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# Survive and Thrive 2019

## Framework for Understanding Rare Tumors in Ovarian Cancer

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# Objectives:

- Understand basic classification of rare ovarian cancers
- Review incidence and unique features
- Treatment choices in first line treatment
- Surveillance options
- Role of tumor and somatic genetic testing
- Discuss advocacy for rare tumors

NO DISCLOSURES

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# Challenges and Opportunities for Rare Ovarian Cancers

- Challenge and frustration of having a rare type of an already rare tumor
- Fewer cases to review and learn
- Harder to accrue and complete clinical trials
- Funding for research
- Diversity of mutations in each cell type
- Opportunities for collaborative research and support networking
- Opportunities for targeted therapies

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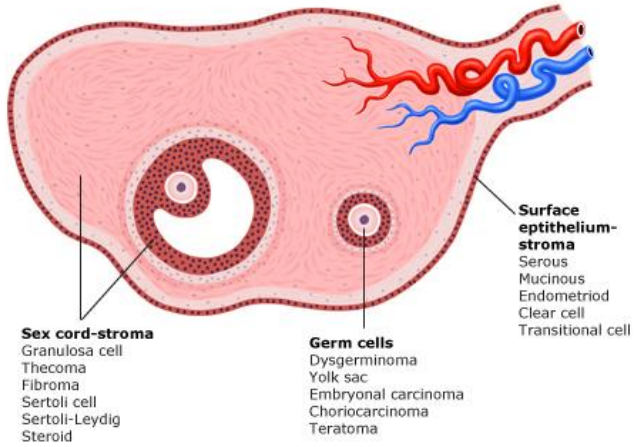
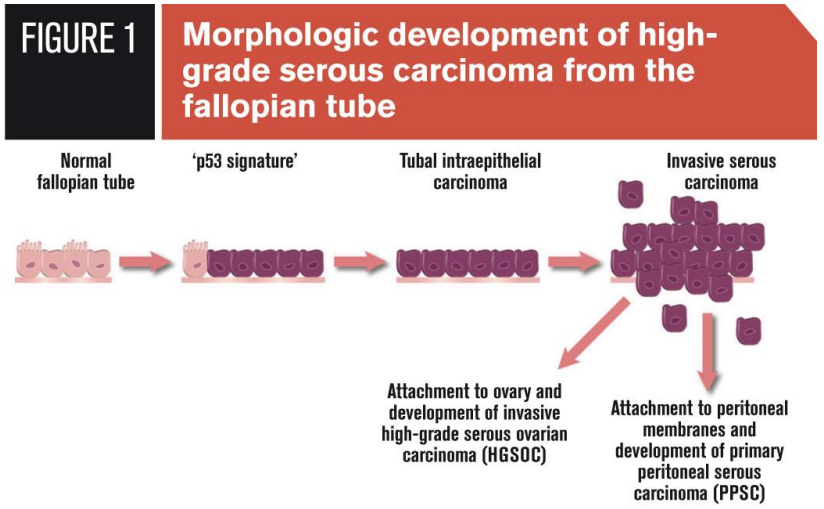



Not that simple

**Ovarian Cancer is not one disease**

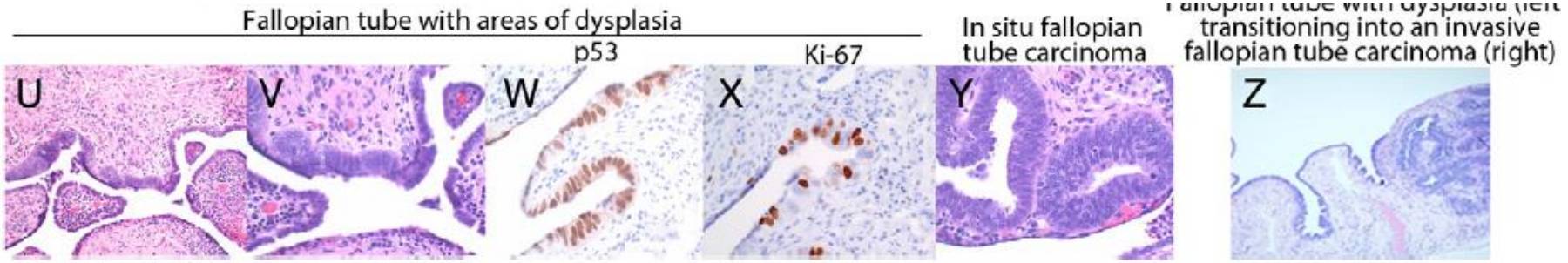



Source: Drapkin R, Karst AM. The new face of ovarian cancer modeling: Better prospects for detection and treatment. *F1000 Med Reports*. 2011;3:22. Used with permission.

