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What's New in Ovarian Cancer

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WHAT'S NEW IN OVARIAN CANCER

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OBJECTIVES

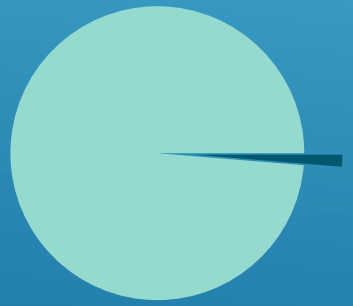
- Review trends in incidence and mortality in ovarian cancer
- Describe the role of hereditary and somatic genetic testing
- Discuss current patient evaluation recommendations for women presenting with ovarian cancer
- Discuss primary treatment options for a new diagnosis of ovarian cancer
- Discuss new therapies in recurrent disease

CLINICAL PRESENTATION & EVALUATION

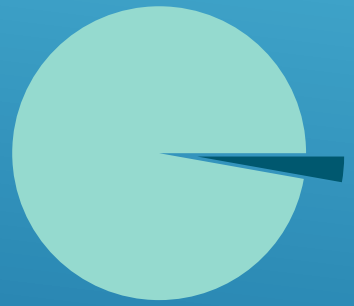
- Suspicious/palpable pelvic mass on abdominal/pelvic exam and/or ascites, abdominal distension
- Symptoms without source of malignancy
  - bloating, pelvic/abdominal Pain, difficulty eating or early satiety, urinary changes
- Ultrasound (TVUS), and/or CT A/P. PET/CT or MRI if indeterminate lesions.
- CA 125 and potentially other markers
- Family History
- Refer to GYN Oncology for clinically suspicious lesions.
  - GI additionally in some cases
- Diagnosis by previous surgery or tissue biopsy often a source of referrals

OVARIAN CANCER IS RELATIVELY RARE COMPARED WITH OTHER CANCERS

Incidence in United States[1,2]		Prevalence in United States[1]
11.4	**22,530**	**229,875**
new cases per 100,000 women per year[a]	*2019 projected total new diagnoses*	*based on 2016 estimates*



1.3%
Proportion of all new cancer diagnoses in USA in 2018[1]



2.5%
Proportion of all US cancer diagnoses in women up to 2015[3]

A woman's lifetime risk of getting ovarian cancer is about 1 in 78[2]

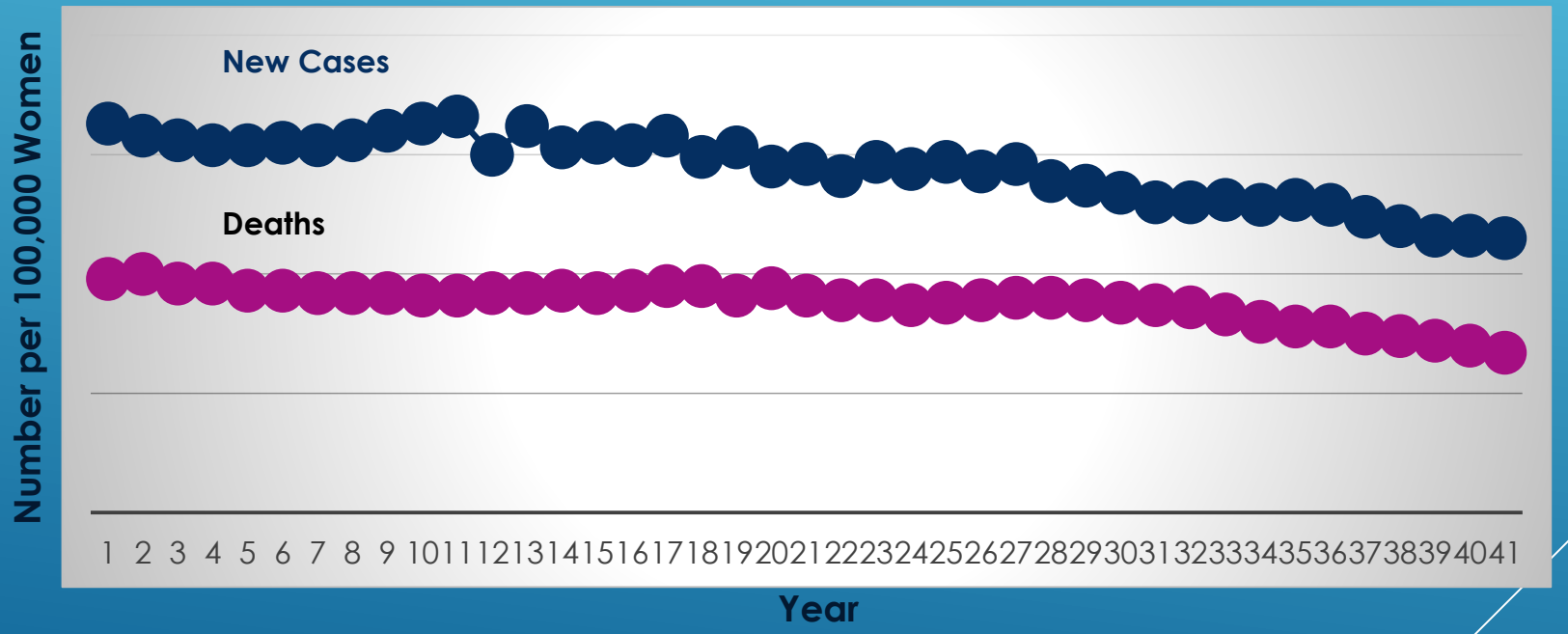
[a] Age-adjusted data from 2011–2016.

