.19, 95%-CI 0.05 - 0.77), but not in patients with MMR-proficient EECs (hazard ratio 0.92, 95%-CI 0.37 - 2.31).

Conclusions: Adjuvant radiotherapy improved disease-specific survival in patients with MMR-deficient EECs, but not in those with MMR-proficient EECs. This study demonstrates the predictive ability of MMR IHC to identify women who likely have increased benefit from radiotherapy.
Impact of non-compliance with guidelines in early type 1 endometrial cancers management, study from FRANCOGYN group.

Hélène Costaz, Sofiane Bendifallah, Emilie Raimond, Clémentine Jankowski, Sabrina Dridi, Vincent Lavoué, Pierre Collinet, Lobna Ouldamer, Cyril Touboul, Alexandre Bricou, Marie-Martine Padeano, Catherine Loustalot, Olivier Graesslin, Marcos Ballester, Charles Coutant, Centre GF Leclerc, Dijon, France; Centre Hospitalier Universitaire de Tenon, Paris, France; CHU Reims, Reims, France; CRCLCC E. Marquis, Rennes, France; CHRU, Lille, France; University Hospital of Tours, Tours, France; Institut Gustave Roussy, Villejuif, France; APHP- Centre Hospitalier Jean Verdier, Bondy, France; Centre Georges-François Leclerc, Dijon, France; Department of Surgery/Georges François Leclerc Comprehensive Cancer Care Centre, Dijon, France; CHRU Reims, Reims, France

Background: To standardize surgical practices, ESMO-ESGO-ESTRO consensus conference published in 2016 new guidelines on the management of endometrial cancer. The main objective of this study was to evaluate the impact of non-compliance with current surgical guidelines on disease-free survival and overall survival.

Methods: 852 patients with presumptive stage I and II type 1 endometrial cancer were included in a multicenter retrospective study, conducted between January 2000 and November 2015. The main objective of this study was to evaluate the impact of non-compliance with current surgical recommendations on overall survival and disease-free survival.

Results: Our study shows that 34.3% of patients (n = 292) did not benefit from optimal surgical treatment. These patients did not have a lombo-aortic lymphadenectomy (LAL) and were at high risk of recurrence. There is a significant difference in disease-free survival in favor of patients undergoing surgery according to the recommendations, (Hazard Ratio (HR): 0.37 (Confidence interval (95% CI): 0.26-0.54), p < 0.001). In multivariate analysis, optimal surgical procedure performance is an independent factor for disease-free survival with HR at 2.04 (95% CI: 1.14-3.68), p = 0.01. There is a significant difference in overall survival in favor of patients undergoing surgery according to the recommendations, (HR: 0.31 (95% CI): 0.19-0.49), p < 0.001. In multivariate analysis, there is a trend toward significance with HR: 2.24 (95% CI: 1-5.05), p = 0.05. Older patients, patients with a larger BMI, patients with no indication of LAL at the preoperative ESMO classification, and no node involvement in are factors contributing to the decision of not to perform a LAL: p < 0.001, p = 0.03, p < 0.001 and p < 0.001 respectively. Conclusions: This study shows that patients with early type 1 endometrial cancer have improved recurrence-free survival and a statistical trend for an increased overall survival when recommended surgery is performed. Despite the current context of therapeutic de-escalation, we must strive to achieve the recommended optimal surgery, even if it requires secondary surgical revision, to avoid underestimation of patients with a poorer prognosis. To improve endometrial cancers management, amelioration of the preoperative assessment by increasing the sensitivity of emboli detection should be considered.
Genomic biomarkers of recurrence in low-grade, early-stage endometrial adenocarcinoma.

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Background: Endometrial cancer is the most common gynecologic malignancy in developed countries with over 60,000 new cases diagnosed in the United States each year. Adjuvant therapy is often omitted for low-risk, early-stage disease (FIGO stage IA, grade 1) but 1 in 20 women suffer recurrence after surgery alone. Hence, there is an important need for biomarkers of recurrence in this population to guide therapeutic management. Methods: We retrospectively analyzed 74 patients with FIGO stage 1A, grade 1 endometrial endometrioid adenocarcinoma treated at our institution with hysterectomy alone between 2009-2016. All patients had targeted genomic assessment of their tumors (OncoPanel; somatic mutations, copy number variations and structural variants across 300 cancer genes). The primary outcome of interest was freedom from recurrence (FFR). Outcomes were compared by the logrank test and survival estimates calculated by Kaplan-Meier method. Results: We identified 14 patients who recurred at a median time of 23.6 months after surgery and 60 patients without recurrence at a median follow-up of 38.9 months. Age (median 57 years; log-rank p = 0.91) and BMI (median 31 kg/m2; log-rank p = 0.21) were not associated with risk of recurrence. The median somatic mutation count in the cohort was 8. Patients with more than 8 somatic mutations had a significantly higher risk of recurrence (3-year FFR: 74% vs 90%; log-rank p = 0.004). At the level of individual genes, there were four genes that were significantly associated with recurrence: CTNNB1 (p = 0.046), RHPN2 (p = 0.020), SF1 (p = 0.044), SQSTM1 (p = 0.034). Patients with a mutation in one or more of these four genes had a significantly higher risk of recurrence (3-year FFR: 62% vs 93%; log-rank p = 0.0004). Conclusions: We have identified overall somatic mutation burden and mutations in a subset of four genes (CTNNB1, RHPN2, SF1, SQSTM1) as determined by a validated 300-gene panel used in routine clinical practice as prognostic biomarkers for patients with low-risk, early-stage endometrial endometrioid adenocarcinoma. These patients may benefit from the addition of adjuvant therapy. Validation with larger cohorts and prospective studies is warranted.
The prognostic significance of white adipose tissue inflammation in advanced-stage, high-grade, and serous endometrial cancers.

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Background: Obesity is associated with worse outcomes in endometrial cancer, but the underlying mechanisms are poorly understood. In other obesity-related cancers, white adipose tissue inflammation (WATi) is an independent predictor of shortened cancer-specific survival. We hypothesized that WATi occurs in patients with endometrial cancers and is a prognostic marker of shortened survival. Methods: We conducted a retrospective cohort study in which patients with stage III or IV grade 3 endometrioid (G3) or serous endometrial cancer were included. Eligible subjects had archived omental and/or peri-nodal adipose tissue available. WATi was detected by the presence of dead/dying adipocytes surrounded by CD68+ macrophages forming a crown-like structure (CLS). Clinicopathologic data were abstracted from medical records. For association with WATi, Wilcoxon rank sum test was used for continuous variables, Fisher’s exact test for categorical variables. Log rank test was used to assess the association of WATi and survival. Results: A total of 95 patients who underwent debulking surgery from 2001–2017 were included (median age, 67 years; range, 33-86 years). Of these, 51 (54%) had WATi. The presence of WATi was unaffected by race, tumor histology or stage. Patients with WATi had a higher median body mass index (BMI) than those without WATi (32.17 and 27.33 kg/m², respectively; P = 0.001) and were more likely to be obese (P = 0.01). Patients with the most severe WATi (n = 20) had shorter progression-free survival (PFS) and a trend suggesting shorter overall survival (OS) than those patients with less severe or no WATi (n = 75) (median PFS 15.8 vs 59.2 months, respectively, P = 0.001; median OS 33.9 vs 59.4 months, respectively, P = 0.059). Conclusions: Visceral adipose inflammation is prevalent in obese patients with advanced G3 and serous endometrial cancer. Severe inflammation was associated with significantly worse PFS.
Identifying a potential biomarker for anti-PD-1 immunotherapy in patients with advanced stage, surgically-resectable endometrial cancer.