Epithelial ovarian cancer

What is the Cell of origin?

- fallopian tube origin
- ovarian surface lining cells
- endometriosis
- lining of the peritoneal cavity

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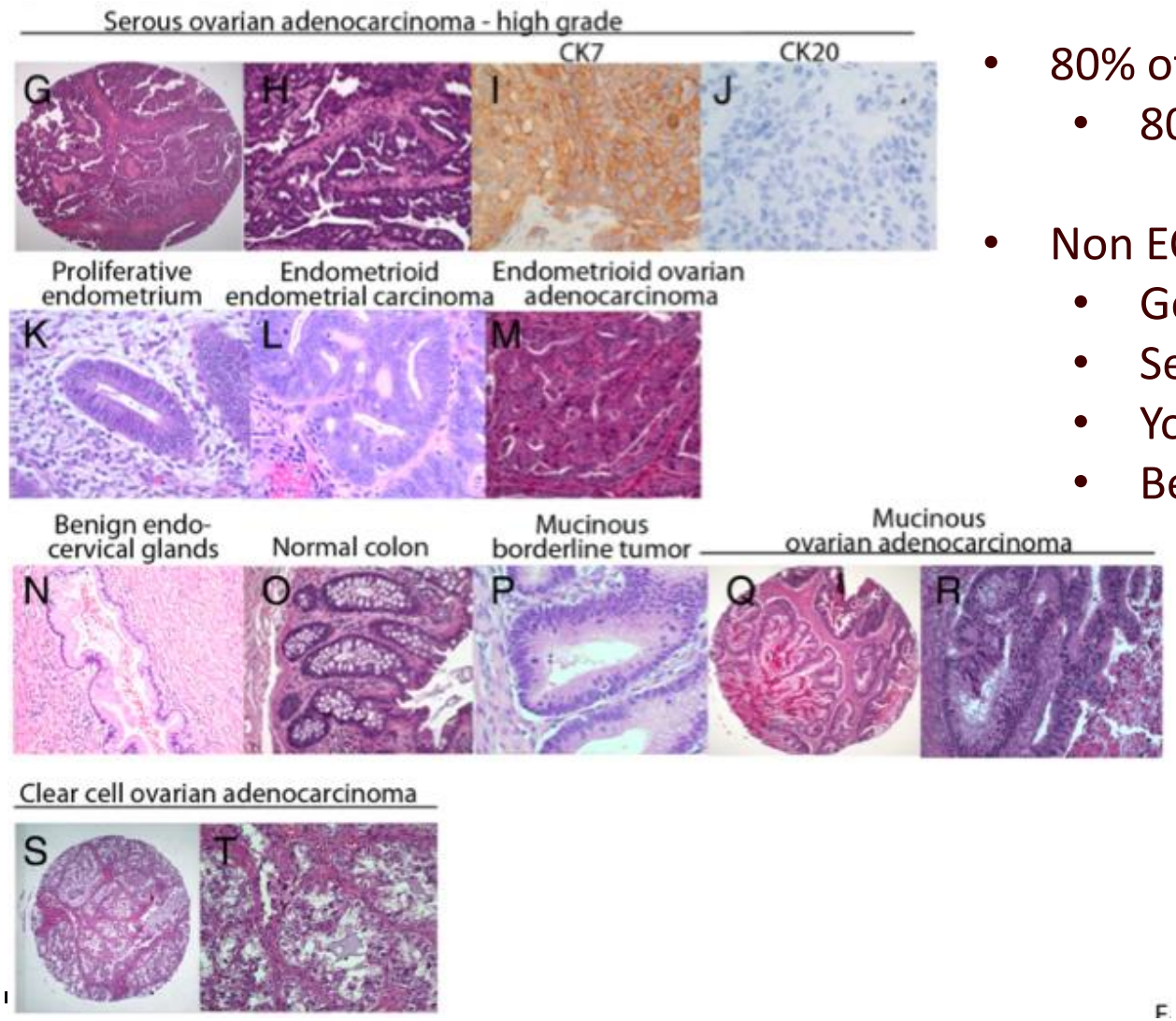
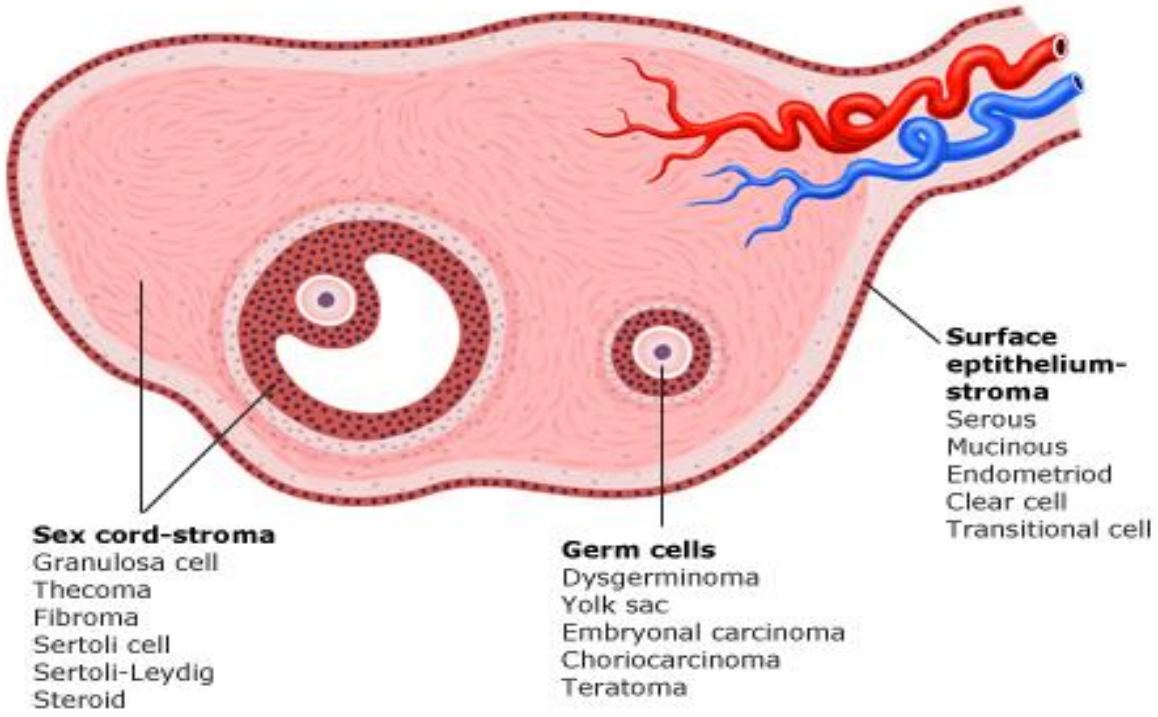
# Epithelial Ovarian Cancers (EOC)




