higher TMB levels linked to the HRDsig+ status indicate potential for immunotherapy efficacy.

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158P Human papillomavirus integration site mapping in advanced cervical cancer: The NRG Oncology/GOG-0240 NIH Cancer Moonshot

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Background: We have previously reported on the genomic and transcriptomic landscape according to mutational analyses, RNA sequencing and micro-RNA characterization in the GOG-0240 phase 3 randomized trial of bevacizumab for recurrent/metastatic (R/M) cervical cancer. Because HPV integration is required for cervical carcinogenesis we interrogated samples for viral sequences.

Methods: Serum and matched tumor samples underwent HPV subtyping and HPV integration site mapping. Clinical endpoints studied included progression-free survival (PFS) and overall survival (OS).

Results: 182 (40.2%) tumor samples from 452 patients with untreated R/Mdisease from GOG-0240 were determined to have sufficient analyte yield for molecular analyses. Of these, 127 (67%) had serum available to serve as a germline control. HPV DNA was detected in 79% of cases, including 49% HPV16 and 27% HPV18. There was a trend for superior PFS among patients with HPV 18+ tumors who were treated with bevacizumab, and worse OS among samples without detectable HPV (Figure). This was supported by RNA analyses for actively transcribed virus. Although most cases were associated with small numbers of integration sites, there were subsets with relatively larger numbers with a wider range of HPV16 DNA integration sites (0—160) occurred compared to HPV18 DNA integration sites (0—80). Integration sites included 37 genes including ERBB2 (HER2); the most represented HPV DNA insertion site was near retinoblastoma binding protein 8 (RBBP8), a known target for inactivation by the HPV oncoprotein E7 which when complexed with BRCA1 is involved in DNA repair and genomic maintenance.

Conclusions: To our knowledge this is the largest study of HPV insertion site mapping and provides data on >30 potential targets of viral integration as well as a putative role for BRCA1-mediated homologous recombination in R/M cervical cancer. ClinicalTrials.gov NCT00803062.

Clinical trial identification: This is sub data analysis from the following study: NCT0080306.

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159P Identification of 4 molecular HR+/HER2- breast cancer subtypes with distinct biological and clinical behaviors using spatial transcriptomics

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Background: HR-positive, HER2-negative ($HR^+/HER2^-$) breast cancers (BC) show notable heterogeneity; some patients relapse despite being classified as low-risk by gene expression assays. We used spatial transcriptomics (ST) to explore tumor microenvironment (TME) heterogeneity and identify clinically distinct subtypes.

Methods: ST (10x Visium) was applied to 86 frozen $HR^+/HER2^-$ tumors of no special type. H&E slides were morphologically annotated and ST spots were deconvoluted using external scRNA-seq data. Unsupervised clustering identified spatial transcriptome profiles and WGCNA uncovered gene modules. Multikernel learning integrated spatial clusters, morphology, cell-type infiltration, and significant module's scores to define spatial subtypes. These were projected onto the METABRIC $HR^+/HER2^-$ cohort (n=1041) for validation using gene signatures.

Results: We identified four spatial subtypes with distinct microenvironments, biology, and clinical outcomes. The Endocrine-Responsive subtype (n=23) had strong estrogen signaling, low proliferation, low-risk scores (by computing Oncotype and MammaPrint), and best outcomes (95.7% 10-years relapse free survival (10y RFS)). The Stromal-Enriched subtype (n=14) showed ECM remodeling, fibroblast enrichment, and high relapse (64.3% 10y RFS) despite low-risk scores (both Oncotype and MammaPrint). The Proliferative-Inflammatory subtype (n=33) was marked by high proliferation, strong interferon signaling, an inflamed yet immunosuppressive TME, with the worst prognosis (57.6% 10y RFS). The Luminal-Mixed Adaptive subtype (n=16) showed partial HER2 activation, high-risk scores, and high relapse (68.7% 10y RFS). Subtype assignment was independent of tumor size, age, and nodal status ($p>0.05$). All subtypes were reproduced in METABRIC, confirming biological and clinical relevance. In METABRIC, the Endocrine-Responsive subtype also exhibited better RFS compared with all other subtypes ($p=0.0019$).

Conclusions: ST uncovers prognostically meaningful subtypes of $HR^+/HER2^-$ BC, defined by immune-stromal features often missed by standard assays. These findings could inform personalized treatment strategies pending further validation.

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