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Background: The FDA approval of pembrolizumab for patients with MSI-H or dMMR tumors has led to the treatment of a select cohort of endometrial cancer (EC) patients. We sought to ascertain tumor immune modulatory effects in the front-line setting for advanced stage III/IV EC patients regardless of MSI-H or dMMR. The primary objective was to determine the safety of preoperative and maintenance pembrolizumab. The secondary objective was to examine pembrolizumab-induced changes in peripheral immune effector phenotype in order to identify potential biomarkers of clinical response.

Methods: In an open label, single-arm Phase I trial, 8 EC patients were treated with 2 doses of preoperative pembrolizumab IV prior to surgery followed by chemotherapy and 4 doses of pembrolizumab IV. As an initial study, pre- and post-treatment (on the day of surgery) peripheral blood was collected from 3 patients as well as a healthy control and processed for high-dimensional single-cell mass cytometry (CyTOF) using an optimized antibody panel.

Results: Six of 8 patients completed the treatment. One patient had rapid cancer progression and another had an exacerbation of comorbidities. Peripheral blood from 3 patients with pathological response were then immunoprofiled using CyTOF. Data analysis revealed that the frequencies of CD8+ T cells, B cells and CD56+CD16- NK cells were lower, whereas the frequency of CD14+CD16-HLA-DRhi classical monocytes was higher in the cancer patients compared to controls. Cancer patients had lower frequencies of circulating CD4+ and CD8+ naive T cells but higher frequencies of effector CD8+ and CD4+ T cells. Notably, the median expression of Granzyme B in CD8+ and CD4+ T cells was higher and median expression of signal regulatory protein (SIRP), CD172a-b on monocytes was lower for cancer patients compared to control. The frequencies of NK and myeloid cells expressing CD137(4-1BB), PD-1+NK cells, and PD-L1+DCs were greater in post-compared to pre-pembrolizumab.

Conclusions: This is the first trial to evaluate the use of neoadjuvant pembrolizumab in advanced stage EC patients. Here, we present peripheral immune correlative data and show an increase in markers of activation in patients with pathologic responses to pembrolizumab. Additional data from this ongoing study will help us to identify candidate predictive biomarkers. Clinical trial information: NCT02630823.

V V Pavan Kedar Mukthinuthalapati, Muhammad Zain Farooq, Shweta Gupta; John Stroger Hospital of Cook County, Chicago, IL; John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Recent studies have shown that obesity related cancers are increasing in incidence in the US as the rates of obesity rise and some cancers, like colorectal cancer, are occurring in younger age groups. We studied trends in incidence of endometrial cancer (EC), one of the obesity related cancers, in a population wide analysis. Methods: We analyzed data from all cases of EC between 2000 and 2015 from 18 US cancer registries using the National Cancer Institute’s Surveillance, Epidemiology and End Results Program. SEER*Stat was used to query the database for annual percent changes (APC), incidence ratios and percent change in incidence across different age groups, years of diagnosis, histologic subtypes, grade and race. We also studied the reported rates and trends of obesity in the US. Results: APC of age-adjusted EC incidence between 2000 and 2015 was +0.9% (95% confidence interval (CI) 1.1-0.6, p value <0.05). Incidence of EC rose from 17.8 per 100,000 to 19.7 per 100,000 during the same duration. APC for EC incidence for age groups 20-39 and >40 were +3.2% (p-value <0.05) and +0.8% (p value <0.05), respectively. For the age-group 20-39, endometrioid EC was the only histologic subtype that rose in incidence, with an APC of +5.5% and absolute percentage change of 156%. The APC of EC in 20-39 age group was more for whites (3.5%, p-value <0.05) and Asians (2.2%, p-value <0.05) than blacks (1.8, p-value <0.05). CDC reported an increase in obesity rates in adults from 30.5% in 2000 to 37.7% in 2014. Table shows trends of EC incidence in age groups 20-39 and >40 years across various histologic subtypes. (Abbreviations: S significant, NS not significant, NC non-calculable). Conclusions: Endometrial cancer, especially of endometrioid histology, is increasing in incidence and is occurring more often in the younger population. The concomitant rise in obesity rates during the same period point towards a possible causality of the increased in incidence of EC. Population based strategies are needed to decrease the trends in obesity so as to decrease the risk of endometrial cancer in younger women.

<table>
<thead>
<tr>
<th>Age group</th>
<th>20-39</th>
<th>&gt;40</th>
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<tr>
<td>Histology</td>
<td>%age change from 2000 to 2015 &amp; APC (95% CI)</td>
<td>Statistical significance</td>
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<tr>
<td>Endometrioid EC</td>
<td>+5.5 (4.5-6.6)</td>
<td>S</td>
</tr>
<tr>
<td>Serous</td>
<td>NC</td>
<td>NS</td>
</tr>
<tr>
<td>Clear</td>
<td>NC</td>
<td>NS</td>
</tr>
<tr>
<td>Mucinous</td>
<td>-62.4</td>
<td>NC</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>170.65 (154.5-188.7)</td>
<td>S</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>276.7</td>
<td>NC</td>
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p53 and p16 expression profiles reveal three prognostically relevant subgroups in vulvar cancer: A TMA based study by the AGO-CaRE-translational study group.

Linn Lena Woelber, Katharina Prieske, Christine Eulenburg, Nikolaus de Gregorio, Rüdiger Klapdor, Matthias Kalder, Elena Ioana Braicu, Sophie Fuerst, Maximillian Klar, Hans-Georg Strauss, Grit Mehlhorn, Werner Meier, Atanas Mustea, Julia Kathrin Jueckstock, Georg Schmidt, Dirk Bauerschlag, Martin Hellriegel, Sven Mahner, Eike Burandt; AGO & Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Department of Epidemiology, University Medical Center Groningen, Groningen, Netherlands; AGO & Department of Gynecology and Obstetrics, University of Ulm, Ulm, Germany; Department of Gynecology and Obstetrics, Hannover Medical School, Hannover, Germany; University Hospital Marburg, Phillipps University, Marburg, Germany; NOGGO and Department of Gynecology with Center for Oncological Surgery, Medical University of Berlin, Berlin, Germany; Department of Obstetrics and Gynecology, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; NOGGO and University Medicine Greifswald, Department of Gynaecology and Obstetrics, Greifswald, Germany; Frauenklinik Innenstadt Munich University, Munich, Germany; Frauenklinik und Poliklinik des Klinikums rechts der Isar, Technische Universität München, Munich, Germany; UFK Kiel, Kiel, Germany; University Medical Center Goettingen, Gottingen, Germany; Ludwig-Maximilians-Universität München and University Medical Center Hamburg-Eppendorf, Germany; University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Currently, there are two major pathways for tumorigenesis of vulvar squamous cell carcinoma (VSCC) – an HPV-dependent with p16 overexpression as a surrogate for HPV-associated transformation and an HPV-independent route linked to lichen sclerosus, characterized by p53 mutation. A possible correlation of HPV dependency with a favourable prognosis has been proposed. Methods: The AGO CaRE-1 study is a retrospective survey of pts with primary VSCC FIGO stage ≥1B (UICC-TNM version 6) treated at 29 gynecologic cancer centers in Germany 1998-2008 (n = 1,618). For this CaRE-translational sub-study available FFPE tissue was collected centrally (n = 648). A tissue micro array (TMA) was constructed; p16 and p53 expression was determined by immunohistochemistry (IHC). HPV status and subtype were analyzed by PCR. Results: p16 IHC was interpretable in 550 TMA spots and considered positive in 166/550 (30.2%). HPV DNA was detected in 78.4% of the p16+ tumors, with HPV 16 being the most common subtype (88.3%). Pts with p16+ tumors were younger at diagnosis (63 vs. 70 yrs for p16- tumors; p = 0 < 0.01) and showed lower rates of lymph-node involvement (29.0% vs. 39.7%; p = 0.021). p53 IHC was interpretable in 597 spots, 187/597 (31.3%) were considered positive. Pts with p53+ tumors were older at first diagnosis (71 vs. 66 yrs; p = 0.001 for p53- tumors) and showed lymph-node involvement more often (43.3% vs. 31.1%; p = 0.007). There was a relevant number of tumors with neither p16 nor p53 overexpression (221/535); while co-expression of p53 and p16 was rare (12/535). For survival analyses, three groups were defined: p53+ (n = 163), p16+/p53- (n = 151) and p16-/p53- (n = 221). 2-y-disease-free (DFS) and overall survival (OS) rates were significantly different between the groups: DFS: p53+ 47.0%; p16+/p53- 53% and p16-/p53- 65.5% (p < 0.001); OS: 70.4%, 72.6% and 82.7% (p = 0.003), respectively. Adjustment for age and nodal status showed consistent p16 and p53 effects regarding DFS. Conclusions: p16 overexpression is associated with an improved prognosis in VSCC while p53 positivity is linked to an adverse outcome. Our data provide evidence of a clinically relevant third subgroup of VSCC with a p53-/p16- phenotype showing an intermediate prognosis that needs to be further characterized.

