#3718. ID8-Luc Syngeneic Ovarian Cancer Model for Preclinical Evaluation of Immunomodulatory Molecules

Sumithra Urs, Sheri Barnes, Stacey Roys and Maryland Rosenfeld Franklin
Labcorp Early Development Laboratories Inc., Ann Arbor, Michigan

Introduction and Background

- Ovarian cancer (OC) is a gynecological malignancy with a high mortality rate of over 14,000 deaths annually in the U.S. Even though ~80% of OC patients initially go into remission after first line treatment (surgery and chemotherapy), more than 60% relapse within 16-18 months.
- Low neoantigen burden and the immunologically “cold” nature of OC makes it a challenging malignancy. Recent success with immunotherapies in other cancers provides some hope for ovarian cancer patients. One of the most promising data reported that the presence of tumor infiltrating lymphocytes positively correlates with improved survival of OC patients.
- As novel methods such as immunotherapy and/or combination therapies are essential to improve clinical outcome of patients, characterization of relevant murine models are needed. This work evaluates the ID8-Luc murine ovarian carcinoma model and tests sensitivity to immunomodulatory agents.
- We have established the ID8 murine ovarian surface epithelial carcinoma cell line derived from C57BL/6 mice as a preclinical syngeneic model to track and monitor disease progression and therapeutic outcomes. Our model relies on the intraperitoneal delivery of luciferase-expressing ID8 cells to mimic aspects of human disease.

Materials and Methods

- Female 6-7 week old C57BL/6 albino mice (Envigo) were implanted intraperitoneally (IP) with ID8-Luc cells. Tumor engraftment and progression was monitored by bioluminescence imaging (BLI) with an IVIS Spectrum (Perkin Elmer).
- Immune profiling was performed on peritoneal ascites from untreated mice, digested to a single cell suspension (Miltenyi, Germany) for flow cytometry. Comprehensive T cell (MI-CompT™) and myeloid cell (MI-TAM™) panels were acquired on an Attune™ NxT flow cytometer (Thermo Fisher Scientific) and analyzed with FlowJo software (FlowJo LLC, Ashland, Oregon).
- Checkpoint inhibitor antibodies were acquired from Bio X Cell (West Lebanon, NH) and dosed intraperitoneally. Paclitaxel was purchased from Enzo Life Sciences (Farmingdale, NY) and dosed intravenously.
- Treatments were initiated either on Day 7 or on Day 14 post-implant. Mice were randomized into treatment groups based on BLI.

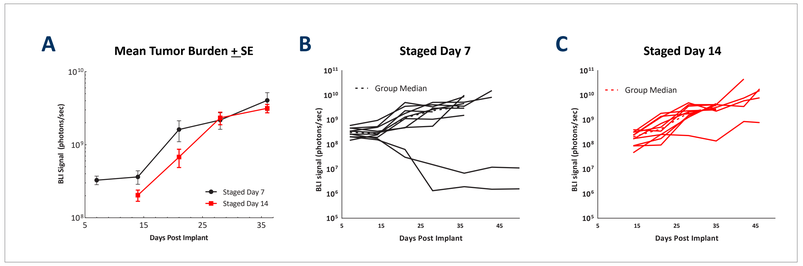

Figure 1. Successful *in vivo* growth of ID8-Luc. Mean (A) and individual (B & C) tumor burden of ID8-Luc as determined by BLI over time. IP implant of ID8-Luc cells in C57BL/6 albino mice results in successful tumor take with a median tumor doubling time of 7-8 days and mice remain on study for ~40 days. Spontaneous regressions are seen when mice are placed on study 7 days post-implant (B). This can be overcome by placing mice on study at day 14 post-implant (C). Clinical signs include abdominal distention due to accumulation of ascites and enlarged pancreas. Nodules on the pancreas, liver, spleen and abdominal wall are the major necropsy observations (data not shown).

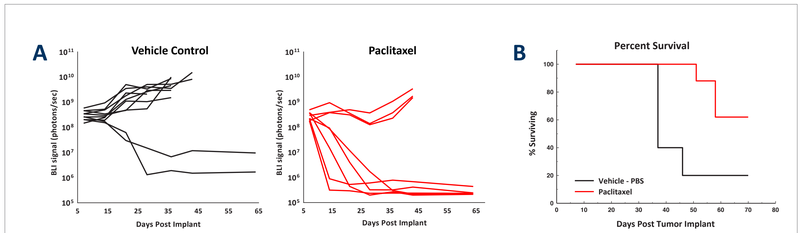

Figure 2. ID8-Luc model is sensitive to paclitaxel. Mice with ID8 tumors were treated with paclitaxel (A). Paclitaxel treatment showed sensitivity in 62.5% (5/8) of the animals resulting in 50% tumor-free survivors (TFS) (B).

