Does immunotherapy make sense in gynecologic cancers?

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Disclosures

Merck
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- Consulting
Established tumors are not just composed of cancer cells

Kerkar SP, Restifo NP. Cancer Res 2012;72:3125-3130
Tumor immunology and immunotherapy in 1 slide

**In situ vaccines**
- Surgery
- Radiation
- Chemotherapy
- Ablative therapies
- Targeted therapies
- Tumor-targeting antibodies
- Oncolytic viruses

**Tumor**
- TAA/TSA
- Cytokines

**Whole modified tumor cells (GVAX)**
- Whole TAA Protein (MAGE A3)
- DNA expressing TAA (VGX3100)
- TAA/TSA Peptide (ISA101)
- TAA encoded by virus vector (PROSTVAC)
- TAA encoded by bacterial vector (CRS-207, ADX S11-011)

**Dendritic cell (DC) loaded with TAA/TSA protein or peptides**

**Anti-PD-1, Anti-PD-L1, Anti-4-1BB, OX40, GITR**

**Treg, MDSC**
- CD28
- B7-1,2
Biomarkers explored in immunotherapy (response/resistance)

- **Tumor microenvironment**
  - TILs (high vs. low)
  - Immunosuppressive molecules (IDO, PD-L1) (high vs. low)
  - Immunosuppressive populations (Treg, MDSC) (high vs. low)
  - TCR clonality (high vs. low)
  - IFNg signature (high vs. low)

- **Tumor cells**
  - Mutational/neoantigen load (high vs. low)
  - Endogenous retroviruses (high vs. low)
  - Type I IFN signaling pathways (high vs. low)

- **Blood**
  - PBMC:
    - Lymphocyte proliferation and activation markers (Ki-67, ICOS) (high vs. low)
  - MDSC percentages (high vs. low)
  - RNA/DNA:
    - TCR clonality (pre and on-treatment)
    - Gene expression
  - Serum
  - Cytokines
  - Serologic responses to CT antigens

- **Host**
  - Genetic polymorphisms in immune genes
  - Gut microbiome
Existing biomarkers: Rationale for immunotherapy in gynecologic cancers

- **Ovarian cancer**
  - Patients with high number of TILs at diagnosis have superior outcomes
  - Patients with immunoreactive TCGA gene expression phenotype have superior outcomes

- **Cervical cancer (and other HPV-driven cancers)**
  - Presence of foreign HPV epitopes should promote tumor immune recognition

- **Endometrial cancer**
  - Neoepitope abundance in MMR-deficient tumors promotes tumor immune recognition
Tumor microenvironment: infiltration with CD8+ lymphocytes in melanoma predicts response to PD-1 blockade

Tumeh et al., Nature 2014
Tumor microenvironment: inflammatory gene expression signatures

Type I IFN signature is associated with clinical benefit from CTLA-4 blockade in melanoma
Chiappinelli et al., Cell 2015

IFNγ signature in pre-treatment tumors is associated with response in different cancers
Ayers et al., JCI 2017
Tumor microenvironment: PD-L1 expression in tumor cells and immune cells enriches for responders, but not in all tumor types

Presence of TILs and immune gene expression signatures are prognostic in ovarian cancer (hence immunotherapy makes sense)

TIL counts per HPF
- Negative (17%)
- Low: 1-2 (17%)
- Moderate: 3-19 (44%)
- High: >20 (22%)

JAMA Oncology 2017
Verhaak et al., JCI 2013
PD-1 blockade has limited activity in GYN cancers

Hamanishi et al., JCO 2015, Frenel et al., JCO 2017; Ott et al., JCO 2017
1. Single-agent immunotherapies are not sufficient for most GYN patients

2. Existing biomarkers are not sufficient in guiding GYN patient selection for immunotherapy
Tumor cells: mutational load and neoantigens as predictors of clinical benefit

MMR-D CRC/anti-PD-1

Bladder/anti-PD-L1

NSCLC/anti-PD-1+anti-CTLA-4

Most GYN cancers exhibit low mutational burden

Alexandrov et al., Nature 2013
BRCA mutation is associated with TIL infiltration and increased neoantigen load in HGSOC

Strickland et al, Oncotarget 2016
Neoepitope load does not always predict the immune phenotype and fate of ovarian tumor lesions

Jimenez-Sanchez et al., Cell 2017
Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): a monogenic disease driven by loss of BRG1 (SMARCA4)

Jelinic et al., Nat Genetics 2014; Witkowsky et al., Nat Genetics 2014; Ramos et al., Nat Genetics 2014
Despite low tumor mutational burden SCCOHTs exhibit immune-active tumor microenvironment.

Jelinic, Ricca, Merghoub, Levine, and Zamarin, JNCI: 2018
Mutations in SWI/SNF component PBRM1 predict response to immunotherapy in kidney cancer

Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing
Ovarian and endometrial cancers exhibit recurrent alterations in chromatin remodeling complex components

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Altered in 60% of all ovarian and 62% of endometrial cancers
Alterations in some driver pathways can predict resistance to immunotherapy

**Beta-catenin pathway in melanoma**

**PTEN pathway in melanoma**

Spranger et al., Nature 2015

Peng, et al., Cancer Discovery 2016
Changes in peripheral blood biomarkers can enrich for responders to immunotherapy

- **Absolute lymphocyte count (ALC)**
  - On treatment ALC increase is associated with survival in melanoma patients treated with ipilimumab (Ku G., et al., Cancer 2010)

- **ICOS+CD4+ lymphocytes**
  - On treatment sustained increase in ICOS+ CD4+ lymphocytes is associated with survival in melanoma patients treated with ipilimumab (Carthon, et al., CCR 2010)

- **CD8+PD-1+Ki67+ lymphocytes/tumor burden**

- **Serum autoantibodies**
  - Upregulation of serum autoantibodies predicts response to CTLA-4 blockade in prostate cancer (Kwek et al, J Immunol 2012)
Peripheral blood: T cell receptor (TCR) clonality

Low pre-treatment TCR clonality in blood has prognostic value. Possibly predictive value?

DCB is associated with increased peripheral expansion of intratumoral TCR clones

Snyder A et al. PLoS Medicine 2017
Host: stool microbiota signatures

Gopalakrishnan et al., Science 2018
Immunotherapy in GYN cancers makes sense, but will likely require combinations in most patients.

There is no single biomarker: optimal patient selection will depend on integration of tumor, blood, host, and environmental factors and these should be analyzed within the context of all trials.

Pitt et al., Immunity 2016