Use of nivolumab as salvage therapy in heavily pretreated patients with gynecologic malignancies.

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Background: There are limited effective treatments for gynecologic cancer patients who have been previously treated with multiple lines of chemotherapy. Immune checkpoint inhibitor (ICI) therapy has demonstrated significant activity in certain cancers but has been inconclusive in most gynecologic malignancies. The objective of this study was to determine the impact of salvage ICI therapy in heavily pretreated gynecologic oncology patients. Methods: An IRB approved retrospective study was performed of women with gynecologic cancer treated with nivolumab on a compassionate use program between October 2015 and January 2018. Patient demographics, disease characteristics, pathology and treatment history were collected. Survival probabilities were calculated. Results: Twenty-eight women were identified. Median age at start of treatment was 63 years with a median of 4 prior lines of chemotherapy. Median ECOG status was 2. Disease site was evenly distributed among uterus, ovary and cervix. 67.9% of patients completed 3 or more cycles of treatment. Median PFS of all patients was only 2.6 months however when comparing patients who received 2-3 cycles (n = 13) with those who received 4 or more (n = 9), median PFS was statistically significant 2.4 months vs 6.4 months (p = 0.0005). When looking at treatment response, 7 patients had partial response/stable disease after 3 cycles (25%). Median PFS of the 7 “responders” was 6.6 months vs 2.5 months of the non-responders (p < 0.001). Only 1 of 9 patients with uterine cancer had a disease response and that patient’s tumor was MSI high. Five patients had low grade serous ovarian cancer. Four of them had a treatment response with a median PFS of 6.1 months (range 3.8 – 25 months). Adverse events were experienced by 68% of patients; most commonly being fatigue (46.4%), arthralgia (25%), and anemia (21.4%). Only 1 patient experienced a grade 3-4 event (a diffuse maculopapular rash). Conclusions: In patients with heavily pretreated gynecologic malignancies with suboptimal performance status, immune checkpoint inhibitor therapy may prolong survival without significant toxicity. Also, there may be a role for ICI in patients with historically chemo resistant low grade serous ovarian cancers.
BEATcc (ENGOT-Cx10/GEICO 68-C/GOG3030/JGOG1084): A randomized, open label, phase III study of cisplatin and paclitaxel chemotherapy with bevacizumab (CTx plus B) with or without atezolizumab (Atz) as first-line treatment for metastatic, persistent, or recurrent (m/r) carcinoma of the cervix (CCx).

Ana Oaknin, Laurence Gladieff, Nicoletta Colombo, Guillermo Villacampa, Mansoor Raza Mirza, Ugo De Giorgi, Leslie M. Randall, Munetaka Takekuma, Antonio González-Martín; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; GINECO, Institut Claudius Regaud, Toulouse, France; MaNGO & European Institute of Oncology and University of Milan-Bicocca, Milano, Italy; Oncology Data Science (ODysSey) Group, Vall d’Hebron Institute of Oncology, Barcelona, Spain; Nordic Society of Gynecologic Oncology (NSGO) and Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; GOG-F & University of California, Irvine, Orange, CA; JGOG, Department of Gynecology, Shizuoka Cancer Cener Hospital, Shizuoka, Japan; GEICO and Clínica Universidad de Navarra, Madrid, Spain

Background: The combination of CTx plus B is first line treatment for most patients (pts) with m/r CCx not amenable for local therapy based on GOG240 results. GOG240 regimen showed an improvement in overall survival (OS) compared to CTx alone: 16.8 vs. 13.3 months (HR 0.77, 95% CI 0.62–0.95, p = 0.007). However, further improvement in first line therapy outcomes is an unmet need. Immune-checkpoint inhibitors are breakthrough therapies in several tumor types, and their development in CCx is supported by a strong scientific rationale. Human papillomavirus infection (HPV) causes more than 90% of CCx cases. PD-L1 is a HPV biomarker and is found frequently up-regulated in CCx. Nivolumab and pembrolizumab (Pb) (anti-PD-1 antibodies) have shown response rates of 26.3% and 14.3%, respectively, in pretreated m/r CCx. This has led to the recent FDA approval of Pb in pretreated m/r CCx. The BEATcc trial (NCT03556839) evaluates the addition of the anti-PD-L1 agent Atz to GOG240 regimen as first line treatment for m/r CCx, following the synergistic rationale between anti-VEGF agents and PD-1/PD-L1 blockade. Methods: Eligible pts: m/r CC with adequate organ function. Pts will be randomized 1:1 to either Arm A (control): C 50 mg/m² + Tx 175mg/m² + B 15 mg/kg (CTx plus B) i.v. D1 Q3W or Arm B (experimental): CTx plus B + Atz 1200 mg i.v. D1 Q3W. Stratification factors: prior chemo-radiation, histology and Chemotherapy backbone (CTx vs carboplatin-Tx). Treatment is planned until disease progression, unacceptable toxicity or withdrawal of consent. Pts with a complete response after ≥6 cycles or those with unacceptable CTx toxicity may be allowed to continue only on biologics therapy. An Independent Data Monitoring Committee will analyze the safety of the first 12 pts in the experimental arm completing 2 treatment cycles. The primary endpoint is OS. The study started enrolling in October 2018 and will enroll approximately 404 pts across Europe, Japan, and the US. Clinical trial information: NCT03556839.