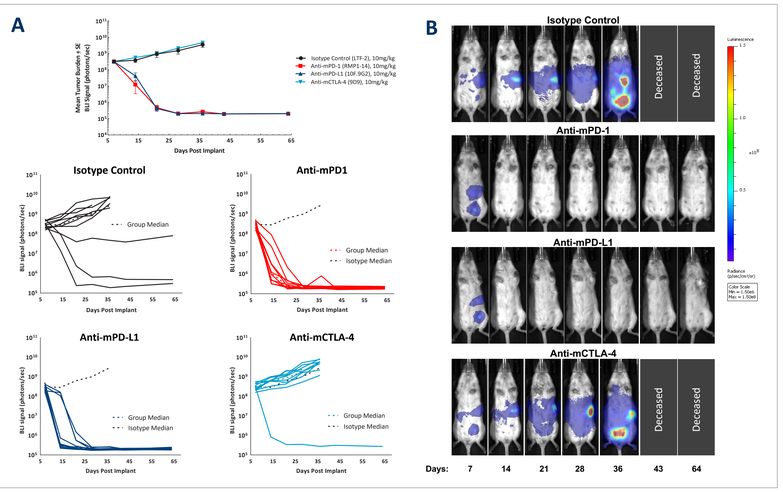

Figure 3. ID8-Luc is sensitive to early treatment with immune checkpoint inhibitors. Mean and individual tumor burden (A) and representative bioluminescence images (B) of ID8-Luc tumor bearing mice treated with checkpoint inhibitors starting on day 7 post-implant. Early treatment with either anti-mPD-1 or anti-mPD-L1 elicited a strong response resulting in complete regression and 100% TFS. The model was refractory to anti-mCTLA-4 treatment where disease progression was similar to the control group. The control group demonstrated 20% spontaneous regression.

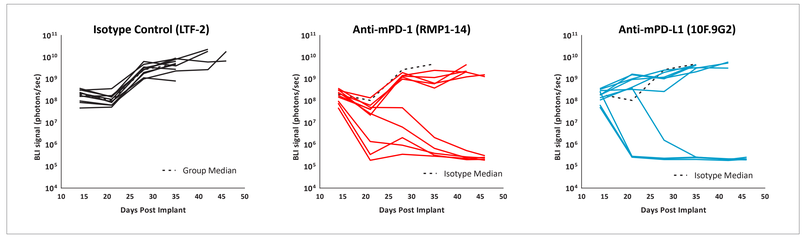

Figure 4. ID8-Luc is sensitive to late treatment with checkpoint inhibitors. Mice with ID8-Luc tumors were treated with checkpoint inhibitors starting 14 days post-implant. Treatment with anti-mPD-1 or anti-mPD-L1 elicited an “all or none” response but showed less overall activity when compared to treatment initiation on day 7 (Figure 3).

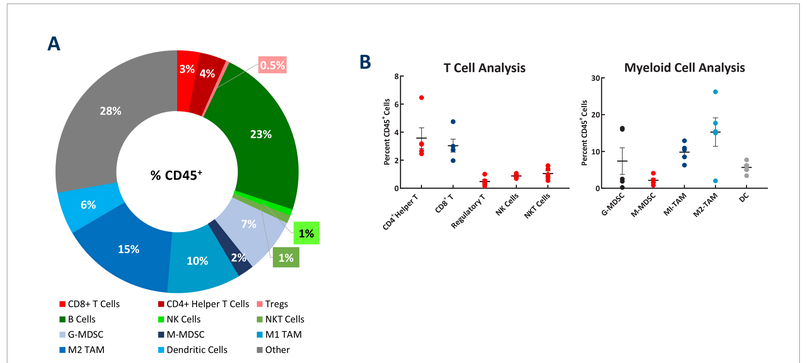

Figure 5. Immune profile of ID8-Luc model. Ascites was collected from 5 untreated mice and analyzed for myeloid and lymphoid cell panels by flow cytometry. The ascites contained a relatively large population of B cells and myeloid derived cells; the lymphoid population was minimally represented (A). The myeloid population has a high percentage of TAMs with more M2-TAMs compared to M1-TAMs (B).

Results and Conclusions

- Intraperitoneal implant of ID8-Luc cells successfully induces disease in the peritoneum of syngeneic mice.
- The model has a median doubling time of 7-8 days and a median overall survival time of ~35-40 days which allows a 2-3 week window to evaluate anti-tumor response of test agents.
- ID8-Luc model shows sensitivity to paclitaxel treatment, a standard of care in ovarian cancer patients.
- These results show the degree of response to checkpoint inhibitor varies with time of treatment initiation. Early treatment can be very effective while a delayed treatment results in fewer responders.
- The lack of T-cell infiltration and presence of large myeloid cell population in the immune profile is characteristic of a non-immunogenic tumor model.

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