1. National Cancer Institute. SEER Cancer Stat Facts: Ovarian Cancer. http://seer.cancer.gov/statfacts/html/ovary.html. Published April 2019. Accessed May 9, 2019. **2.** American Cancer Society. Key Statistics for Ovarian Cancer. https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. Last revised January 8, 2019. Accessed January 9, 2019. **3.** American Cancer Society. Cancer Facts & Figures 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Published 2018. Accessed May 09, 2019.

EPIDEMIOLOGICAL TRENDS SHOW A DECLINE IN OVARIAN CANCER INCIDENCE AND MORTALITY

- **Over the last decade, ovarian cancer incidence has declined by 1.5% on average each year, while mortality has declined by 2.3% on average each year**

5 Year Survival Is 47.6%



National Cancer Institute. SEER Cancer Stat Facts: Ovarian Cancer. http://seer.cancer.gov/statfacts/html/ovary.html. Published April 2019. Accessed May 9, 2019.

FIGO OVARIAN CANCER STAGING

Stage	Stage Definitions[1]	Relative 5-Year Survival (%)[2]		
		Invasive Epithelial	Stromal	Germ Cell
I	**Tumor confined to ovaries/fallopian tube(s)** • IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube • IB: Tumor limited to both ovaries (capsule intact) or fallopian tubes • IC: Tumor limited to 1 or both ovaries or fallopian tubes with surgical spill (IC1), capsule ruptured/tumor on ovarian or fallopian tube surface (IC2), or malignant cells in ascites or peritoneal washings (IC3)	78–93	99	98
II	**Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer** • IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries • IIB: Extension to other pelvic intraperitoneal tissues	61–82	79	90
III	**Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with confirmed spread to peritoneum outside the pelvis and/or metastasis to retroperitoneal LNs** • IIIA1: Positive retroperitoneal LNs only • IIIA2: Microscopic extrapelvic (above pelvic brim) peritoneal involvement with or without positive retroperitoneal LNs • IIIB: Macroscopic peritoneal metastasis beyond pelvis up to 2 cm, with or without metastasis to retroperitoneal LNs • IIIC: Macroscopic peritoneal metastasis beyond pelvis more than 2 cm, with or without metastasis to retroperitoneal LNs (includes extension of tumor to liver and spleen capsule without parenchymal involvement)	28–63	63	87
IV	**Distant metastasis excluding peritoneal metastases** • IVA: Pleural effusion with positive cytology • IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal LNs and LNs outside of the abdominal cavity)	19	36	64

FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node.

1. Prat J, et al. *Int J Gynaecol Obstet*. 2014;124(1):1-5. **2.** American Cancer Society. Survival Rates for Ovarian Cancer, by Stage. https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html. Last revised April 11, 2018. Accessed May 09, 2019.