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Background: Cervical cancer arises in the setting of persistent infection with high-risk human papillomavirus subtypes. Many patients with early-stage and locally advanced carcinoma can be salvaged with radical surgery and chemoradiation, respectively. However, women with recurrent/metastatic disease represent a poor prognostic group with high unmet clinical needs. Incorporation of anti-angiogenesis therapy has emerged as a therapeutic option, but the survival benefit of 3.7 months over chemotherapy (CT) alone is modest (Tewari et al. NEJM 2014). Because viral tumor antigen-specific T cells reside predominantly in programmed cell death 1–expressing T-cell compartments, checkpoint inhibition may unleash a diverse antitumor T-cell response. Based on the 14.3% objective response in KEYNOTE-158, the US FDA granted accelerated approval to pembrolizumab (pembro) in June 2018 for second-line therapy and beyond. Methods: KEYNOTE-826 is a phase 3, randomized, double-blind, placebo-controlled, multinational trial of CT with pembro or with placebo for first-line treatment of recurrent, persistent, or metastatic cervical cancer. Patients not previously treated with CT for recurrence who are not amenable to curative treatment will be randomized 1:1 to CT + pembro 200 mg or placebo every 3 weeks. The CT regimen (paclitaxel 175 mg/m² + cisplatin 50 mg/m² or carboplatin AUC 5, with or without bevacizumab 15 mg/kg) will be selected by the investigator before randomization. Stratification factors include metastasis status at diagnosis, bevacizumab use (yes/no), and tumor PD-L1 status (combined positive score <1, 1 to <10, or ≥10). Treatment will continue until disease progression, unacceptable toxicity, or voluntary patient withdrawal for up to 35 cycles (~2 years). Primary endpoints are progression-free survival (PFS) per RECIST v1.1 assessed by blinded independent central review and overall survival. Secondary endpoints are objective response, duration of response, 12-month PFS, patient-reported quality of life, and safety. Enrollment is ongoing. Clinical trial information: NCT03635567.
Trial in progress: Phase II study of stereotactic body radiation therapy and atezolizumab in the management of recurrent, persistent, or metastatic cervical cancer.

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Background: There is no consistent recommendation for management of metastatic cervical cancer beyond first line therapy with chemotherapy and bevacizumab. Pembrolizumab is now approved for PD-L1 positive or MSI-H/dMMR metastatic or recurrent cervical cancer. Numerous pre-clinical studies have provided evidence to combine radiation therapy with immune checkpoint inhibition to improve response rates. The evidence is strongest for short course, hypofractionated radiation regimens. We hypothesize treatment with atezolizumab with hypofractionated radiation therapy will improve objective response rate (ORR) compared with atezolizumab alone in patients with recurrent, persistent, or metastatic cervical cancer. Methods: The study is designed as a prospective, single arm, nonrandomized, open-label, phase II trial of stereotactic body radiation therapy (SBRT) with 24 Gy in 3 fractions to patients with $\geq 2$ metastatic sites followed 1 week later by atezolizumab (1200 mg IV every 3 weeks) for patients with recurrent, persistent, or metastatic cervical cancer. Dose reductions will not be allowed. The primary objective of the study is to evaluate the ORR by Immune-Modified Response Evaluation Criteria in Solid Tumors (irRECIST) criteria following SBRT and atezolizumab. Secondary endpoints include progression free survival, overall survival, local control, and adverse events. Correlative aims include assessing blood and tissue biomarkers (i.e. PD-L1, mutation burden, TCR repertoire etc.) for association with clinical benefit. A total of 26 patients will be enrolled. An interim analysis will be performed to assess efficacy after 13 patients become evaluable. This study is open with 2 patients enrolled at the time of submission. Clinical trial information: NCT03614949.
CALLA: Efficacy and safety of durvalumab with and following concurrent chemoradiotherapy (CCRT) versus CCRT alone in women with locally advanced cervical cancer: A phase III, randomized, double-blind, multicenter study.

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Background: CCRT is the standard of care for locally advanced cervical cancer. CCRT with PD-1/PD-L1 pathway blockade may promote a more immunogenic environment through increased phagocytosis, cell death, and antigen presentation, leading to enhanced immune-mediated tumor surveillance. This Phase 3, randomized, multicenter, international, double-blind, placebo-controlled study is designed to determine the efficacy and safety of durvalumab with and following CCRT vs. CCRT alone in women with locally advanced cervical cancer (NCT03830866). Methods: The study will enroll immunotherapy-naïve adult patients (pts) with histologically confirmed cervical adenocarcinoma or cervical squamous or adenosquamous carcinoma (FIGO Stages IB2-IIB with node [N] positive and IIIA-IVA with any N) and no prior definitive surgical, radiation, or systemic therapy for cervical cancer. Approximately 714 pts will be randomized 1:1 to receive either durvalumab (1500 mg intravenously [IV]) or placebo every 4 weeks for 96 weeks. All pts will receive CCRT to the pelvis or pelvis + para-aortic radiotherapy field (45 Gy), followed by image-guided brachytherapy with cisplatin (40 mg/m²) IV or carboplatin (AUC2) IV once weekly for 5 weeks (6th dose optional). Randomization will be stratified by disease stage (FIGO Stage < III and N positive, FIGO Stage ≥ III and N negative, or FIGO Stage ≥ III and N positive) and region (US, Canada, EU, South Korea, and Japan vs. rest of the world). The primary endpoint is progression-free survival (assessed by investigator per RECIST v1.1 or histopathologic confirmation of local tumor progression). Secondary endpoints are overall survival, objective response and complete response (CR) rates, duration of response in pts with CR, incidence of local or distant disease progression or secondary malignancy, disease-related symptoms, and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CX24). Pharmacokinetics, immunogenicity, and safety of durvalumab will also be assessed. Pt enrollment is ongoing. Clinical trial information: NCT03830866.
DUO-O: A randomized phase III trial of durvalumab (durva) in combination with chemotherapy and bevacizumab (bev), followed by maintenance durva, bev and olaparib (olap), in newly diagnosed advanced ovarian cancer patients.

Philipp Harter, Mariusz Bidziński, Nicoletta Colombo, Anne Floquet, Maria Jesús Rubio Pérez, Jae-Weon Kim, Stephanie Lheureux, Christian Marth, Gitte-Bettina Nyvang, Aikou Okamoto, Alexander Reuss, Giovanni Scambia, Fabian Trillsch, Mehmet Ali Vardar, Els Van Nieuwenhuysen, Jasmine Lichfield, Paul Rugman, Philip Twumasi-Ankrah, Carol Aghajanian; Kliniken Essen-Mitte, Evangelische Huysss-Stiftung/Knappschaft GmbH, Essen, Germany; Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland; Istituto Europeo di Oncologia, Milan, Italy; Institut Bergonie, Bordeaux, France; Hospital Universitario Reina Sofia de Córdoba, Córdoba, Spain; Seoul National University Hospital, Seoul, South Korea; University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada; Department of Gynecology and Obstetrics, Medical University of Innsbruck, Innsbruck, Austria; Odense Universitetshospital, Odense, Denmark; The Jikei University School of Medicine, Tokyo, Japan; Biostatistics, Coordinating Center for Clinical Trials, Philipps-University of Marburg, Marburg, Germany; Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy; Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Klinikum der Universität München, LMU München, Munich, Germany; Medical Faculty, Department of Obstetrics and Gynecology, University of Cukurova, and Department of Gynecologic Oncology, Balcali Hospital, Adana, Turkey; UZ Leuven, Leuven, Belgium; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Gaithersburg, MD; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Ovarian cancer (OC) is the leading cause of death from gynecologic cancers in US women. Despite high response rates to first-line treatment, ~70% of patients (pts) relapse within 3 years and then remain largely incurable. First-line treatment needs to be improved to achieve long-term remission in pts and improve the cure rate. The Phase III SOLO1 trial showed a meaningful clinical benefit for olap maintenance therapy in newly diagnosed OC pts with a BRCA mutation (Moore et al N Engl J Med 2018). Preliminary data suggest that combining a PD-L1 inhibitor, anti-angiogenic and PARP inhibitor (triplet therapy) may achieve a synergistic antitumor effect. The DUO-O study (NCT03737643) evaluates the efficacy and safety of treatment combinations involving standard-of-care platinum-based chemotherapy (chemo), VEGF inhibitor bev, anti-PD-L1 antibody durva and PARP inhibitor olap, in women with newly diagnosed advanced OC. Methods: Eligible pts for this double-blind, randomized, Phase III study must have newly diagnosed, advanced, high-grade epithelial OC and either have completed primary surgery or plan to have interval debulking surgery. Depending on their tumor BRCA mutation (tBRCAm) status (determined by central test), pts will join one of two independent cohorts. Pts in the non-tBRCAm cohort (n~906) will be randomized (1:1:1) before cycle 2 to: a) chemo + bev + placebo (for 6 cycles) followed by bev (15 mg/kg [total 15 months]) + placebo maintenance treatment (IV and tablets); b) chemo + bev + durva (6 cycles) followed by bev + durva (1120 mg q3w [total 15 months]) + placebo (tablets) maintenance treatment; or c) chemo + bev + durva (6 cycles) followed by bev + durva + olap (300 mg bd tablets [24 months]) maintenance treatment. Pts in the open-label tBRCAm cohort (n~150) will receive 6 cycles of chemo + durva followed by durva + olap maintenance therapy, with optional use of bev. The primary endpoint of progression-free survival will be assessed by modified RECIST 1.1. Key secondary endpoints include overall survival, overall response rate and duration of response. Enrollment began in January 2019. Clinical trial information: NCT03737643.

