Abstract O009/#786 Table 1

Efficacy endpoint/ Statistical test	Efficacy population		ITT population	
	Rucaparib (n=220)	CT (n=105)	Rucaparib (n=233)	CT (n=116)
Median PFS[a] (95% CI), months	7.4 (7.3–9.1)	5.7 (5.5–7.3)	7.4 (6.7–7.9)	5.7 (5.5–6.7)
Stratified Cox proportional hazard model	HR 0.639 (95% CI 0.489–0.835); P=0.0010		HR 0.665 (95% CI 0.516–0.858); P=0.0017	
RECIST ORR[b], n/N (%) [95% CI]	85/211 (40.3) [33.6–47.2]	31/96 (32.3) [23.1–42.6]	85/224 (37.9) [31.6–44.7]	32/106 (30.2) [21.7–39.9]
Stratified Cochran-Mantel-Haenszel test	P=0.1287		P=0.1250	

[a]Primary endpoint; [b]Secondary endpoint; only patients with measurable disease were included in this analysis.
CT, chemotherapy; HR, hazard ratio; ITT, intent to treat; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

Results 233 pts were randomized to rucaparib and 116 to CT (visit cutoff Sep 30, 2020); 179 (51.3%) had platinum-resistant, 96 (27.5%) had partially platinum-sensitive, and 74 (21.2%) had fully platinum-sensitive disease. 23 pts (6.6%) with BRCA reversion mutations and 1 pt without a BRCA mutation were excluded from the efficacy population. Median PFS was significantly longer with rucaparib vs CT in both the efficacy and ITT populations (Table). In an exploratory analysis of pts with BRCA reversion mutations, median PFS was shorter with rucaparib (n=13) vs CT (n=10); 2.9 vs 5.5 months, hazard ratio 2.769 (95% CI, 0.989–7.755). ORR was not significantly different between the rucaparib and CT arms in both populations (Table). Adverse events were consistent with the known safety profiles of rucaparib and CT.
Conclusions Patients with BRCA-mutated advanced, relapsed OC who received rucaparib had a significant improvement in PFS vs SOC CT. No new safety signals were identified. This is the first prospective report from a randomized trial demonstrating that the presence of a BRCA reversion mutation predicts for primary resistance to rucaparib.

O010/#784 ADJUVANT CHEMOTHERAPY FOLLOWING CHEMO-RADIATION AS PRIMARY TREATMENT FOR LOCALLY ADVANCED CERVICAL CANCER COMPARED TO CHEMO-RADIATION ALONE: THE RANDOMISED PHASE 3 OUTBACK TRIAL

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Background Cervical cancer is a common cause of cancer-related death among women worldwide. Standard treatment for locally advanced disease is chemoradiation. However, a significant percentage of women still relapse and die from the development of distant metastatic disease. OUTBACK was designed to determine the effects of giving adjuvant chemotherapy after chemoradiation on survival.
Methods OUTBACK is an international randomized phase 3 trial of the Gynecologic Cancer InterGroup (GCIG). Participating groups (countries) included ANZGOG (Australia and New Zealand), NRG (USA, Saudi Arabia, Canada, China), and Singapore. Eligible women had locally advanced cervical cancer (FIGO 2008 stage IB1 & node positive, IB2, II, IIIB or IVA) that was suitable for primary treatment with chemo-radiation with curative intent. Women were randomly assigned to either standard cisplatin-based chemo-radiation (control) or standard cisplatin-based chemo-radiation followed by adjuvant chemotherapy (ACT) with 4 cycles of carboplatin and paclitaxel, after stratification for nodal status, participating site, FIGO stage, age, and planned extended-field radiotherapy. The primary end point was overall survival (OS) at 5 years. Secondary endpoints included progression-free survival (PFS); adverse events (AE); and patterns of disease recurrence. The target sample size of 900 provided 80% power with 95% confidence to detect an improvement in OS at 5 years from 72% (control) to 80% (ACT), with some over-accrual to account for non-compliance with ACT and loss to follow-up.
Results 919 of 926 women recruited from April 2011 to June 2017 were eligible and included in the primary analysis: 463 assigned ACT, 456 control. ACT was started in 361 (78%) women assigned to receive it. Median follow-up was 60 months (IQR 45–65). OS at 5 years was similar in those assigned ACT versus control (72% vs 71%, difference <1%, 95% CI -6 to +7; P = 0.91). The hazard ratio for OS was 0·91, (95% CI 0.70 to 1.18). PFS at 5 years was similar in those assigned ACT versus control (63% vs 61%, difference 2%, 95% CI -5 to +9; P = 0.61). The hazard ratio for PFS was 0·87, (95% CI 0.70 to 1.08). AE of grade 3–5 within a year of randomisation occurred in 81% who were assigned and received ACT versus 62% assigned control. There was no evidence of differences between treatment groups in AE beyond 1 year of randomisation. Patterns of disease recurrence were similar in the two treatment groups.
Conclusion Adjuvant chemotherapy given after standard cisplatin-based chemoradiation for women with locally advanced cervical cancer did not improve OS or PFS.

