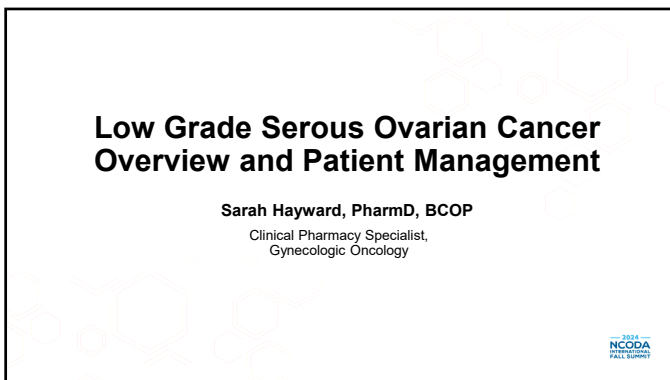
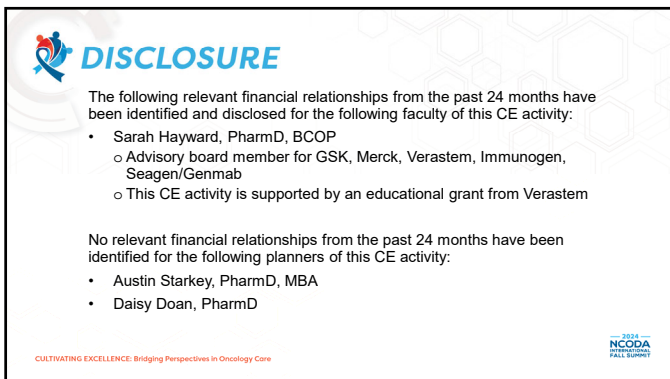




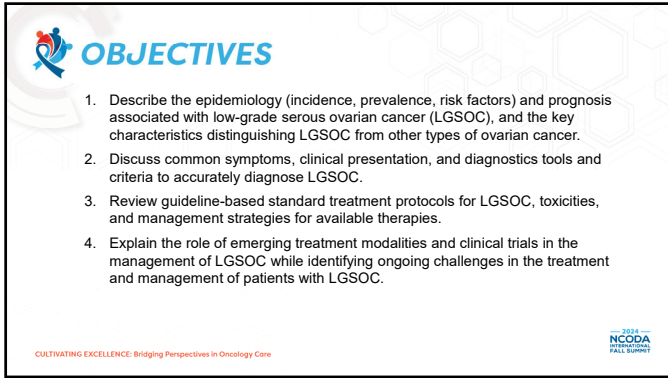
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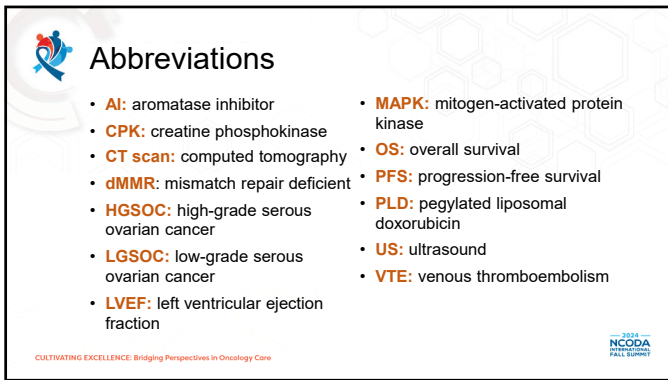
OBJECTIVES

1. Describe the epidemiology (incidence, prevalence, risk factors) and prognosis associated with low-grade serous ovarian cancer (LGSOC), and the key characteristics distinguishing LGSOC from other types of ovarian cancer.
2. Discuss common symptoms, clinical presentation, and diagnostics tools and criteria to accurately diagnose LGSOC.
3. Review guideline-based standard treatment protocols for LGSOC, toxicities, and management strategies for available therapies.
4. Explain the role of emerging treatment modalities and clinical trials in the management of LGSOC while identifying ongoing challenges in the treatment and management of patients with LGSOC.