PRIMARY TREATMENT

- **Maximum Surgical Debulking**
  - Aim of surgery is to confirm diagnosis, define extent of disease spread (staging), and resect all visible tumor tissue
- **Platinum Based Chemotherapy-cornerstone of adjuvant therapy**
- **Always consider clinical trial options**

National Comprehensive Cancer Network® (NCCN®) Recommendations for Primary Surgical Treatment Based on Clinical Stage

Stage IA (fertility desired)MN	Stage IB (fertility desired)	Stage IA–IV Surgical Candidate (fertility not desired)	Bulky Stage III/IV or Poor Surgical Candidate
• Evaluation by gynecologic oncologist (GYN ONC) • Unilateral salpingo-oophorectomy (USO) • Comprehensive surgical staging	• Evaluation by GYN ONC • Bilateral salpingo-oophorectomy (BSO) • Comprehensive surgical staging	• Evaluation by GYN ONC • Total abdominal hysterectomy (TAH)/BSO • Comprehensive staging and debulking as needed	• Evaluation by GYN ONC • Histologic confirmation (biopsy preferred) • Consider neoadjuvant chemotherapy (category 1[c]) ± interval debulking surgery with TAH/BSO

DIAGNOSIS BY PREVIOUS SURGERY. ROLE FOR ADDITIONAL SURGERY?

- **Uterus Intact**
- **Adnexa Intact**
- **Omentum not removed**
- **Documentation of staging incomplete**
- **Residual disease, potentially resectable**
- **Occult invasive carcinoma found at time of risk reducing surgery**
- **Incomplete lymph node dissection**
- **Resectable=Surgery**

PLATINUM BASED CHEMOTHERAPY CORNER STONE

- **One of the platinum-based chemotherapy options recommended in the NCCN Guidelines as postoperative treatment for epithelial ovarian cancer is IV paclitaxel 175 mg/m^2 followed by carboplatin AUC 5–6 Day 1; repeat every 3 weeks**
- *Common Side Effects*:
  - **Myelosuppression**
  - **Alopecia**
  - **HSR's**
  - **Peripheral Neuropathy**
  - **GI disturbances**
  - **Other less common side effects**

BIOLOGIC IMPORTANCE OF OVARIAN CANCER

- Ovarian cancer is characterized by complex cellular and molecular processes.
  - Heterogeneous
- Histological subtypes impact prognosis
- The identification of molecular aberrations, such as *BRCA1/2*mutations and homologous recombination repair pathway deficiencies have shaped treatment strategies
- The tumor microenvironment affects the disease process and potentially clinical outcomes
- Biomarkers

GERMLINE VS. SOMATIC MUTATIONS

Germline Mutations
-Inherited from parents and become incorporated into DNA of every cell in the body of offspring

Somatic Mutations
-Acquired alterations in DNA that occur after conception that can (but do not always) cause cancer or other diseases

Germline Testing	Somatic Testing
• Well-established technique, easy extraction of DNA • Accurate and reproducible • Prognostic and predictive value supported by robust data • Assess risk of developing other cancers • Clinically relevant for family members • Will identify smaller number of patients who may benefit from treatment	• NGS will identify more patients who may benefit from treatment • Can help patients understand potential extent of benefit • Can serve as a triage for germline testing

NGS, next-generation sequencing.

Frey MK, et al. *Gynecol Oncol Res Pract.* 2017;4:4.

FDA-APPROVED OPTIONS FOR FIRST LINE MAINTENANCE THERAPY

Registrational Clinical Trial(s)	Drug	Indication	Biomarker Testing Required?	Recommended Dosing
GOG-0218	Bevacizumab[1]	Bevacizumab in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent for treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	No	15 mg/kg IV q3w in combination with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg q3w as a single agent, for a total of up to 22 cycles or until disease progression, whichever occurs earlier
SOLO-1	Olaparib[2]	Olaparib maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} or s*BRCA*^{mut} advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to 1L platinum-based chemotherapy	Yes, FDA-approved companion diagnostic to select patients with g*BRCA*^{mut} disease	300 mg (two 150-mg tablets) bid