Plenary 5: Oral Abstract Presentations

O011/#287 PROGNOSTIC SIGNIFICANCE OF 'P53 SIGNATURE' (FIELDS OF DYSPLASIA) AND IN SITU MARGIN STATUS IN ORGAN-CONFINED HPV-INDEPENDENT P53 ABNORMAL VULVAR SQUAMOUS CELL CARCINOMA

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Objectives Vulvar squamous cell carcinomas (VSCCs) can be stratified by HPV and TP53 mutation status to prognostically significant risk groups using p16 and p53 IHC. Treatment guidelines do not address optimal management of high molecular risk (TP53 mutated) pre-invasive neoplasia found at resection margins. Herein, we used p53 IHC to evaluate margin status in a retrospective cohort of HPV-independent (HPV-I) p53abn VSCCs.
Methods Surgically staged I-II HPV-I p53abn VSCCs from a single institution underwent margin (re)assessment using p53 IHC. Cases were segregated to i) morphologic dVIN at margin ii) vulvar skin with abnormal p53 IHC staining at margin and subtle morphologic features insufficient for dVIN iii) margins clear by morphology & p53 IHC TP53 mutation status was evaluated by next-generation sequencing (group ii). Clinicopathologic and outcome data was collated using a standardized collection tool.

Abstract O011/#287 Table 1 Clinicopathologic characteristics of organ-confined p53abn vulvar squamous cell carcinoma by margin status

Group	Total		(i) dVIN margin +		(ii) p53abn* margin+		(iii) Margins clear		p ⌘
	n	(%)	n	(%)	n	(%)	n	(%)	
Total	57	100.0%	16	28.1%	11	19.3%	30	52.6%	
Follow-up (years, median)	4.5		4.1		3.8		5.3		1*
Age [years, median, (SD)]	78.8	(12.5)	75.0	(13.5)	78.8	(15.6)	79.8	(9.8)	0.185*
Stage I	57	100.0%	16	100.0%	11	100.0%	30	100.0%	
II	1	1.8%	0	0.0%	0	0.0%	1	3.3%	
Tumour size [cm, median (SD)]	2.6	(2.5)	1.8	(3.8)	1.8	(2.0)	3.5	(2.0)	0.2*
Died of disease	14	24.6%	5	31.3%	3	27.3%	6	20.0%	0.309▪
Recurrent disease	28	49.1%	10	62.5%	8	72.7%	9	30.0%	0.006▪

☆ insufficient morphologic features for dVIN diagnosis
⌘ *p* values are calculated between (i+ii) and (iii)
✱ Mann-Whitney U-test
▪ Fisher's exact test
▲Chi-Square
SD, standard deviation; dVIN, differentiated vulvar intraepithelial neoplasia; abn, abnormal; IHC, immunohistochemistry; LVI, lymphovascular invasion; PNI, perineural invasion.

