Ofranergene Obadenovec (VB-111), an anti-cancer gene therapy, induces immunotherapeutic effect in platinum resistant ovarian cancer: histopathology findings

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BACKGROUND

VB-111 is a Novel, First-in-class Anti-cancer Gene Therapy

- VB-111 (Ofranergene Obadenovec) is a targeted anti-cancer viral based gene therapy with dual mechanism of action:
  - The non replicating Adenovirus S viral vector includes a transgene that targets angiogenic endothelium, leading to angiogenic cells apoptosis and vascular disruption
  - VB-111 Induces an anti-tumor directed immune response

Ovarian Cancer

- Ovarian cancer is the leading cause of death from gynecologic cancers and often only diagnosed when advanced
- The accumulation of tumor infiltrating lymphocytes (TILs) is a predictive biomarker for improved prognosis in ovarian cancer
- TIL manipulation was shown to inhibit ovarian cancer progression in preclinical and clinical studies
- Therapeutic viral administration in tumors promotes strong antiviral immune response and cytokine production, reconditioning the tumor microenvironment and transforming the tumors from immunologically “cold” to “hot”

METHOD

- Post treatment biopsies from studies NCT01711970 and NCT03398655 were obtained from 3 patients with recurrent platinum-resistant ovarian cancer treated with intravenous VB-111 1x1013 VP every 2 months in combination with weekly paclitaxel
- H&E and Immunohistochemistry were performed for CD8 and CD4 intratumoral T cells
- Results were compared to pre-treatment specimens and to untreated controls, and were correlated to radiographic and clinical outcomes

RESULTS

VB-111 Induced Antitumor Immune-Response

Study NCT01711970

- VB-111 treatment increased tumor infiltrating CD4 T cells (15-20 cells/HPF) and Cytoxic CD8 T cells (28-38 cells/HPF). Regions with apoptotic cancer cells were detected (Figure 3)
- Specimens taken from untreated controls showed minimal or no tumor cell infiltration

Study NCT03398655

- Specimens were taken from a patient with recurrent platinum resistant high grade serous carcinoma before VB-111 treatment, but after previous treatment by 3 prior lines including taxol, carboplatin, lipomub, IL-2, bevacizumab & olaparib (germline BRCA 2 mutation carrier). Pre treatment specimen showed minimal T cell infiltration in the tumor (4 cells/HPF) (Figure 4)
- One month after VB-111 treatment, metastatic lesion demonstrated tumor infiltrated with CD8 T cells (74 cells/HPF) and CD4 T cells (21 cells/HPF)
- 4.5 months following first drug administration (post 3rd VB-111 dose), the liver lesion showed necrotic and fibrotic tissue with no viable tumor lymphocytic aggregate, intense staining for CD8 (157 CD8+ cells/HPF), intense staining for CD4 T cells (80 cells/HPF) and pigmented macrophages
- Histologic findings were associated with complete CA-125 GCIG response, and radiologic response which was initially seen as lesion liquidification followed later by radiologic RECIST 1.1 response (Figure 5)
- To date, over 1 year since starting treatment, patient is still on VB-111 treatment, and has a durable response per RECIST

SUMMARY AND CONCLUSIONS

- VB-111 induced an immunotherapeutic effect manifested as tumor infiltration with CD8 T cells and evidence of tumor necrosis
- Pathologic findings were associated with durable clinical CA-125 and RECIST responses
- Turning immunologically “cold” tumors “hot” may contribute to the favorable clinical and survival outcomes seen in the VB-111 studies and may have implications on other “cold” solid tumors such as GI and Breast. Further studies are planned
- The OVAL study, a pivotal, placebo controlled phase III study in patients with platinum resistant ovarian cancer evaluating the efficacy and safety of VB-111 in combination with weekly paclitaxel is ongoing and recruiting patients