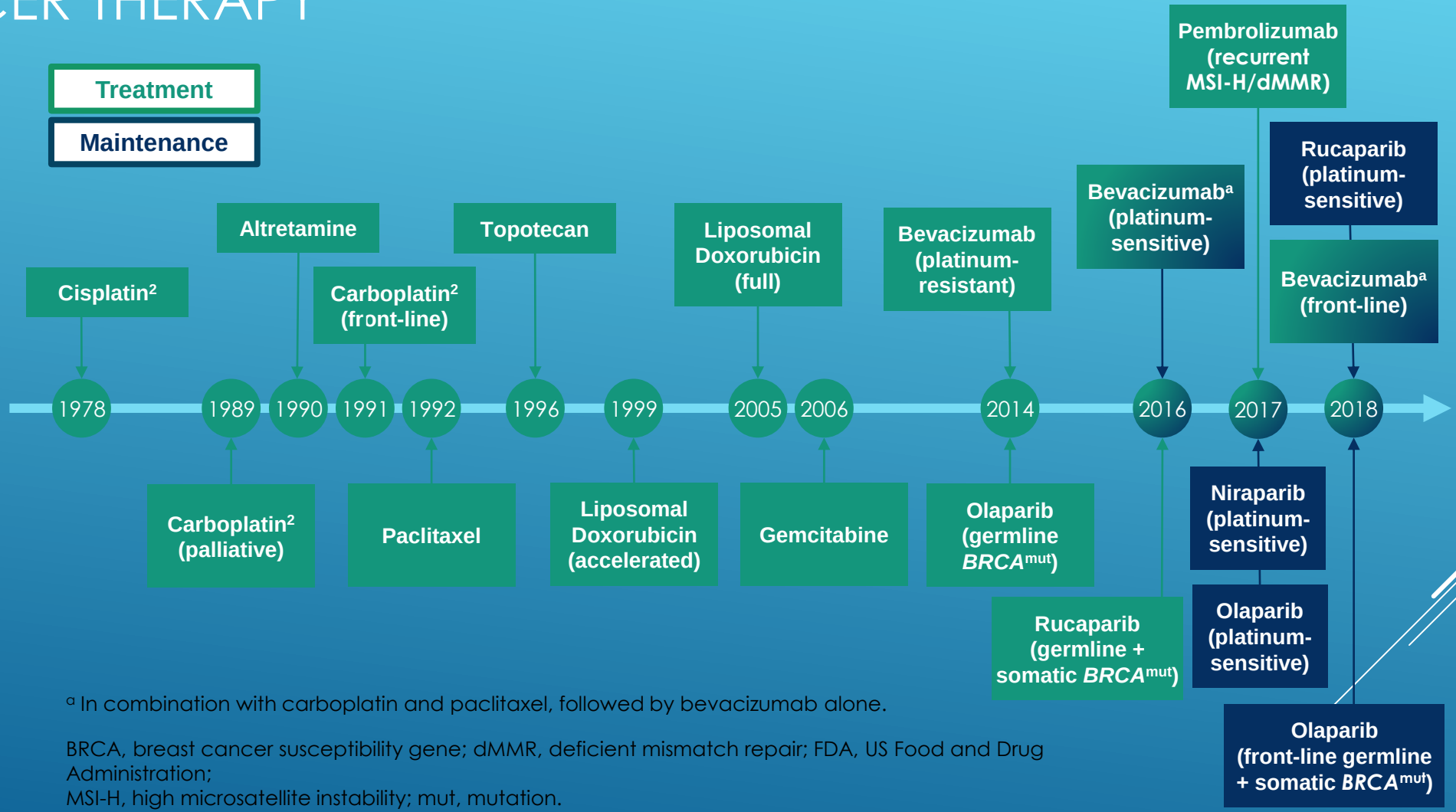
bid, twice daily; BRCA, breast cancer susceptibility gene; CR, complete response; FDA, US Food and Drug Administration; IV, intravenous; g, germline; L, line; mut, mutation; PR, partial response; q3w, every 3 weeks; s, somatic.

1. Bevacizumab package insert. Genentech, Inc; June 2018. 2. Olaparib package insert. AstraZeneca Pharmaceuticals LP; December 2018.

