Abstract 0011/#287 Table 1 Clinicopathologic characteristics of organ-confined p53abn vulvar squamous cell carcinoma by margin status

Group	Total		(i) dVIN margin +		(ii) p53abn ^a 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

0012/#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 pre-treatment 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, $|\log_2FC|>1$, $FDR < 0.25$), 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.

0013/#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 $\geq$ 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 $\geq$ 3 AEs occurred in 12 patients (92%). The RP2D was

Abstract 0013/#573 Figure 1

AUC, area under the curve; DL, dose level; DLT, dose-limiting toxicity; TV, tisotumab vedotin.

Drugs administered IV on day 1 of 21-day cycle.

Patients were treated for at least 2 cycles to evaluate DLTs.

Escalation to the next DL was permitted when fewer than 1 in 3 patients at the current DL experienced a DLT.

The recommended phase 2 dose (RP2D) was highest planned DL reached with DLTs in no more than 1 in 6 patients.

TV 2.0 mg/kg + pembrolizumab 200 mg Q3W. Two patients had cOR. In Arm C, 13 patients received 5 cycles (median) of TV + 4 cycles of carboplatin. Grade ≥ 3 AEs occurred in 8 patients (62%). The RP2D was TV 2.0 mg/kg + carboplatin AUC 5 Q3W. Four patients had cOR.

Conclusions TV plus bevacizumab, pembrolizumab, or carboplatin was tolerated and had an acceptable safety profile with encouraging activity in patients with r/mCC.

0014/#828

EFFICACY AND SAFETY OF SOCAZOLIMAB IN RECURRENT OR METASTATIC CERVICAL CANCER: RESULTS FROM THE PHASE I TRIAL FOLLOWED BY AN EXPANSION STUDY

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Objectives This study (ClinicalTrials.gov identifier: NCT03676959) is a phase I plus expansion study investigating the antitumor activity and safety of socazolimab, an anti-PD-L1 monoclonal antibody, in recurrent or metastatic cervical cancer.

Methods All patients received one or more lines of chemotherapy for recurrent or metastatic disease. Patients received 5mg/kg socazolimab every 2 weeks as one cycle for total of 24 cycles. Tumor imaging was performed every 8 weeks for 48 weeks. The primary end points were safety and objective response rate (ORR) assessed per RECIST 1.1 evaluated by independent radiology review committee (IRC). Progression free survival (PFS), duration of response (DOR) and overall survival (OS) were the secondary end points.

Results Ninety-four patients were treated. Median age was 51.5 years, and 58.5% of patients had ECOG performance status of 1. Fifty-six patients had PD-L1-positive tumors

(CPS ≥ 1). Twenty-nine patients had PD-L1-negative tumors (CPS < 1). Median follow-up was 14.75 months. ORR was 18.1% (95% CI, 10.9% to 27.4%), with 3 complete and 14 partial responses. PD-L1-positive patients had an ORR of 19.6% (95% CI, 10.2% to 32.4%). PD-L1-negative patients had an ORR of 20.7% (95% CI, 8.0% to 39.7%). Median PFS and OS were 4.5 and 15.8 months respectively. Median DOR was not reached. TRAE occurred in 62.1% of patients. Grade 3 to 4 TRAE occurred in 8.4% of patients.

Conclusions Socazolimab demonstrated durable antitumor activity and manageable safety in patients with recurrent or metastatic cervical cancer. Based on these results, China National Medical Products Administration (NMPA) grants breakthrough Therapy Designation to socazolimab for the cervical cancer indication.

Plenary 6

0015/#436

COMPREHENSIVE GENOMIC PROFILING OF LOW-GRADE SEROUS CANCERS AND ASSOCIATED CLINICAL OUTCOMES

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Objectives The genetic landscape of low-grade serous carcinomas (LGSCs) is poorly described. We sought to characterize somatic mutational profiles of LGSCs and correlate findings with clinical outcomes.

Methods Patients with LGSC (n=123) consented to an IRB-approved protocol of tumor-normal massively parallel sequencing that included 341–505 cancer-related genes. Clinical outcomes and frequency of genetic alterations, including somatic mutations and copy number alterations, were assessed and compared using the Fisher exact test.

Results Among 123 sequenced tumors, median tumor mutational burden was low (1.8 mutations/Mb). Recurrent alterations included those affecting KRAS (32%), NRAS (11%), BRAF (10%), CDKN2A (9%), and ERBB2 (5%) (see figure 1). KRAS mutations were more frequent in patients ≥ 50 years of age at LGSC diagnosis than in patients < 50 years of age (41% vs 23%, respectively; $p < 0.05$); in those with platinum-sensitive vs. platinum-resistant disease (41% vs 19%, respectively; $p = 0.05$); and in patients surviving ≥ 5 years compared with < 5 years (39% vs 11%, respectively; $p < 0.05$). BRAF mutations were more frequent in platinum-resistant compared with platinum-sensitive disease (19% vs 3%, respectively; $p < 0.05$). CDKN2A alterations were associated with risk of recurrence, while none of the patients with CDKN2A-wildtype tumors developed recurrence (13% vs 0%, respectively; $p < 0.05$). Recurrence was also associated with higher median fraction of genome altered ($p < 0.05$).

Conclusions The presence of KRAS mutations in LGSC may be associated with less aggressive phenotypes and older age at diagnosis. CDKN2A and BRAF alterations may be associated with recurrence and platinum resistance, respectively.