Immunotherapy for ovarian and cervical cancers

John B. Liao, MD, PhD

Strong rationale for immunotherapy in ovarian cancers

- Presence of tumor infiltrating lymphocytes in ovarian cancers associated with improved prognosis.
- A high CD8+ to regulatory T cell ratio is associated with improved prognosis.
- Multiple immunosuppressive players including:
  - Regulatory T cells
  - Myeloid derived suppressor cells
  - Inhibitory cytokines
  - Engagement of PD-1 with ligand PD-L1

Multiple negative trials evaluated use of immunotherapies for ovarian cancer

- ICIs used as monotherapies showed generally low response rates
- Phase 3 trials with the addition of ICI to chemotherapy have not shown advantage over chemotherapy alone
- Autologous tumor cell vaccine as maintenance therapy after frontline treatment did not show a significant improvement in recurrence free survival

Current use of immunotherapy for ovarian cancers

- Tumor agnostic approvals for ICI
  - MMR deficient or MSI high
  - High tumor mutational burden

- PD-L1 expression inconsistently associated with response to PD-1/PD-L1 directed therapies

- Tumor sequencing should be employed for all patients and may guide targeted therapies and clinical trial recommendations

Differences in responses to immunotherapies should be considered

- Data validating CA-125 in immunotherapy are limited.
- Responses to immunotherapy often more delayed and more durable
- Atypical radiographic responses may occur
  - Pseudoprogression
  - Lymph node progression
  - Ascites
- Most common radiographic response criteria do not account for delayed responses and pseudoprogression

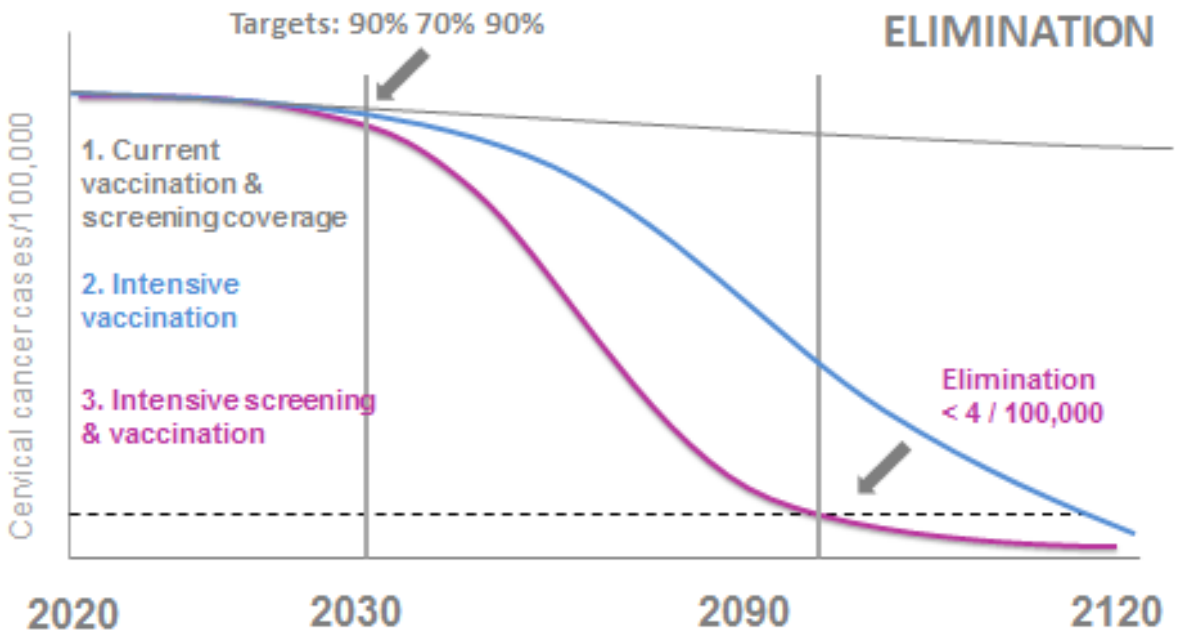
Investigational immunotherapy strategies for ovarian cancer

- Vaccines
- Cellular therapies, CAR T cells, engineered T cells
- Oncolytic viral therapies
- Bispecific antibodies
- Intraperitoneal chemoimmunotherapy

Summary

- Clinical trial enrollment should be offered
- Next generation sequencing should be offered to all patients with newly diagnosed ovarian cancer.
- For recurrent TMB-H and/or MSI-H/dMMR ovarian tumors, treatment with ICIs should be considered.
- Tumor PD-L1 expression should not be used for treatment decisions for ICI use in ovarian cancer.

Global Elimination of Cervical Cancer



1. Vaccinate 90% of girls against HPV by age 15
2. Screen 70% of women with high-precision tests at 35 and 45 years
3. Treat 90% of precancerous lesions and invasive cancer cases

World Health Organization, 2019

Pembrolizuamb approved for PD-L1 positive tumors in recurrent/metastatic cervical cancer that progress on or after chemo

- KEYNOTE 158 was a multicohort, nonrandomized basket trial
- KEYNOTE 158 demonstrated a 14.6% response rate in PD-L1 positive tumors in recurrent/metastatic cervical cancer treated with pembrolizumab monotherapy
- Response rate comparable to second line cytotoxic chemotherapy agents
- Median OS was 11 months

Pembrolizumab with chemotherapy +/- bevacizumab approved for persistent, recurrent, metastatic PD-L1 positive

- KEYNOTE 826, phase 3, placebo controlled, double blind randomized trial enrolled 617 patients
- ORR was 68% in PD-L1+ patients compared to 50% in PD-L1- patients
- Median PFS 10.4 months with pembrolizumab compared to 8.2 months without

Colombo 2021

Pembrolizumab with chemotherapy +/- bevacizumab : immune related toxicities

- 33.9% of patients receiving pembrolizumab experience immune related AEs.
- 11.4% were grade 3-5
- Hypothyroidism most common irAE (18.2% any grade)
- Hyperthyroidism second most common irAE followed by colitis

Pembrolizumab with chemoradiation for locally advanced cervical cancer

- Merck reports ENGOT-cx11/KEYNOTE-A18, a phase 3, randomized, double-blind study of pembrolizumab with chemoradiotherapy has met primary endpoint, PFS
- On the other hand, randomized phase III CALLA trial, which compared CRT plus durvalumab to CRT alone for the treatment of high-risk locally advanced cervical cancer, did not reach its primary PFS endpoint

Investigational immunotherapy strategies for cervical cancer

- Vaccines
  - Long peptides
  - Listeria
  - DNA
- Engineered TCR cellular therapies, CAR T cells, TIL therapy
- HPV targeting vaccines in combination with ICI, CRT, cellular therapies

Summary

- For all patients with cervical cancer, clinical trial enrollment should be offered, as feasible.
- For recurrent or metastatic cervical cancer that is PD-L1-positive (CPS≥1) and has progressed on or after chemotherapy, pembrolizumab should be considered.
- For metastatic cervical cancer that is PD-L1-positive (CPS≥1), pembrolizumab with chemotherapy with or without bevacizumab should be considered.
- For anti-PD- (L)1-resistant cervical cancer, currently there are no data to inform the sequencing of therapies and/or rechallenge with an ICI.