MITO 37- PROTOCOL SYNOPSIS

Title	**Ki67 as a predictor of response to PARP inhibitors in platinum sensitive BRCA Wild Type ovarian cancers**
Coordination and responsibility for the study	Giorgio Valabrega, Istituto di Candiolo, Fondazione del Piemonte per l'oncologia (FPO). Valentina Tuninetti, Istituto di Candiolo, Fondazione del Piemonte per l'oncologia (FPO).
Sponsor	Fondazione del Piemonte per l'Oncologia (FPO-IRCCS)
Type of study	Retrospective
Population	All patients with platinum sensitive (Progression Free Survival > 6 months) high grade serous or endometrioid BRCA WT ovarian carcinoma in maintenance with Niraparib or Rucaparib following partial or complete response after at least 4 cycles of platinum-based chemotherapy.
Study Rationale	Currently, the best predictor of response to PARP inhibitors in ovarian cancer (OC) is the presence of germline/somatic BRCA 1 or 2 mutations. Recent evidence from randomized trials has shown that other subpopulations carrying homologous recombination deficiency (HRD) can benefit from PARP inhibition [1-9]. Unfortunately, HRD tests are not always reproducible and do not apply to different PARP inhibitors (PARPi) [5,9]. Moreover, their high cost makes difficult to implement commercial tests in daily clinical practice. As a consequence, most, BRCA WT platinum sensitive ovarian cancer patients are treated with PARPi although nearly half of them may derive no benefit from treatment. While the need to develop a reliable low cost-academic test is mandatory, the evaluation of currently available low cost biomarkers may also lead to remarkable results in clinical practice. Ki67 is a well-established indicator of tumor proliferation in several malignancies [12-15]. Ki67 has been shown to correlate with metastasis and the clinical and pathological stage of tumors [16-18]. Furthermore, it has been shown that Ki67 expression is higher in malignant tissues with poorly differentiated tumor cells as compared with normal tissue. Due to its predictive role, pKi67 expression identifies subpopulations of cells who are more likely to respond to a given therapy [16-18]. In ovarian cancer retrospective series, low ki67 is associated with platinum resistance and poor prognosis [17]. There are many reports showing that patients with OC, who have high proliferation index (PI) detected using ki-67 immunostaining, are more likely to have poor prognostic factors, including advanced FIGO stage, higher tumor grade, bulk residual tumor, and poor response to chemotherapy, and also have a less favorable 5-year survival compared with those with low PI. Kritpracha et al. [19], showed that in 105 patients with locally advanced OCs, the percentage staining of ki-67 expression ranged from 0.3 to 100%, with a median of 11.9%. Ki-67 staining was higher in serous tumors than in other types (p= 0.048). The 5-year overall survival (OS) was 15.1% in the high ki-67 (≥ 11.9%) and 36.5% in low ki-67 (< 11.9%) patients, respectively. Median survival times in the two groups were 1.8 years and 3.0 years, respectively (p < 0.008). Heeran et al [20] analysed ki-67% in 606 patients with OC using 10% cut-off level for Ki-67 overexpression and 51% of the OCs were positive. The frequency of ki-67% expression increased with increasing FIGO stage (p=0.003) and histological grade (p > 0.0001).

	Layfield et al. [21] demonstrated that ki-67 had prognostic significance in late stage OC. Exploratory methods to assess ki-67% confirmed that in 50 women affected by locally advanced OC, 15% was a cutpoint that could dichotomize patients into two prognostic groups based on OS. The median OS of patients whose carcinoma had a high ki-67 expression (> 15%) was 16 months compared with 30 months in patients with ki-67 expression > 15%.
Design	About 300 patients treated within MITO centers will be included in the study. Clinical outcome following PARPi maintenance, will be measured as response rate (RR) and progression free survival (PFS) in ki67 high and ki67 low patients. A comparison between the two groups will be carried out. • **First part of the study**: defining the best cut-off of ki-67 expression in OCs. • **Second part of the study**: correlate Ki67 status (high vs low) with clinical outcome (RR and PFS) following PARPi maintenance • Ki67 will be assessed on specimens from primary surgery (upfront/IDS or tumor biopsy) and from the most recent surgery before PARP maintenance
Partecipating Centers	MITO centers able and available to locally assess ki67.
Inclusion criteria	1. Platinum sensitive (Progression Free Survival > 6 months) high grade serous or endometrioid BRCA WT ovarian carcinoma in maintenance with Niraparib or Rucaparib following partial or complete response after at least 4 cycles of platinum-based chemotherapy
Exclusion criteria	1. Histology other than high grade serous or endometrioid BRCA WT ovarian carcinoma
Primary objective	To retrospectively correlate Ki67 status (high vs low) with clinical outcome following PARPi maintenance after partial or complete response during platinum based chemotherapy for platinum sensitive relapse.
Primary endpoints	Locally assessed Response Rate (RR) and Progression Free Survival (PFS)
Duration of the study	October 2020: submission to FPO-IRCCS EC November-December 2020: data collection
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