- 80% of ovarian cancers are EOC
  - 80% are Serous carcinomas
- Non EOC
  - Germ Cell Tumors
  - Sex Cord Stromal Tumors
  - Younger age
  - Better outcomes

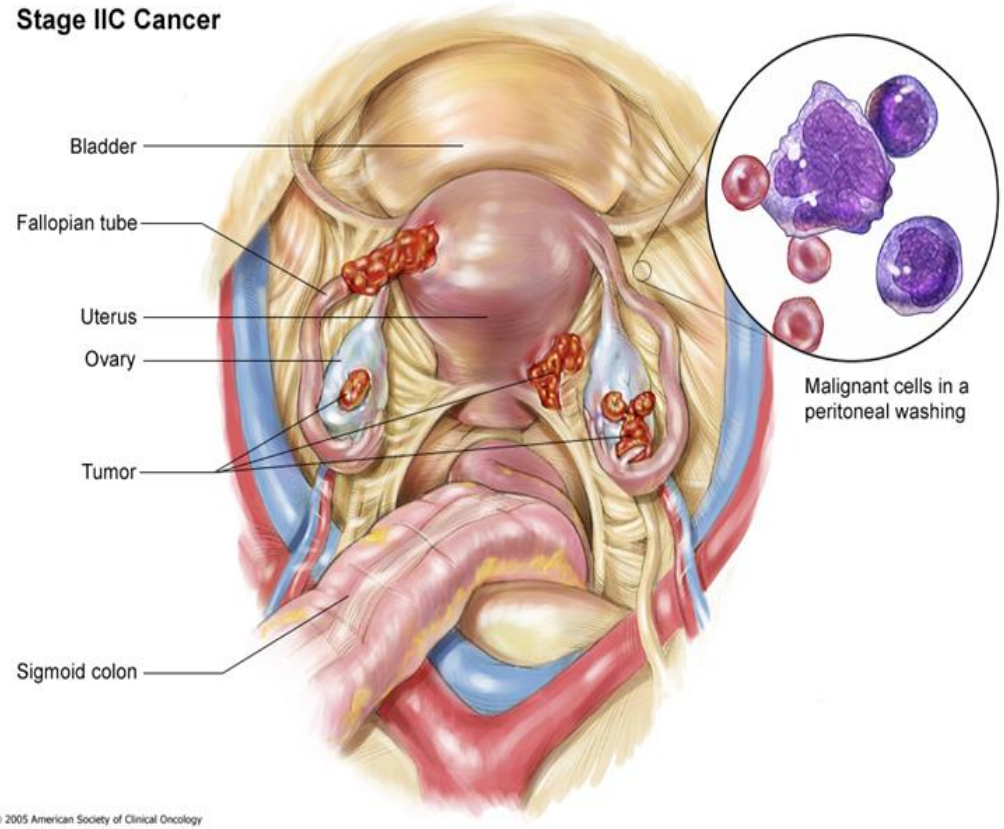
Lengyel E. Am J Path, Vol. 177, No. 3, Sep. 2010

# Types of Ovarian Cancer




**5-8% of ovarian cancers**

**~5%**

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**Epithelial Ovarian Cancer**
**Fallopian Tube Cancer**
**Primary Peritoneal Cancer**

# Rare Ovarian Cancers

- Epithelial Ovarian Cancer (high grade serous) ~ 80%
- Malignant Ovarian Germ Cell Tumors 5%
- Sex Cord Stromal Tumors 1.2%
- Rare Epithelial Ovarian Cancers
  - Clear Cell Carcinoma
  - Endometrioid Carcinoma
  - Mucinous carcinomas
  - Low grade serous carcinomas

# Cell types of epithelial ovarian cancers

| Type | WHC, % |
|---|---|
| Serous | 67.8 |
| Mucinous | 3.4 |
| Endometrioid | 8.6 |
| Clear Cell | 12.6 |
| Transitional | 0.6 |
| Mixed | 5.7 |
| Undifferentiated | 0.6 |
| Other | 0 |

These cell types may have differences in

<u>CLINICAL</u>

- Clinical presentation
  - Age; symptoms
- Optimal treatment regimens
- Recurrence risk
- Response to treatment

<u>BIOLOGIC/MOLECULAR</u>

- Different molecular mutations
- Different pathways that are turned on or off that promote cancer development

# Framework:

- Treatment Options
  - Primary
    - Maintenance
  - Recurrence
- Follow-up and Surveillance
- Unique Genetics or tumor mutations
- Novel therapies or clinical trials

***Use this framework to ask questions about your specific cancer***

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# Malignant Germ Cell Tumors of the Ovary

- Dysgerminoma
- Yolk Sac Tumors
- Embryonal carcinoma
- Choriocarcinoma
- Immature teratoma

# Sex Cord Stromal Malignant Ovarian Tumors 5-8%

- Adult granulosa cell tumor
- Juvenile granulosa cell tumor
- Sertoli-Leydig cell tumors 0.5% of ovarian cancers
- Sex cord tumor with annular tubules