RECURRENT DISEASE

- **Follow-up/monitoring visits are suggested every 2–4 mo for 2 years, then 3–6 mo for 3 years, then annually after 5 years**
- **Most advanced ovarian cancers will recur during or after first-line treatment.**
- **Median progression-free survival decreases upon each subsequent recurrence.**
- **Patients with ovarian cancer whose disease recurs at least 6 months after treatment completion are considered to be platinum- or chemotherapy-sensitive.**

LANDMARK FDA APPROVALS IN OVARIAN CANCER THERAPY



[a] In combination with carboplatin and paclitaxel, followed by bevacizumab alone.

BRCA, breast cancer susceptibility gene; dMMR, deficient mismatch repair; FDA, US Food and Drug Administration;
MSI-H, high microsatellite instability; mut, mutation.

1. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 15, 2019. **2.** Kelland L. *Nat Rev Cancer.* 2007;7(8):573-84.

PLATINUM RESISTANT DISEASE

- Single-agent chemotherapy may result in response
- Double-agent chemotherapy resulted in similar response levels to single-agent treatment, but with more toxicity
- Patients with germline or somatic *BRCA* mutations may also respond to PARP inhibitors
  - Clinical activity has also been demonstrated in patients with HRD-positive disease
- Bevacizumab addition to chemotherapy improves response, PFS, and QoL, but does not improve OS

BRCA, breast cancer susceptibility gene; HRD, homologous recombination deficiency; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; QoL, quality of life; wt, wild-type.

1. Herzog TJ. *Clin Cancer Res*. 2004;10(22):7439-49. 2. Oronsky B, et al. *Med Oncol.* 2017;34(6):103. 3. Domchek SM, et al. *Gynecol Oncol.* 2016;140(2):199-203. 4. Konecny GE, et al. Presented at SGO Annual Meeting, 2017. Abstract 1. 5. Moore KN, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5514.
6. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-8. **7.** Stockler MR, et al. *J Clin Oncol*. 2014;32(13):1309-16

PARP INHIBITION SUMMARY

- **PARP inhibition is synthetically lethal for tumors with homologous recombination deficiency**
- **Currently, 3 PARP inhibitors are approved for patients with ovarian cancer across multiple indications**
  - **First Line maintenance therapy: Olaparib (*BRCA*^{mut})**
  - **Second Line maintenance therapy regardless of biomarker status (ie, including *BRCA*^{wt} and *BRCA*^{mut}): Olaparib, rucaparib, niraparib**
  - **Treatment therapy after multiple prior lines of chemotherapy: Olaparib (g*BRCA*^{mut}) and rucaparib (*BRCA*^{mut})**
- **Hematological adverse reactions are commonly associated with PARP inhibitors. Regular lab monitoring.**
- **Ongoing clinical trials are examining the efficacy of PARP inhibition across various lines of therapy and treatment approaches, including combination regimens**
- **PARP inhibition has shown clinical efficacy in patients without HRD**

BRCA, breast cancer susceptibility gene; g, germline; HRD, homologous recombination deficiency; L, line; mut, mutation; PARP, poly ADP ribose polymerase; wt, wild-type.

1. Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137-54. **2.** Olaparib package insert. AstraZeneca Pharmaceuticals LP; December 2018. **3.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **4.** Niraparib package insert. TESARO, Inc; February 2019. **5.** ClinicalTrials.gov: NCT02282020, NCT02446600, NCT02470585, NCT02477644, NCT02502266, NCT02655016, NCT02855944, NCT03106987, NCT03278717, NCT03402841, NCT03519230, NCT03522246, NCT03534453, NCT03598270, NT03602859, NCT03642132, NCT03705156, NCT03709316, NCT03737643, NCT03740165, NCT03806049. Accessed January 15-16, 2019.
6. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.

FURTHER OPTIONS

- Programmed Death Ligand 1 (PDL-1)
  - Helps define the population most likely to benefit from immunotherapy
  - Pembrolizumab (Ketruda)
  - Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
- Immune Mediated Side Effects
- Clinical Trials
  - New Trial Coming
    - GOG-2018
      - Paclitaxel +/- for Recurrent Platinum-Resistant Ovarian Ca
    - CL-OVA-PO1
      - Autologous Dendritic Cells Loaded with Autologous Tumor Associated Antigens for Advanced Epithelial Ovarian Carcinomas

“ONCE YOU CHOOSE HOPE, ANYTHING’S POSSIBLE” CHRISTOPHER REEVE