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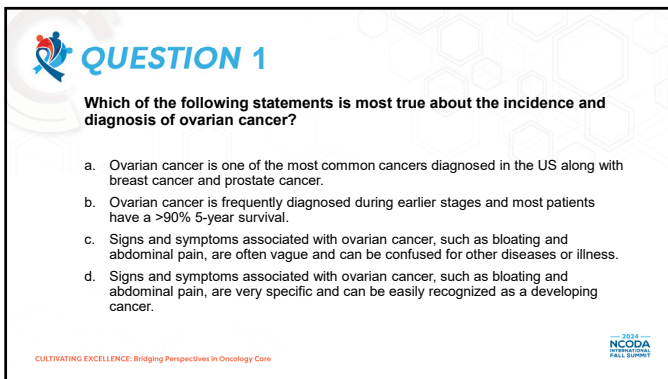
Abbreviations

- **AI:** aromatase inhibitor
- **CPK:** creatine phosphokinase
- **CT scan:** computed tomography
- **dMMR:** mismatch repair deficient
- **HGSOC:** high-grade serous ovarian cancer
- **LGSOC:** low-grade serous ovarian cancer
- **LVEF:** left ventricular ejection fraction
- **MAPK:** mitogen-activated protein kinase
- **OS:** overall survival
- **PFS:** progression-free survival
- **PLD:** pegylated liposomal doxorubicin
- **US:** ultrasound
- **VTE:** venous thromboembolism

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QUESTION 1

Which of the following statements is most true about the incidence and diagnosis of ovarian cancer?

- a. Ovarian cancer is one of the most common cancers diagnosed in the US along with breast cancer and prostate cancer.
- b. Ovarian cancer is frequently diagnosed during earlier stages and most patients have a >90% 5-year survival.
- c. Signs and symptoms associated with ovarian cancer, such as bloating and abdominal pain, are often vague and can be confused for other diseases or illness.
- d. Signs and symptoms associated with ovarian cancer, such as bloating and abdominal pain, are very specific and can be easily recognized as a developing cancer.

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Ovarian Cancer Statistics – US 2024

% of all new cancer cases 1%	% of all cancer deaths 2.1%	5-Year Survival 50.9%
18th most common cancer (all)	Frequently diagnosed in later stages	Median age at diagnosis 63 y/o

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Histology of Ovarian Cancer

- Ovarian cancer includes multiple histological subtypes
- Proper diagnosis requires identification by pathology
- Epithelial ovarian cancer is the most common and includes fallopian tube and primary peritoneal cancers.

```

graph TD
    OC[Ovarian Cancer] --> E[Epithelial 95%]
    OC --> NE[Non-Epithelial 5%]
    E --> TI[Type I]
    E --> TII[Type II]
    NE --> GC[Germ Cell]
    NE --> SSC[Sex-cord stromal]
    NE --> O[Others]
    
```

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Histology of Ovarian Cancer

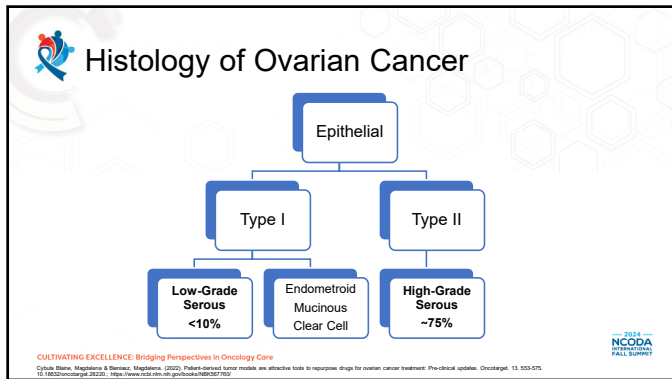
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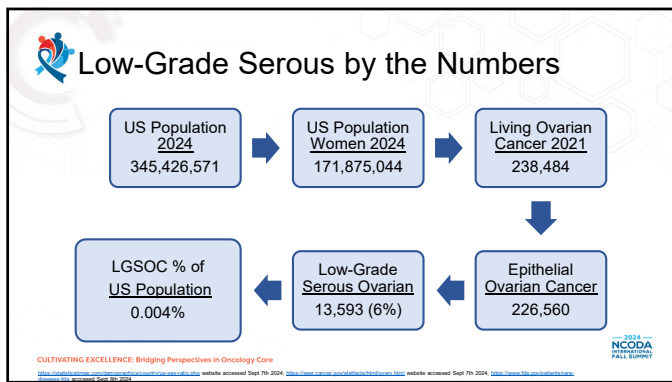
graph TD
    OC[Ovarian Cancer] --> E[Epithelial 95%]
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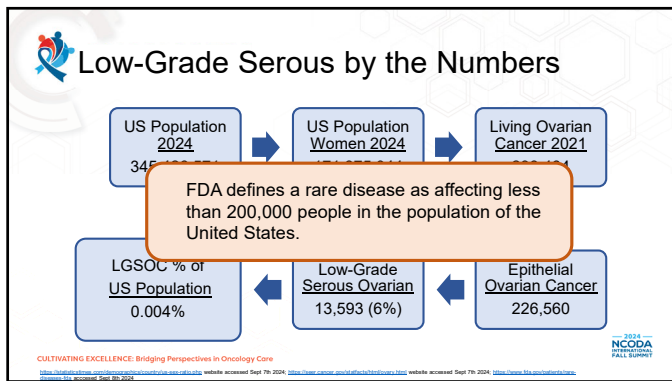
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12