- Indolent, slower growing
- Late recurrences

# Sex Cord Stromal Tumors

- **Unique features**
  - Younger patients 20-30s
  - Can secrete hormones (estrogen or testosterone)
  - Average size 16 cm ; pelvic mass at presentation
- **Treatment Options**

| | |
|---|---|
| Primary | Surgery; Fertility sparing options<br>Chemotherapy |
| Recurrence | Repeat surgery<br>Chemotherapy |

- **Follow-up and Surveillance**
  - Tumor markers
  - Decision regarding imaging
- **Unique Genetics**

| | |
|---|---|
| Granulosa cell tumors | Tumor Mutation FOXL2 mutation |
| Sertoli-Leydig cell tumors | DICER 1 genetic mutation |

- **Novel therapies or clinical trials** **GOG 264**

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# DICER 1 – Hereditary Cancer Mutation

- Inherited germline mutation
- Sertoli-Leydig tumors
- Other cancers: pleuropulmonary blastoma, cervical sarcoma

# Rare Epithelial Ovarian Cancers

- Endometrioid carcinoma (10 %)
- Clear cell carcinoma (5-10 %)
- Mucinous carcinoma (3-4 %)
- Low grade serous carcinoma (< 5%)
- Carcinosarcoma (2-5%)
- Transitional cell carcinoma (< 2%)
- Small cell carcinoma (< 3%)

# Low grade serous carcinoma

- **Unique features**
  - Younger patients than average EOC
  - Better overall survival may be seen
- **Treatment Options**

| | | | |
|---|---|---|---|
| Primary | Surgery; Fertility sparing options | | |
| | Chemotherapy | Stage II – IV | Concern for chemoresistance |
| | Consider Hormonal maintenance phase | | |
| Recurrence | Repeat surgery in select cases | | |
| | Chemotherapy | ex. Doxil, Avastin, | |

- **Follow-up and Surveillance**
  - Tumor markers — CA125
  - Decision regarding imaging
- **Unique Genetics or tumor characteristics**
  - Estrogen or Progesterone receptor positive — hormonal targets
  - Mutations in KRAS/BRAF/MAPK signaling pathway
  - Should get genetic testing but BRCA mutations less common ~5%
- **Novel therapies or clinical trials**
  - Avastin
  - Endocrine therapy
  - MEK inhibitors

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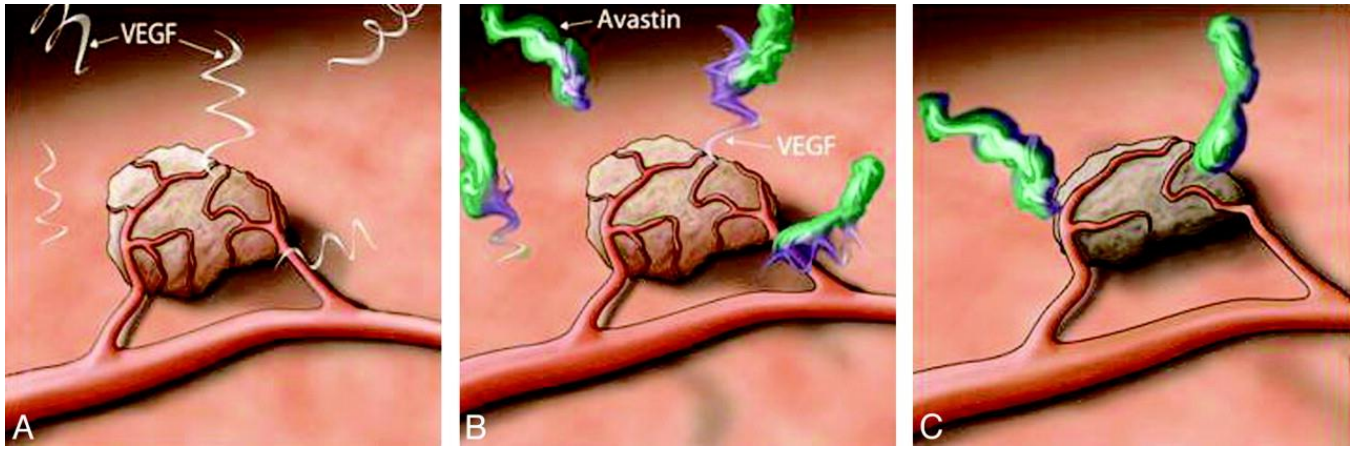
# Low grade serous carcinoma: Endocrine therapy Options