ENGOT-Ov41/GEICO-69-Q/ANITA trial: A phase III randomized, double-blinded trial of platinum-based chemotherapy (CT) with or without atezolizumab (ATZ) followed by niraparib maintenance with or without ATZ in patients with recurrent ovarian, tubal or peritoneal cancer (OC) and platinum treatment-free interval (TFIp) >6 months.

Antonio González-Martín, Nicoletta Colombo, Florian Heitz, Rene dePont Christensen, Frédéric Selle, Ignace Vergote, Ana Oaknin; GEICO and Clínica Universidad de Navarra, Madrid, Spain; MaNGO & European Institute of Oncology and University of Milan-Bicocca, Milano, Italy; AGO study group & Kliniken Essen-Mitte, Department for Gynecology and Gynecologic Oncology Essen, Germany, Essen, Germany; Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark; Gyneco-Arcady Group & Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France; BGOG & University Hospital Leuven, Leuven, Belgium; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Platinum-based CT is the treatment of choice for OC patients (pts) with TFIp > 6 months suitable for platinum. Niraparib is an oral PARP inhibitor that significantly prolongs the progression-free survival (PFS) of OC pts when given as maintenance therapy after a response to platinum-rechallenge (both in gBRCA and non-gBRCA mutated pts). Atz is a humanized monoclonal antibody targeting PD-L1 that showed activity in heavily pretreated OC pts. Combination of anti-PD-L1 and CT may improve the activity of the anti-PD-L1 antibody by increasing the amount of antigens released after immunogenic cell death induced by CT. Combination of PARPi and anti-PD-L1/PD-1 has shown synergy in preclinical models and promising clinical activity in certain indications. Methods: ANITA (NCT03598270) is a phase III, randomized (1:1), double-blinded, multi-center study to assess the efficacy of the addition of Atz to platinum-based doublet CT followed by maintenance niraparib in patients with recurrent high grade serous or endometrioid OC with a TFIp > 6 months. Approximately 414 patients with ECOG 0-1, known BRCA status, at least one measurable lesion and ≤ 2 prior lines will be randomized to placebo of Atz (Arm A) or Atz (Arm B) in combination with one of three possible standard platinum-based CT regimens (investigator’s choice) followed by maintenance niraparib in combination with placebo or Atz, according to randomization, if experiencing response or stable disease by RECIST after CT. Stratification factors: 1) Platinum-based regimen (paclitaxel-carboplatin vs gemcitabine-carboplatin vs PLD-carboplatin); 2) Platinum-free interval (6-12 vs > 12 months); and 3) BRCA status (mutated vs non-mutated). Dose of Atz is 1200 mg q3 weeks or 840 mg q2 weeks depending on the platinum-based regimen selected. Niraparib initial dose (300 vs 200 mg) is decided based on body weight and platelet counts after CT according to RADAR analysis. Primary endpoint is PFS based on investigator assessment by RECIST v1.1. Clinical trial information: NCT03598270.
ENGOT-OV44/FIRST study: A randomized, double-blind, adaptive, phase III study of platinum-based therapy with dostarlimab (TSR-042) + niraparib versus standard-of-care (SOC) platinum-based therapy as first-line treatment of stage 3/4 non-mucinous epithelial ovarian cancer (OC).

Anne-Claire Hardy-Bessard, Kathleen N. Moore, Mansoor Raza Mirza, Bernard Asselain, Andres Redondo, Jacobus Pfisterer, Sandro Pignata, Diane M. Provencher, David Cibula, Anna K.L. Reyners, Lubomir Bodnar, Rosalind Margaret Glasspool, Christos A. Papadimitriou, Rami Eitan, Sileny Han, Linda R. Duska, Bj Rimel, Sebastien Hazard, Jian Chen, Eric Pujade-Lauraine; CARIO-HPCA and Cooperative Gynecological Cancer Research Group (GINECO), Plerin, France; Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Nordic Society of Gynecologic Oncology (NSGO) and Rigshospitalet University Hospital, Copenhagen, Denmark; Institut Curie and GINECO, Paris, France; Hospital Universitario La Paz-IdiPAZ and Spanish Ovarian Cancer Research Group (GEICO), Madrid, Spain; AGO Study Group Germany, Gynecologic Oncology Center, Kiel, Germany; MITO-Italy, Division of Gynecologic Oncology, Instituto Nazionale Tumori-IRCCS- Fondazione G. Pascale, Napoli, Italy; University of Montreal, Montreal, QC, Canada; CEECOG, Gynecologic Oncology Center-Department of Obstetrics and Gynecology-General University Hospital in Prague, Prague, Czech Republic; DGOG-Holland, Groningen, Netherlands; PGOG, Military Institute of Medicine, Warsaw, Poland; SGCTG/NCRI-UK, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; HeCOG-Greece, Aretaieio University Hospital, Athens, Greece; ISGO-Israel, Rabin Medical Center, Tel Aviv University, Petah Tikva, Israel; BGOG & Department of Gynaecology and Obstetrics, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; University of Virginia, Charlottesville, VA; Cedar Sinai Medical Center, Los Angeles, CA; TESARO, Inc., Waltham, MA; ARCAGY-GINECO, Paris, France

