

**Methods** 3 patients were included in this study. DNA was extracted from ten FFPE tumour samples (5 from primary surgery and 5 from recurrences) and whole blood. Whole exomes sequencing (WES) was performed on Illumina's Next-Seq platform to a depth of at least 10X. Sequence data were trimmed, aligned and single nucleotide variants and copy number alterations were called.

**Results** All samples were microsatellite stable, 2 of the 3 patients had an elevated tumour mutational burden (TMB) (defined as >10 mutations/Mb). In the patient with low TMB we identified a class 3 'kinase-dead' BRAF variant, D594G with concordant near-whole chromosome 1 amplification, covering the NRAS proto-oncogene. Single gene testing confirmed wild type EGFR and KRAS. This lady did not respond to a trametinib. The second case identified a pathogenic NBN R43\* mutation with associated non pathogenic mutations in other DNA damage response genes. This patient who had previously declined cytotoxic chemotherapy has had a partial response to platinum based chemotherapy. The third patient did not have a targetable mutation but is awaiting PD-L1 testing.

**Conclusions** WES may be helpful in refractory LGSOC when standard treatment options have been exhausted. Two of our patients had an elevated TMB suggesting that the efficacy of immunotherapy in LGSOC should be investigated.

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### CYTOREDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) IN PATIENTS WITH ADVANCED OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER: OUR EXPERIENCE IN 108 PATIENTS

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**Objectives** Current evidence suggests that complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a feasible option for patients with advanced ovarian, fallopian tube or primary peritoneal cancer with potential benefits that may exceed the survival outcomes of current - surgical debulking and intravenous platinum- and taxane-based chemotherapy.

**Methods** It is a retrospective study including 108 patients with primary or recurrent peritoneal carcinomatosis, operated between 2013 and 2019, with a mean age of 53.7 years.

**Results** Seventy eight patients (72%) had primary debulking and 30 (27%) had surgery for a recurrent disease. The peritoneal cancer index (PCI) was below 15 in 50 patients (46%) and above 15 in 58 (53%), respectively. Together with total peritonectomy, large bowel resection was performed in 55 patients (50.9%), small bowel resection in 13 (12%), and splenectomy in 38 (35%). Other upper abdominal procedures included liver resection (13%), colectomy (35%), gastric

resection (1.8%), diaphragm resection (12%), etc. Microscopically complete cytoreduction (CC0) was achieved for 68 patients (63%), macroscopic cytoreduction (CC1) for 35 (32%), and gross tumour debulking (CC2) for 5 (4%). Only 3 patients (2.7%) have been reoperated. For HIPEC, Cisplatin and respectively, Doxorubicin were both used for 30 patients (27%), Other regimen included Cisplatin plus Doxorubicin (41%), Cisplatin plus Mitomycin or Mitomycin alone. Nine patients (8%) died of disease, 15 (13%) are alive with recurrent disease, and 84 (77%) are disease-free, but the follow-up is short.

**Conclusions** HIPEC after extensive CRS for advanced gynecological cancer with peritoneal carcinomatosis is a feasible option with promising results.

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### MOLECULAR DETERMINANTS OF CDK4 INHIBITOR ACTIVITY IN LOW-GRADE SEROUS OVARIAN CANCER

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**Objectives** Effective therapies for low-grade serous ovarian cancer (LGSC) patients are urgently needed. CDKN2A/B (p16) loss and hormone receptor (ER/PR) expression are well described in LGSC. We aimed to study p16-CDK4-Rb pathway status and CDK4/6 inhibitor (CDK4/6i) activity in LGSC cell lines.

**Methods** Protein expression of p16, CDK4, CDK6, Rb, p-Rb, CCDN1 and E2F were evaluated by western blot in 13 LGSC and 2 breast cancer (BCa) lines. Gene mutation and copy-number (CN) data on the selected candidates were obtained using whole-exome sequencing (WES) analyses. CN data on 93 LGSC FFPE tumors was also obtained. Palbociclib (CDK4/6i) effects were evaluated using IC50 assays.

**Results** None of the LGSC lines had detectable mutations in p16, CDK4, CDK6, Rb, p-Rb, CCDN1 or E2F genes. CDK4/CDK6 protein expression was present in all lines. Absence of p16 protein expression and CDKN2A CN loss was detected in 84.6% (11/13) LGSC cell lines. Interestingly, total and phosphorylated Rb were detected in both BCa lines, but only in 53.8% (7/13) LGSC lines. RB1 hemizygous CN loss was detected in 7.7% (1/13) LGSC lines and in 7.5% (7/93) LGSC tumors. Palbociclib had limited cytotoxic effects in the BCa and LGSC cell lines tested.

**Conclusions** Palbociclib mainly has cytostatic effects in LGSC in-vitro and its activity does not correlate with either p16 or CDK4 expression. About half of our cell lines showed Rb loss, likely mediated by post-translational events. Rb-proficiency is required for drug efficacy in other cancers, and may account for our observations. These results raise important considerations for clinical trial design.