

cancer in family members. Knowing BRCA status is a very important factor to plan the therapeutic strategy in ovarian cancer.

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NIRAPARIB AS MAINTENANCE THERAPY IN PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER: A GEICO STUDY WITHIN THE SPANISH EXTENDED ACCESS PROGRAM

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Introduction/Background* In the ENGOT-OV16/NOVA trial, niraparib demonstrated a significantly longer PFS in patients (pts) with recurrent platinum-sensitive ovarian cancer (PSOC) vs placebo as maintenance therapy, regardless of gBRCA/HRD status. Niraparib obtained EU approval in 2017 and an expanded access program (EAP) was initiated.

Methodology A retrospective study of niraparib maintenance therapy was conducted within the Spanish EAP, at 57 hospitals. Niraparib's safety, dose adjustments, and effectiveness in real-world setting were assessed. Patient characteristics and starting dose individualizations were also analyzed. EAP's inclusion required at least 2 previous courses of platinum-containing therapy. For the last course prior to inclusion a response should have been obtained. Although BRCAmut and BRCAwt pts could be included, most were BRCAwt because olaparib was commercialized at that time for pts with BRCAmut and pts were allowed to be included only in specific circumstances.

Result(s)* Between September 2020 and March 2021, 316 pts were included. Median age was 63 years (31-88). More common initial FIGO stages were IIIC, IVB, and IVA (50.0%, 13.6%, 11.1%). 5.7% were BRCAmut, 80.4% BRCAwt, and 13.9% unknown. 93.4% had initial surgery and 22.8% after relapse. Previous bevacizumab was given in 40.8% of pts. Before niraparib, pts had ECOG 0-1 (50.3%-47.5%) and 55.7% had measurable disease. Population weights (Kg) were 43-57 (23.1%), 58-76 (52.2%), and 77-105 (17.7%). 19.7% had baseline platelets <150,000/ μ L, with a median of 203,500/ μ L. Individualized starting dose (ISD) was applied in 203 pts (64.2%); 142 (70%) of them started at 200 mg. Niraparib's mean dose was 201.5 mg (59.2% had ≥ 1 reduction and 63.3% ≥ 1 interruption). 6.0% discontinued due to

niraparib-related adverse events. Main G3-4 hematological toxicities were thrombocytopenia (17.4% ISD-32.0% fixed starting dose (FSD)), anemia (12.4% ISD-17.5% FSD), and neutropenia (7.5% ISD-5.8% FSD). There were not relevant G3-4 non-hematological events. 58 (18.3%) pts were long-term responders (treatment ≥ 1 year). 47 (14.9%) remained on treatment upon analysis.

Conclusion* The use of niraparib as maintenance therapy in pts with recurrent PSOC in real-life setting is safe. The ISD approach improved the safety profile. Results were in accordance with those reported in phase III trials. Overall effectiveness analysis is coming.

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NON-CODING RNA AND MRNA TRANSCRIPTOME DIFFERENCES IN OVARIAN CARCINOMA PATIENTS ASSOCIATED WITH RESISTANCE TO ADJUVANT CHEMOTHERAPY

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Introduction/Background* Epithelial ovarian carcinoma (EOC) is associated with the highest mortality among gynecological carcinomas. High mortality is due to the diagnosis at advanced stages and development of resistance to anticancer therapy regimens based on taxanes and platinum derivatives. In effort to overcome the problem of resistance, novel therapeutic drugs are synthesized and new potential therapeutic targets are under study.

Resistance of cancer cells is a multifactorial process, where deregulation of transcriptome may play important role. In addition, long non-coding RNAs (lncRNAs) with recognized regulatory functions may modulate transcriptome profile and its association with resistance and therapy response. The aim of this study was to analyze transcriptome profile of EOC patients and decipher interactions between protein-coding genes and lncRNAs, which may help to reveal new potential therapeutic targets of EOC.

Methodology Set of 60 EOC patients with different sensitivity to the adjuvant chemotherapy was divided into two groups based on their platinum-free interval (PFI) after adjuvant chemotherapy by platinum derivatives in combination with paclitaxel. Together 37 patients had PFI > 12 months (sensitive; 27 \pm 24 months) and 23 patients had PFI < 12 months (resistant; 5 \pm 3 months). We have performed transcriptome profiling using 3' mRNA QuantSeq FWD kit (Lexogen) with sequencing on the NextSeq500 platform (Illumina). Bioinformatics analysis was carried out by in-house pipeline with final differential expression analysis.

Result(s)* Bioinformatics analysis of transcriptome profile revealed significant differences in the expression profile of EOC patients with different sensitivity to adjuvant chemotherapy. We observed twelve differentially expressed protein coding genes (after false discovery rate correction) – MYH11, JAK2, SETDB2, SUCNR1, IRAG2, CCN5, FOXP2, GCNT3,

KCNN3, LGI4, EGFLAM, HPGDS and four lncRNAs (LINC-HOXD1-1, LINC-MLN-5, LINC-RPIA-2, LINC-LY86-4). For JAK2 and KCNN3 genes, we found in literature the evidence of their potential role in resistance of ovarian cancer.