Risk Factors for Ovarian Cancer

<ul style="list-style-type: none"> - Nulliparity - Hormone replacement therapy (maybe) - Family history - BRCA/Lynch/other gene mutations - Smoking (certain histology) 	<ul style="list-style-type: none"> - One or more pregnancies/births - Oral contraceptives - Breast feeding
--	---

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Graham RW et al. Low-grade serous ovarian cancer: expert consensus report on the state of the science. International Journal of Gynecological Cancer, Jan 2024. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer v2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 9, 2024. To view the most recent visit <https://www.nccn.org>

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Risk Factors for Ovarian Cancer

<ul style="list-style-type: none"> - Nulliparity - Hormone replacement therapy (maybe) - Family history - BRCA/Lynch/other gene mutations - Smoking (certain histology) 	<ul style="list-style-type: none"> - One or more pregnancies/births - Oral contraceptives - Breast feeding
--	---

LGSOC does not have a high association with BRCA mutations

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Graham RW et al. Low-grade serous ovarian cancer: expert consensus report on the state of the science. International Journal of Gynecological Cancer, Jan 2024. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer v2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 9, 2024. To view the most recent visit <https://www.nccn.org>

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QUESTION 2

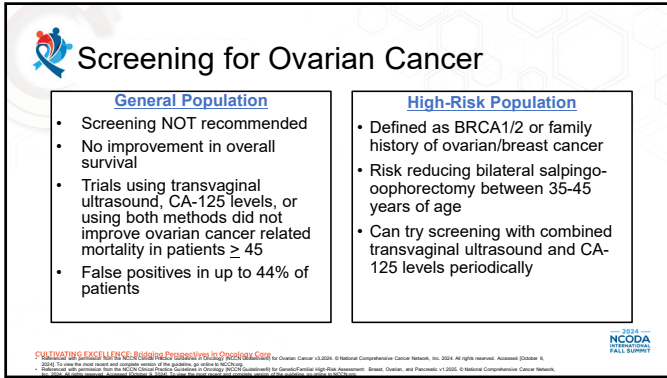
Assorted US and international medical societies recommend routine screening for ovarian cancer for all biological females once they have entered menopause.

Menopause is defined as not having had a period for at least 12 months in a row.

a. True
b. False
c. Maybe

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Screening for Ovarian Cancer

General Population

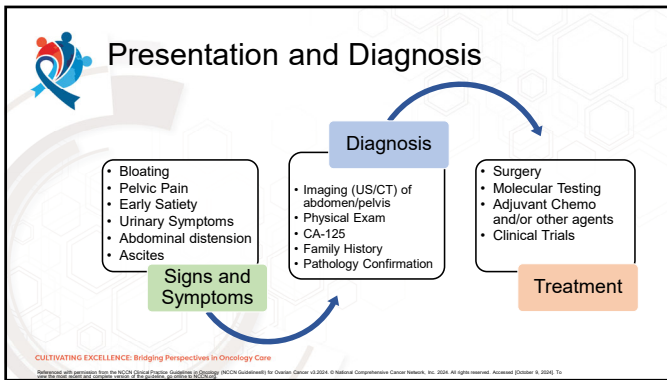
- Screening NOT recommended
- No improvement in overall survival
- Trials using transvaginal ultrasound, CA-125 levels, or using both methods did not improve ovarian cancer related mortality in patients ≥ 45
- False positives in up to 44% of patients

High-Risk Population

- Defined as BRCA1/2 or family history of ovarian/breast cancer
- Risk reducing bilateral salpingo-oophorectomy between 35-45 years of age
- Can try screening with combined transvaginal ultrasound and CA-125 levels periodically

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Presentation and Diagnosis

```

    graph LR
      A[Signs and Symptoms] --> B[Diagnosis]
      B --> C[Treatment]
  
```

Signs and Symptoms

- Bloating
- Pelvic Pain
- Early Satiety
- Urinary Symptoms
- Abdominal distension
- Ascites