- Aromatase inhibitors
  - inhibits peripheral conversion of steroids to estrogen
- Tamoxifen
  - Selective estrogen receptor modulator (anti-estrogen effects)
- Fulvestrant (faslodex) -Fulvestrant
  - selective estrogen receptor degrader (SERD)
  - binds to the estrogen receptor and destabilizing it, causing the cell's normal protein degradation processes to destroy it.
- Leuprolide – GnRH agonist – chemical menopause

# Low grade serous carcinoma: Biologics

- Avastin The bevacizumab compound binds to the free VEGF and reduces the concentration of the free VEGF. *C*, The reduction of available VEGF results in diminished blood supply to the tumor and tumor shrinkage.

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# Low grade serous carcinoma: Targeted therapies

MEK Inhibitors

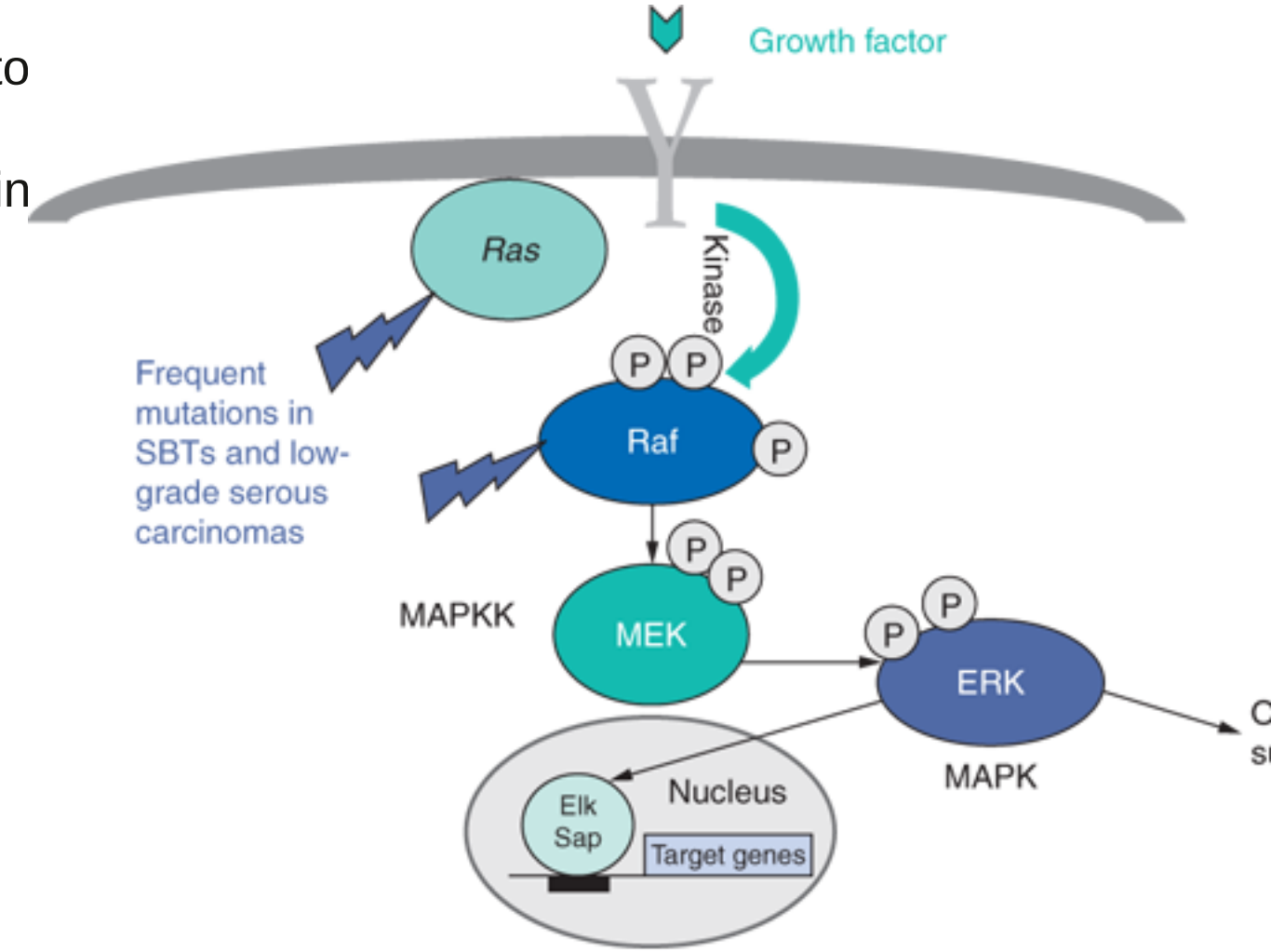
- GOG 239 Selumetinib, a MEK1/2 inhibito