Background: Despite surgery and SOC therapy (paclitaxel and carboplatin ± bevacizumab(bev)), 5-year survival rates remain low for patients (pts) with FIGO stage 3/4 OC. Niraparib (ZEJULA) is the first selective poly(ADP-ribose) polymerase inhibitor (PARPi) approved in the US and Europe for maintenance treatment in pts with recurrent OC regardless of BRCA mut status. Preclinical data suggest synergy with PARPi + anti-PD-1 blockade. Niraparib + pembrolizumab has shown clinical efficacy in pts with platinum-resistant or secondary refractory OC regardless of biomarker status. Dostarlimab is an anti-PD-1 humanized monoclonal with clinical activity as monotherapy in early phase trials. The primary objective of the currently enrolling FIRST trial is to compare PFS (per RECIST v1.1) in pts treated with SOC + dostarlimab + niraparib to SOC. Methods: Eligible pts (up to 912) are FIGO stage 3 (with residual disease, CC0 high risk, or planned neoadjuvant therapy) or stage 4, non-mucinous epithelial OC and ECOG score ≤ 2. After 1 cycle of SOC, pts are stratified by concurrent bev use, BRCA mut/HRR status, and disease burden then randomized as 1:1:2 to 1 of 3 arms (Table). An innovative feature of ENGOT-OV44/FIRST (NCT03602859; EUDRACT 2018-000413-20) is the pre-planned adaptive study design to adapt the control arm to the evolving SOCs in OC, allowing pts in the control arm to receive up to date SOC. These adaptations will occur when practice-changing data are released. Following publication of SOLO1 results, BRCA mut pts will only be randomized to arm 2 or 3 to ensure they receive niraparib. Further adaptations may be incorporated as new data become available, leading to stop randomization in arm 1 or 2 of pts based on their biomarker status. Clinical trial information: NCT03602859.

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<th>Treatment period</th>
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<td>Arm 1*</td>
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<td><strong>Chemotherapy</strong></td>
<td><strong>Maintenance up to 3 years</strong></td>
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<td>SOC + IV placebo Oral placebo + IV Oral niraparib + IV Oral niraparib + IV dostarlimab</td>
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*No BRCA mut pts will be randomized to arm 1 following SOLO1 results.
AGO-OVAR 2.29 (ENGOT-ov34): Atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in recurrent ovarian cancer (ROC).

Frederik Marme, Patricia Pautier, Els Van Nieuwenhuysen, Alexander Reuss, Andres Redondo, Kristina Lindemann, Christian Kurzeder, Christian Marth, Alexander Burges, Klaus Pietzner, Pauline Wimberger, Nikolaus De Gregorio, Philipp Harter; AGO & National Center for Tumor Disease/Department of Gynecology, University of Heidelberg, Heidelberg, Germany; GINECO & Gustave Roussy Cancer Center, Villejuif, France; BGOG & Department of Gynaecology and Obstetrics, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; AGO & Coordinating Center for Clinical Trials, Philipps-University of Marburg, Marburg, Germany; GEICO & Hospital Universitario La Paz, Madrid, Spain; NSGO & Oslo University Hospital, Oslo, Norway; SAKK & University Hospital Basel, Basel, Switzerland; AGO-Austria & Medical University of Innsbruck, Innsbruck, Austria; AGO & Department of Gynecology, University Hospital Munich-Großhadern, Munich, Germany; AGO & Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany; AGO & Department of Gynecology and Obstetrics, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; AGO & Department of Gynecology and Obstetrics, University of Ulm, Ulm, Germany; AGO & Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany

Background: A standard non-platinum based treatment option in patients with relapsed ovarian cancer is bevacizumab in combination with paclitaxel or pegylated liposomal doxorubicin, but responses are still short-lived. Checkpoint-inhibitors as single agent have limited activity in ovarian cancer. However, the role of the checkpoint-inhibitor like atezolizumab, in addition to chemotherapy and bevacizumab in ovarian cancer is so far undefined. Methods: AGO-OVAR 2.29 is a randomized (1:1), double blinded, phase III trial evaluating the efficacy and safety of atezolizumab plus bevacizumab and chemotherapy (weekly paclitaxel or pegylated liposomal doxorubicin) compared with placebo plus bevacizumab and chemotherapy in patients with recurrent ovarian-, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after platinum-based chemotherapy or 3rd relapse. A tumor biopsy available at study entry for PD-L1 testing is mandatory. Patients are treated with chemotherapy plus bevacizumab +/- atezolizumab/placebo until progression or prohibitive toxicity. Co-primary endpoints are overall survival and progression-free survival. It is planned to randomize 664 patients. A safety interim analysis will be done when 24 patients have been randomized and completed at least cycle 1. As of 1st February 2019, 24 patients have been randomized. Clinical trial information: NCT03353831.
Phase 2 trial of tisotumab vedotin in platinum-resistant ovarian cancer (innovaTV 208).

**Haider Mahdi, Steven Robert Schuster, David M. O’Malley, Donna M. McNamara, Reshma A. Rangwala, Shang-Ying Liang, Shweta Jain, Leonardo Nicacio, Hye Sook Chon; The Cleveland Clinic, Cleveland, OH; UC Health Poudre Valley Hospital, Fort Collins, CO; The Ohio State University Comprehensive Cancer Center, Hilliard, OH; Hackensack University Medical Center, Hackensack, NJ; Genmab US, Inc., Princeton, NJ; Seattle Genetics, Inc., Bothell, WA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL**

**Background:** Ovarian cancer (OC) is the most lethal gynecologic cancer, accounting for =185,000 deaths worldwide in 2018. Most patients (pts) initially respond to platinum-based chemotherapy (chemo), but more than 50% of pts recur. Pts who recur in =6 months have platinum-resistant OC (PROC), which is associated with poor prognosis. Standard therapy for PROC includes chemo ± bevacizumab (bev). However, many pts receive single-agent chemo, which demonstrates limited response and survival (=12% ORR, 3-4 mo PFS, =12 mo OS). Therefore, there is an urgent need for novel therapeutic strategies. Tissue factor (TF) is a novel oncogenic target expressed in OC. Tisotumab vedotin (TV) is a first-in-class antibody drug conjugate comprising a TF-targeted fully human monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E. TV has shown encouraging antitumor activity and a manageable safety profile in PROC in the multicohort phase 1/2 innovaTV 201 study. innovaTV 208 is a multicenter, open-label, phase 2 trial with a safety run-in phase for a dose-dense regimen (DDR) evaluating the efficacy and safety of TV in pts with PROC. **Methods:** innovaTV 208 will enroll =142 adult pts with platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer; measurable disease by RECIST v1.1; and ECOG score 0-1. Eligible pts must have received bev-containing treatment for OC. Pts with platinum-refractory disease, increased risk of bleeding, active ocular surface disease, or grade >1 peripheral neuropathy will be excluded. A safety run-in phase for the DDR will be performed in up to 12 pts who received =5 prior treatment regimens for PROC. In the DDR, TV will be given at previously decided lower doses IV 3Q4W for the same dose intensity as the standard 1Q3W dose; the primary endpoint is incidence of DLTs. In phase 2, pts who received =1 prior cytotoxic chemo regimen for PROC will be randomized to receive TV administered as IV 1Q3W or as IV 3Q4W, if shown to be tolerable. The primary endpoint for phase 2 is confirmed ORR by RECIST v1.1. Secondary endpoints include DOR, time to response, DCR, CA-125 response rate by GCIG criteria, PFS, OS, pharmacokinetics, and safety. Clinical trial information: NCT03657043.
ENGOT-OV43/KEYLYNK-001: A phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA nonmutated advanced epithelial ovarian cancer.

