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.

### EP245/#993

**NIRAPARIB INDUCES OVARIAN CANCER CELL APOPTOSIS REGARDLESS OF HOMOLOGOUS RECOMBINATION STATUS THROUGH DOWNREGULATION OF THE ONCOGENIC SRC/STAT3 AXIS**

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**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 oncogetic 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.

### EP246/#636

**THE EFFICACY OF MEK INHIBITORS (MEKI) IN THE TREATMENT OF LOW-GRADE SEROUS OVARIAN CANCER (LGSC): A SYSTEMATIC REVIEW**

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**Objectives** Low response rates of LGSC to traditional systemic therapies prompts the need for novel therapies. LGSC have a high frequency of mutations in the MAPK cascade, which is targeted by MEKi. The primary objective of this systematic review was to assess the overall response rate (ORR) of LGSC to MEKi.
Methods Pubmed, EMBASE, Medline and the Cochrane Database were searched from inception to March 2022. Inclusion criteria were studies assessing the treatment of LGSC with a MEKi in the primary or recurrent setting, published in English. Case reports, case series, conference proceedings, in vitro studies and animal studies were excluded. Studies were screened and assessed for eligibility by two independent reviewers (AK, CC), with conflicts resolved by a third reviewer (TZ). Data was extracted using pre-established criteria.

Results Initial literature search identified 1815 papers; four met eligibility criteria. Three were randomized clinical trials and one was a phase II single-arm prospective cohort study. A total of 680 patients were included, of which 416 were treated with a MEKi alone. All patients were treated for recurrent LGSOC. ORR ranged from 12.1 to 26% and median progression-free survival (PFS) ranged from 7.2 to 13 months.

Conclusions While one study demonstrated significantly improved efficacy of MEKi over physician-choice systemic therapy, another did not show benefit. Two additional studies did not compare MEKi to traditional therapies, limiting their clinical relevance. LGSC with BRAF and KRAF mutations have higher ORR to MEKi. Further prospective and randomized trials are needed to determine the efficacy of MEKi in treating LGSC.

Conclusions In the Indian population, endometriosis did not have any impact on the age at presentation, CA 125 levels, stage of the disease and survival out comes in EC and CCC ovary.