ADVANCED ORTHOTOPIC OVARIAN CANCER PATIENT-DERIVED XENOGRAFT MODELS FOR IMPROVED PRECLINICAL EVALUATION OF IMMUNOTHERAPIES

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Background Ovarian cancer (OC) is a heterogeneous disease, often diagnosed at an advanced stage. After an initial encouraging response rate to first-line treatment, comprising cytoreductive surgery combined with platinum-based chemotherapy, most of such cancers recur. The use of advanced, clinically relevant mouse models allows us to study tumor pathogenesis and to evaluate response to new cancer drugs, which may ultimately prevent recurrence and prolong survival. Most preclinical models however do not fully recapitulate the tumor microenvironment as well as heterogeneity, and thus many drugs fail a successful implementation into clinical practice. We developed and characterized humanized patient-derived xenograft (PDX) murine models, comprising of a functional human immune system and an orthotopically implanted primary ovarian cancer tumor. These models were further used to test treatment response of immune checkpoint inhibitor PD-1, combinatorial immunotherapy targeting PD-L1 and CD73, and novel chimeric antigen receptor (CAR) constructs targeting unique biomarker of OC.

Methods Humanized PDX mice were generated by co-transplantation of CD34+ hematopoietic cells, isolated from the umbilical cord blood and primary ovarian cancer cell suspensions from treatment naïve OC patients. PDX models were characterized by whole exome sequencing (WES) and the developing human immune system in immunodeficient mice was followed longitudinally by flow cytometry. Bioluminescence and 18F-FDG PET-CT imaging of tumor burden, survival analysis, and characterization of tumor-infiltrating immune cells by a 34-surface mass cytometry were performed to assess the treatment responses.

Results Phenotypic and genomic characterization of humanized PDX models was achieved. Mice treated with nivolumab showed a decrease in tumor burden, however no significant survival benefit when compared to untreated controls was identified, nor could a correlation between PD-L1 expression, CD8 T cell infiltration and response parameters been observed. Interestingly, the characterization of immune infiltrating cells identified predominantly myeloid cells as seen in ovarian cancer patients. In a CAR T cell treatment study of OC PDX mice, bioluminescence imaging showed a delayed onset of metastasis and smaller tumor burden, but also severe toxic side effects in CAR T cell treated PDX mice compared to untreated control mice. Results from combinatorial immunotherapy targeting PD-L1 and CD73 are awaited.

Conclusions Humanized orthotopic OC PDX models have been established. Together with the promising advances in new immunotherapeutic targets, clinically relevant mouse models facilitate the development of new immunotherapies targeting the ovarian tumor microenvironment.

Ethics Approval Patient tumor samples were provided by the Gynecologic Cancer Biobank, Women’s Clinic, Haukeland University Hospital, Bergen, Norway (REK ID: 2014/1907, 2015/548, 2018/72). Animal experiments are performed in accordance with the procedures set by the Norwegian State Commission for Laboratory Animals, and the laboratory-animal experiments (FOTS 25412) have been approved by the Norwegian Food Safety Authority.

Consent Written informed consent was obtained from all women before collection of fresh tumor tissues. A copy of the written consent and approval is available for review.