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Background: There is a significant unmet need to develop new regimens for BRCA1/2 nonmutated advanced ovarian cancer (OC). The PARP inhibitor olaparib is approved for women with platinum-sensitive, recurrent OC regardless of BRCA1/2 status and, more recently, for newly diagnosed women with BRCA mutated OC. In the TOPACIO/KEYNOTE-162 study, the combination of the PD-1–blocking antibody pembrolizumab (pembro) and niraparib demonstrated efficacy in platinum-resistant relapsed OC irrespective of BRCA1/2 status. ENGOT-OV43/KEYLYNK-001 (ClinicalTrials.gov, NCT03740165) is a phase 3, randomized, double-blind, active- and placebo-controlled study of pembro plus paclitaxel-carboplatin chemotherapy (CT) followed by olaparib maintenance for first-line treatment of patients with BRCA1/2 nonmutated advanced epithelial OC (EOC). Methods: Patients with stage III or IV BRCA nonmutated EOC, primary peritoneal cancer, or fallopian tube cancer will be stratified by surgery status (no residual tumor after primary debulking surgery [PDS], residual tumor after PDS, or planned interval debulking), bevacizumab use, and PD-L1 status (combined positive score $\geq 10$ or $< 10$). After one lead-in cycle of CT, patients will be randomized 1:1:1 to receive: CT + pembro followed by olaparib maintenance; CT + pembro followed by placebo; or CT + placebo followed by placebo. The CT regimen will be administered for 5 cycles, and pembro 200 mg Q3W will be administered for 35 infusions. Olaparib 300 mg BID maintenance therapy will start after the end of CT as concomitant treatment with pembro until discontinuation or for 2 years if the patient has a complete response. Bevacizumab use is permitted at investigator’s discretion and determined prerandomization. Primary endpoints are investigator-assessed progression-free survival (PFS) per RECIST 1.1 criteria and overall survival. Key secondary endpoints are PFS per RECIST 1.1 assessed by blinded independent central review, PFS after next-line treatment, and safety. Enrollment is currently ongoing. Clinical trial information: NCT03740165.
Phase I (safety assessment) of durvalumab (MEDI4736) with focal sensitizing radiotherapy in platinum resistant ovarian, primary peritoneal or fallopian tube epithelial carcinoma.

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Background: Radiation (RT) of malignant neoplasms can induce immunogenic tumor cell death, alter the tumor micro-environment and enhance recruitment of anti-tumor T cells. Co-administration of focal RT and an immune checkpoint-inhibiting agent may overcome immune-suppressive signals and potentiate systemic responses. A phase I study is underway to assess the safety of RT combined with PD-L1 inhibition in patients with recurrent epithelial ovarian/fallopian tube/peritoneal carcinomas (OV).

Methods: Women with platinum resistant epithelial OV, ECOG PS 0/1 and ≤ 2 lines of treatment in the platinum-resistant setting are eligible. 1 lesion evaluable by RECIST criteria (v 1.1) and 2 additional lesions suitable for RT (minimal treatment volume 4cc) are required. Pre- and on-treatment biopsies for correlative studies are mandatory. The primary objectives are to assess the safety and tolerability of the focal RT combined with the immune checkpoint inhibitor, durvalumab (D), as defined by dose-limiting toxicities (DLTs), and to define the maximum tolerated RT dose and treatment schedule. The secondary objectives are to evaluate the clinical activity of focal RT and D (RECIST (v 1.1), GCIG CA-125, and immune-related response criteria), progression free survival and overall survival. D 1500 mg delivered intravenously every 28 days = one cycle. RT to the 2 selected target lesions is delivered 24-36 hours prior to the infusion of D. The RT starting dose-level is 24Gy (in 4 fractions) per lesion (given Days -1, 1 and 28 of Cycle 1 and Day 1 of Cycle 2). A 3+3+3 design will permit more extensive exploration of toxicity if DLTs are observed (Table). Investigator assessed DLTs are defined by CTCAE v. 4.03 and include the following: any grade ≥3 adverse event suspected to be related to D or RT (necrosis or recall reactions at previously irradiated sites, RT induced bowel perforation, any unexpected grade 3 or greater toxicity at the site of RT), any grade ≥2 allergic or autoimmune event that involves vital organ function, and any other grade 3 allergic or autoimmune events that do not resolve to grade 1 before the next scheduled dose of D. Treatment may continue up to 12 months. Enrollment began August 2018. To date, no DLTs have been observed at dose level 1 (n= 3) and enrollment is ongoing. Clinical trial information: NCT03283943.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Durvalumab dose (q 28 days)</th>
<th>Total Radiation dose given per target lesion (2 targets per patient)</th>
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<tbody>
<tr>
<td>1 (starting dose level)</td>
<td>1500 mg</td>
<td>24 GY/4 fractions</td>
<td>3+3+3</td>
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<tr>
<td>2</td>
<td>1500 mg</td>
<td>32 GY/4 fractions</td>
<td>3+3+3</td>
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EUDARIO/ENGOTov-48: A European multicenter randomised phase II trial on the combination of the HSP90 inhibitor ganetespib with carboplatin followed by maintenance treatment with niraparib (+/- ganetespib) compared to platinum-based combination-chemotherapy followed by niraparib in relapsed platinum-sensitive ovarian cancer patients.

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Background: Carboplatin (C) mainly acts by forming interstrand crosslinks (ICL) within the DNA double helix, which can only be removed by the Fanconi Anemia (FA) pathway. HSP90 inhibitors destabilise a number of HSP90 client proteins, such as those governing the FA DNA repair pathway and the G2/M checkpoint (e.g. Chk1 and Wee1). Kramer et al. (Cell Death Differ, 2017) showed that the HSP90 inhibitor Ganetespib (G) virtually eliminates a functional FA DNA repair complex, therewith preventing the repair of DNA ICL in vitro and vivo. In parallel, G abrogated Chk1 and Wee1 expression and circumvented a G2/M arrest. Consequently, cells with unrepaired DNA damage rushed into mitosis, which resulted in massive tumour cell death. Furthermore, HSP90 inhibition has been shown to reduce the amount of BRCA1 in the cell therewith broadening sensitivity towards PARPi and preventing acquired PARP resistance. Our trial approach is tested in ovarian carcinomas with a mutant p53 background. EUDARIO (EUDRACT 017-004058-40) is funded by the European Commission (FP7 project GANNET53). Methods: Eligible patients have relapsed platinum-sensitive ovarian cancer, no limits in prior lines, high-grade (but clear cell) histology or carcinosarcoma, disease measurable or evaluable according to RECIST 1.1. Patients are randomised into 3 treatment arms (1:1:1), a) control arm: C+Gemcitabine or C+Paclitaxel (q3w, 6 cycles, investigator’s choice) followed by Niraparib, b+c) 2 experimental arms: C (AUC5, d1) + G (150mg/m², d1) q3w 6 cycles followed by either Niraparib alone (arm b) or by Niraparib+G (arm c; G at 100mg/m² weekly, limited to 9 months). Niraparib (200/300mg/day) is given in case of SD, PR or CR after platinum-based treatment until disease progression. The main analysis will combine both experimental arms b+c and jointly compare them against arm a using log-rank test. Primary endpoint is PFS, secondary endpoints are PFS2, TFST, TSST, safety, ORR, PRO, OS. The first patient was dosed in January 2019. Clinical trial information: NCT03783949.
Phase Ib clinical investigation of intraperitoneal ipilimumab and nivolumab in patients with peritoneal carcinomatosis due to gynecologic malignancy.