Results 57 HPV-I p53abn VSCCs, FIGO stage I-II, were evaluated (Table 1). TP53 mutations were identified in 10/11 cases with subtle morphologic abnormalities insufficient for dVIN diagnosis and p53abn IHC extending to margins (synonymous with p53 signature). Positive in situ margins (dVIN and p53 signature) were observed in 27 (47.4%) of cases and significantly associated with disease recurrence (p=0.006).
Conclusions These findings demonstrate: • p53abn IHC staining at margins, without sufficient morphologic features for dVIN diagnosis, predicts an equivalent or higher recurrence risk compared to morphologic dVIN • p53 IHC is critical for accurate assessment of margin status in HPV-I p53abn VSCC • The need to evaluate biologically-informed treatment approaches for high molecular risk (TP53 mutated) disease in prospective interventional studies

O012/#207 MULTI-OMICS CHARACTERIZATION OF MOLECULAR FEATURES CORRELATED TO PERINEURAL INVASION IN CERVICAL CANCER

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Objectives Perineural invasion (PNI) is an important pathological feature of cervical cancer, which is often associated with poor prognosis. However, the underlying molecular mechanisms remain unknown.
Methods We performed whole-exome sequencing on 42 pretreatment tumor samples (PNI:20; nonPNI:22) along with the matched blood samples and RNA-seq sequencing on 43 tumor samples (PNI:21, nonPNI:22). We performed an integrated bioinformatic analysis to identify at the gene, pathway, omics and tumor-microenvironment levels to explore the genetic determinants responsible for PNI in cervical cancer.
Results Among 45 known cervical cancer driver genes, we detected 34 in at least one patient in this cohort, including PIK3CA as the most frequently mutated genes (38%), and followed by KMT2C (19%). Comparing with nonPNI, PNI tumors harbor significantly more FBXW7 loss-of-function mutations (PNI:6; nonPNI:1, p=0.04) and copy-number gain of NKX2–1, PDGFRA (NKX2–1, p=0.007; PDGFRA, p=0.04). PNI tumors show significantly lower tumor mutation burden than non-PNI (p = 0.048). We identify 318 genes significantly dysregulated in PNI tumors relative to non-PNI tumors (upregulated: 118; downregulated: 200, $|\log_2 FC|>1$, FDR < 0.25), including downregulation of two tumor-suppressor genes, SOX17 and PTCH1. Interestingly, we find the deactivation of immune-related hallmark pathways in PNI tumors, including interferon_gamma_response, interferon_alpha_response and IL2_STAT5_signaling. Consistently, compared with nonPNI, there are significantly fewer $CD8^+$ cells in the tumor microenvironment of PNI tumors (p=0.008).
Conclusions Loss-of-function mutations in FWXB7 and downregulation of SOX17 and PITH1 are likely responsible for PNI in cervical cancer, and a tumor immunosuppressive environment may also be a contributing factor.

O013/#573 TISOTUMAB VEDOTIN (TV) + BEVACIZUMAB OR PEMBROLIZUMAB OR CARBOPLATIN IN RECURRENT/METASTATIC CERVICAL CANCER (R/MCC): PHASE 1B/2 ENGOT-CX8/GOG-3024/INNOVATV 205 STUDY DOSE-ESCALATION RESULTS

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Objectives Tisotumab vedotin (TV) monotherapy has shown a manageable and tolerable safety profile with clinically meaningful and durable antitumor activity in previously treated r/mCC (Lancet Oncol. 2021;22:609–619). The potential of investigational TV combination regimens in r/mCC was assessed in a multi-cohort phase 1b/2 trial (NCT03786081).
Methods Patients with r/mCC with progression on/after or ineligible for/intolerant to standard-of-care were treated with escalating doses of TV + bevacizumab (Arm A) or pembrolizumab (Arm B) or carboplatin (Arm C) all given Q3W (figure 1). Primary objectives were to determine recommended phase 2 dosing (RP2D) and evaluate safety/tolerability.
Results A maximum tolerated dose was not reached with any combination. In Arm A, 15 patients received 9 cycles (median) for both TV and bevacizumab. Grade≥3 adverse events (AEs) occurred in 5 patients (33%). The RP2D was TV 2.0 mg/kg + bevacizumab 15 mg/kg Q3W. Five patients had confirmed objective response (cOR). In Arm B, 13 patients received a median of 5 cycles of TV and 4 cycles of pembrolizumab. Grade≥3 AEs occurred in 12 patients (92%). The RP2D was