between chemo-naïve to chemo-exposed patients (figure 1, cPARG: 23.8% vs. 78.4%, p<0.001). cPARG was associated with a decreased proliferation score (Ki-67 8.0% vs. 19.5%, p=0.03) and decreased overall survival (figure 2). PARG expression could be induced by chemotherapy in chemo-sensitive cells but not in isogenic chemo-resistant cells.

Conclusions PARG localizes to the nucleus in ovarian cancer cells but shifts to the cytoplasm following chemotherapy. Localization of PARG to the cytoplasm is associated with poor survival. The association between PARG expression and resistance to chemotherapy or PARP inhibitors warrants further investigation.

Objectives To elucidate an off-target mechanism by which niraparib induces ovarian cancer cell apoptosis regardless of homologous recombination (HR) status through downregulation of the oncopgenic SRC/STAT3 axis.

Methods A variety of techniques were used to determine the underlying mechanisms by which niraparib regulates the SRC/STAT3 axis including tumor organoid formation, cell viability assays, colony formation assays, real-time PCR, western blot, apoptosis assays, cell transfections, in-cell and in-vitro thermal shift assays, and confocal microscopy.

Results Niraparib exhibited more potent antitumor effects than olaparib in both HR deficient and proficient models. In addition to inhibiting PARP catalytic function, niraparib-promoted cell death in ovarian cancer cells was found to be mediated by its inhibitory effects on activated STAT3 (p-STAT3). Niraparib altered the expression of STAT3 downstream target genes, specifically those involved in apoptosis. The anti-apoptotic gene BCL-XL (BCL2L1), usually induced by STAT3 activation, was significantly reduced while the proapoptotic CASP3, CASP8, and CASP9 genes, which are suppressed by STAT3 activity, were markedly upregulated. Niraparib-mediated inhibition of the STAT3 pathway was found to be at least partially attributed to the downregulation of SRC kinase activity as demonstrated in all tested ovarian cancer cell lines and patient-tumor-derived organoid models.

Conclusions Niraparib inhibits the growth of ovarian cancer cells, regardless of HR status, more effectively than olaparib. Unlike olaparib, which is known to activate STAT3, niraparib inhibits STAT3 activity by interfering with SRC tyrosine kinase. These findings provide a potential off-target mechanism by which niraparib may provide benefit to ovarian cancer patients regardless of HR biomarker status.