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Background: The peritoneal cavity is a frequent site of metastasis and recurrence for gynecologic malignancy, including approximately 80% of epithelial ovarian cancer (EOC) that presents with peritoneal involvement. These observations have led to the use of intraperitoneal (IP) route of administration for traditional cytotoxic chemotherapy. IP immunotherapy is a recognized but under explored area of clinical investigation with many potential advantages. Indeed, IP administered antibodies in both animals and human subjects are associated with absent or much lower peripheral blood concentrations. In addition to higher local and lower systemic exposure, other theoretical advantages include preferential binding to intraperitoneal and intratumoral immune cells, and absorption through the draining lymphatics of the peritoneal cavity. These pelvic and peri-aortic lymph nodes represent the most relevant lymphoid organs and as such may be the ideal site for T cell activation and trafficking back to the peritoneal tumor. Methods: The trial (NCT03508570) is a single-institution phase Ib trial to determine the recommended phase II dosing (RP2D) of IP administration of nivolumab in combination with ipilimumab. For the purpose of dose finding, the assessment period for dose limiting toxicity (DLT) is 12 weeks. The trial starts with a safety lead-in to confirm the safety of IP nivolumab before combining it with ipilimumab. A maximum sample size of 12 will be used to find the RP2D for nivolumab, up to 24 patients for the combination, and a planned expansion will be carried out such that at least 12 EOC patients are treated at RP2D of the intraperitoneal combination strategy. The secondary objectives are to describe the pharmacokinetics and toxicities, and to estimate the clinical benefit rate for the expansion cohort. Translational objectives include description of immunologic and biologic changes in serial blood and IP fluid collections as well as pre and on-treatment biopsies. Eligibility criteria include recurrent or progressive biopsy-confirmed platinum resistant EOC or other gynecologic cancer with measurable peritoneal disease, and no exposure to prior treatment with checkpoint inhibition. Enrollment began in January of 2019 with 3 subjects enrolled to date. Accrual update will be provided at the annual meeting. Clinical trial information: NCT03508570.
A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer.

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Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. Pembrolizumab (PEMBRO) is a monoclonal antibody targeting programmed cell death receptor 1 (PD-1). Preliminary analyses of a phase 1b/2 study of LEN + PEMBRO showed promising antitumor activity and a manageable safety profile in advanced endometrial cancer (EC).

Methods: A multicenter, randomized, open-label, phase 3 study (KEYNOTE-775/E7080-G000-309; clinicaltrials.gov NCT03517449) will evaluate efficacy and safety of LEN + PEMBRO vs treatment of physician’s choice (TPC) in patients with advanced EC. Patients must be aged ≥ 18 years, have advanced EC that progressed after 1 prior platinum-based therapy, have measurable disease per RECIST v1.1, and an Eastern Cooperative Oncology Performance Status ≤ 1. Patients must have mismatch repair (MMR) status confirmed by central laboratory via immunohistochemistry on archived or fresh tumor biopsy. ~780 patients (~120 MMR-deficient; ~660 MMR-proficient) will be randomized to receive LEN 20 mg orally once daily and PEMBRO 200 mg intravenously (IV) every 3 weeks (Q3W) or TPC. Patients will be randomized first according to MMR status; MMR-proficient patients will be further stratified by ECOG PS, geographic region, and prior history of pelvic radiation. TPC is either doxorubicin 60 mg/m² by IV Q3W or paclitaxel 80 mg/m² by 1-hour IV infusion weekly (3 weeks on/1 week off). The dual primary endpoints are progression-free survival (PFS; per RECIST v1.1 by blinded independent central review) and overall survival (OS). The PFS analysis will occur at the planned interim analysis (~363 OS events in MMR-proficient patients; ~524 PFS events), and the study will have 99% power to detect a hazard ratio (HR) of 0.55 with a 1-sided 0.0005 significance level. A final OS analysis will occur at 518 OS events, when the study will have 90% power to detect a HR of 0.75 with a 1-sided 0.0245 significance level. Secondary endpoints include objective response rate, health-related quality of life, safety and tolerability, and pharmacokinetics. Clinical trial information: NCT03517449.
AtTEnd/ENGOT-en7: A multicenter phase III double-blind randomized controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer.

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Background: Prognosis of advanced/recurrent endometrial cancer (EC) is poor with median survival of 12-15 months for patients with measurable disease. Treatment options are limited, with primary management being chemotherapy with carboplatin and paclitaxel. EC is known to be one of the tumor types with highest mutational load. Ultra- and hyper-mutated EC, which harbor POLE and mismatch repair gene defects respectively, have shown peri-tumoral T cell infiltration and high expression of PD-1 and PD-L1 proteins, suggesting that immune regulation may enhance specific T cell responses and result in improved anti-tumour immunity. Preliminary data in EC patients have shown tumour control activity of the PD-L1 targeting agent atezolizumab.

Methods: 550 patients with newly diagnosed, advanced stage III/IV or recurrent EC will be accrued during a period of 24 months with a 1:2 randomization ratio into two arms: i. control group receiving standard chemotherapy plus placebo IV every 21 days up to 6/8 cycles followed by placebo until progression; ii. experimental group receiving standard chemotherapy plus 1200 mg atezolizumab IV every 21 days up to 6/8 cycles followed by atezolizumab until progression. Standard chemotherapy will consist of 175 mg/m² paclitaxel plus AUC5/6 carboplatin. Stratification factors are: histology, disease stage, microsatellite status, country of experimental site. The study is planned to demonstrate a survival increase and is equally powered for PFS. Secondary endpoints include ORR, duration of response, PFS2, quality of life, adverse events and compliance. The study is sponsored by MaNGO group and will involve sites from ENGOT and GCIG networks across Europe, Japan, Australia and New Zealand. Currently, the trial is open in Italy and in Switzerland where a total of 6 patients have been enrolled. Clinical trial information: NCT03603184.
NRG GYO12: A randomized phase II study comparing single-agent olaparib, single agent cediranib, and the combination of cediranib/olaparib in women with recurrent, persistent or metastatic endometrial cancer.

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Background: The Cancer Genome Atlas and others identified genomic events suggesting that endometrial cancer (EC) should be susceptible to DNA repair inhibition. Mutations in classical homologous recombination genes occur in 22% of EC, ARID1A 41% and PTEN loss occurs in 55% of EC. Data from pre-clinical models suggest poly ADP-ribose polymerase (PARP) inhibitors alone or in combination may be an effective therapeutic strategy in EC (Hansen 2016). Combinations of angiogenic inhibitors and PARP inhibitors have demonstrated synergistic effects and have been well tolerated in other tumor types. This study has been designed to compare 2 experimental arms exploring DNA repair inhibition versus cediranib alone which has previously shown promising activity in GOG 229J (Bender 2015).

Methods: This is a multicenter randomized three arm study for patients with recurrent, metastatic or persistent EC. Patients are randomized 1:1:1 to cediranib PO 30 mg OD; olaparib 300 mg PO BID or the combination of cediranib 20 mg PO OD with olaparib 300 mg PO BID. All treatment cycles are 28 days. Primary endpoint is progression free survival (PFS). The study is powered to detect an increase in median PFS from 3.6 (based on cediranib alone) to 7.2 months with 90% power, using a one-sided test with \( \alpha = 0.05 \) per comparison. Forty patients will be enrolled per arm, with an interim futility analysis planned. Eligibility includes endometroid, serous, and mixed histology EC; at least 1 prior line of chemotherapy (no more than 2 lines for metastatic disease), prior endocrine or immunotherapy is allowed; ECOG PS \( \leq 2 \); adequate hepatic, bone marrow, coagulation and renal function. Archival tumor tissue and blood samples are being collected for translational studies. The study is open across the NRG network; 24 patients are enrolled to date. Amendments are planned to include additional arms investigating combination strategies targeting DNA repair and angiogenesis. Clinical trial information: 03660826.