response rate of 15%, with stable disease in 65% and an acceptable toxicity profile

- MILO Study

Phase 3 study of binimetinib or a chemotherapy chosen by a physician (liposomal doxorubicin, paclitaxel or topotecan)

Did not reach PFS improvement compared to advanced ovarian cancer




Source: B. Y. Karlan, R. E. Bristow, A. J. Li: Gynecologic Oncology: Clinical Practice and
www.obgyn.mhmedical.com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# Clear cell carcinoma

- **Unique features**
  - Perimenopausal age range
  - Can be associated with endometriosis
  - Risks of hypercalcemia, blood clots
- **Treatment Options**

| | | |
|---|---|---|
| Primary | Surgery; | |
| | Chemotherapy | Concern for chemor esistance |
| Recurrence | Chemotherapy | |
| | rare surgery for secondary | |

**Follow-up and Surveillance**

| | |
|---|---|
| Tumor markers | CA125 |
| Decision regarding imaging | |

- **Unique Genetics or tumor characteristics**
  - **ARID1 A mutations**
  - PIK3CAmutations(notedin40%ofOCCC)
    – Targeting the phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway
- **Novel therapies or clinical trials**

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# Clear Cell Carcinoma of the Ovary

- A Phase II Study of Tazemetostat (EPZ-6438) (IND # 138671) in Recurrent or Persistent Endometrioid or Clear Cell Carcinoma of the Ovary, and Recurrent or Persistent Endometrioid Endometrial Adenocarcinoma (CIRB) (NRG-GY014)

**GOG trials:**

- **GOG 254-Phase II evaluation of Sunitinib Malate in the treatment of persistent of recurrent clear cell ovarian carcinoma (Closed to patient entry September 2013; late breaking abstract at 2015 SGO))**
- **GOG 268 A Phase II Evaluation of Temsirolimus (CCI-779) (NCI Supplied Agent: NSC# 683864, IND# 61010) in Combination with Carboplatin and Paclitaxel followed by Temsirolimus (CCI-779) Consolidation as First-line Therapy in the Treatment of Stage III-IV Clear Cell Carcinoma of the Ovary (Closed to patient entry January 2014)**
- **GOG 283: A Phase II Trial of DCTD-Sponsored Dasatinib (NSC #732517 IND #73969) In Recurrent/Persistent Ovary, Fallopian Tube, Primary Peritoneal, Endometrial, or Endometriosis-Associated Clear Cell Carcinoma Characterized for the Retention or Loss of BAF250a Expression. (suspended )**
- **GY-001: A randomized phase II study of XL-184 (cabozantinib) in recurrent clear cell carcinoma (Dr Farley)**
  - **(VEGFR2 inhibitor)**

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# Mucinous ovarian carcinoma

- **Unique features**
  - Presents in early stage often
  - Larger tumors
  - Often can be mets from GI tumors
- **Treatment Options**

| | | |
|---|---|---|
| Primary | Surgery; | |
| | Chemotherapy | Concern for chemoresistance |
| Recurrence | Chemotherapy | |
| | rare surgery for secondary | |

**Follow-up and Surveillance**

| | |
|---|---|
| Tumor markers | CEA |
| Decision regarding imaging | |

- **Unique Genetics or tumor characteristics**
  - KRAS mutations >75%
- **Novel therapies or clinical trials**
  - GI regimens may show promise Avastin HIPEC

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