Conclusion* On the basis of transcriptome profile, we discovered till unknown associations of gene expression levels with response in ovarian carcinoma patients (MYH11, SETDB2, IRAG2, FOXP2 and LGI4) together with four lncRNAs (LINC-HOXD1-1, LINC-MLN-5, LINC-RPIA-2, LINC-LY86-4) with potential role in therapy resistance in ovarian carcinoma patients.

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PRECLINICAL STUDIES SUPPORT THERAPEUTIC APPLICATION OF THE LEUKAEMIC CELL-BASED CANCER RELAPSE VACCINE DCP-001 IN OVARIAN CANCER

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Introduction/Background* Ovarian cancer (OC) causes high mortality due to late diagnosis and high rate of relapse following initial therapy. Immunotherapy in combination with standard treatment modalities forms a promising new treatment approach.

DCP-001 is an intradermally applied cancer relapse vaccine derived from the human leukaemic cell line DCOne[®] and is currently tested in acute myeloid leukaemia patients. To obtain the highly immunogenic DCP-001 vaccine, DCOne cells are shifted towards a mature dendritic cell phenotype. Since DCOne cells express multiple common tumour associated antigens such as WT-1, RHAMM, PRAME and MUC-1, which are also documented as target antigens in OC, DCP-001 vaccination may also be efficacious in OC. To support this hypothesis, the capacity of DCP-001 to induce immune responses against OC was studied in human peripheral blood mononuclear cells (PBMCs) from OC patients and a humanized mouse model for OC.

Methodology The effect of DCP-001 on T cells was evaluated after a 3 week culture of PBMCs with or without DCP-001. Cytotoxic activity was analysed by IFN γ production and CD107a expression when these cells were subsequently cultured with OC cell line SKOV3. The effect of DCP-001 vaccination *in vivo* was evaluated in humanised NCG mouse subcutaneously engrafted with SKOV3 OC cells. Mice received two intra-peritoneal (i.p.) vaccinations with DCP-001 either after or prior to SKOV3 engraftment and tumour size was measured to evaluate the efficacy of DCP-001.

Result(s)* *In vitro*, DCP-001 was shown to activate both CD4⁺ as well as CD8⁺ T cells and to induce formation of memory T cells. Importantly, DCP-001-stimulated CD8⁺ T cells from OC patients were shown to exert a HLA class I dependent, immune response to OC cells. *In vivo*, in an ovarian tumour mouse model, significant reduction of tumour growth rate and partial or even complete tumour regressions were observed in mice vaccinated with DCP-001, particularly when administered as relapse vaccine (prior to tumour engraftment), as compared to PBS treated mice.

Conclusion* These pre-clinical *in vitro* and *in vivo* results support the potential use of DCP-001 as a cancer relapse vaccine

in ovarian cancer, with the aim to reduce disease recurrence following initial standard of care therapy.

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EVALUATION OF THE LOX GENE/PROTEIN AS POTENTIAL PROGNOSTIC MARKER IN OVARIAN CANCER

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Introduction/Background* In our previous microarray study we identified a set of genes (multigene signature) related with different survival of patients with high-grade serous ovarian cancer (HG-SOC) [1]. One of the genes from this signature was LOX, encoding for lysyl oxidase. LOX is engaged in the cross-linking of the extracellular matrix proteins. Various studies have indicated that LOX may act as either an oncogene or a tumor suppressor, depending on the type of tissue/tumor. As our previous study indicated that higher LOX mRNA level was negatively correlated with survival of ovarian cancer patients, we aimed to check whether LOX level determined by immunohistochemistry shows the same dependency and could be useful for clinical practice.

Methodology Two commercially available anti-LOX antibodies (ab174316-Abcam, NB-2530-Novus Biologicals) were validated by western blotting, using protein extracts from six ovarian cancer cell lines and recombinant LOX protein as a control (NBP-59887-Novus Biologicals). Then, immunohistochemical analysis was performed (tissue samples of HG-SOC) and on tissue arrays containing spectrum of different histological type, FIGO stages, etc. (US Biomax). The results were analyzed using Statistica (version-13.1, StatSoft Poland).

Result(s)* Only one antibody (ab174316-Abcam) was positively validated as specific toward LOX and it was used for further analysis. Unfortunately, Kaplan-Meier analysis showed no correlation between LOX protein level and the patients' survival time. Further analysis revealed that LOX level was correlated with primary/metastatic tumor difference: higher stromal LOX expression occurred eight times more often in metastatic than in primary tumors. However, there was no such correlation when LOX expression was assessed in cancer cells.

Conclusion* Although our previous observations indicated that higher LOX mRNA level was correlated with shorter survival of ovarian cancer patients, protein level of LOX does not demonstrate prognostic value in the analyzed group of patients with HG-SOC. However, we observed significantly higher LOX expression in the stroma of metastases compared to that of primary tumors. This observation is consistent with the assumption that LOX is associated with a more aggressive tumor phenotype.

[1] Katarzyna Lisowska et al. doi: 10.1007/s00432-016-2147-y

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