Diagnosis

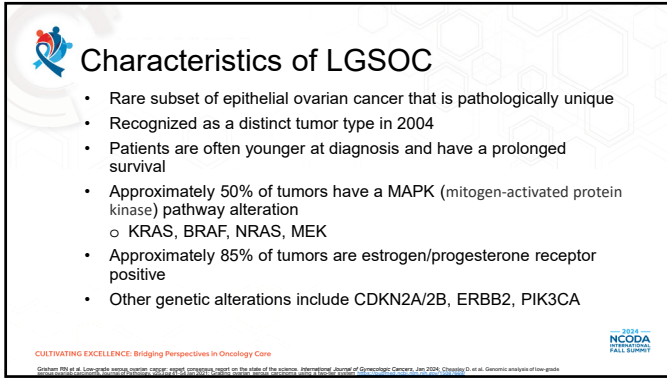
- Imaging (US/CT) of abdomen/pelvis
- Physical Exam
- CA-125
- Family History
- Pathology Confirmation

Treatment

- Surgery
- Molecular Testing
- Adjuvant Chemo and/or other agents
- Clinical Trials

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Characteristics of LGSOC

- Rare subset of epithelial ovarian cancer that is pathologically unique
- Recognized as a distinct tumor type in 2004
- Patients are often younger at diagnosis and have a prolonged survival
- Approximately 50% of tumors have a MAPK (mitogen-activated protein kinase) pathway alteration
 - KRAS, BRAF, NRAS, MEK
- Approximately 85% of tumors are estrogen/progesterone receptor positive
- Other genetic alterations include CDKN2A/2B, ERBB2, PIK3CA

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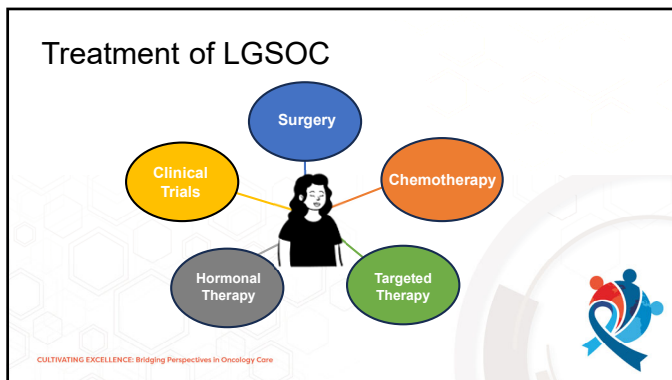


Low-Grade vs High-Grade

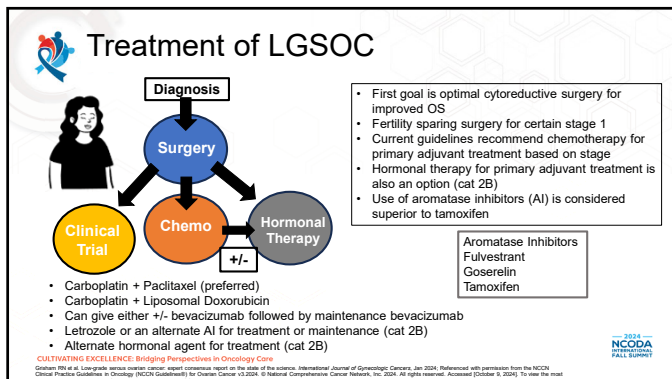
	LGSOC	HGSOC
Age at diagnosis	45-57 years	55-65 years
5-year survival	40-56%	9-34%
Speed of tumor growth	Slow	Rapid
Common gene mutations	KRAS BRAF	TP53
Initial surgery	Primary cytoreductive surgery to no gross residual is key to improved PFS and OS	Primary cytoreductive surgery to no gross residual is key to improved PFS and OS
Response to chemotherapy	More commonly resistant to paclitaxel + carboplatin	Less commonly resistant to paclitaxel + carboplatin

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Vang R, Shi JJ, Korman RL. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biology features, and diagnostic problems. *Adv Anat Pathol*. 2009; 16(1):20-33. Graham RH et al. Low-grade serous ovarian cancer: recent consensus report on the state of the science. *International Journal of Gynecology*. Canada. July 2004.

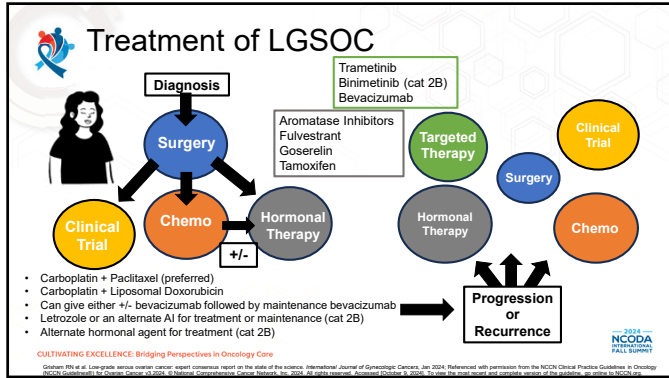
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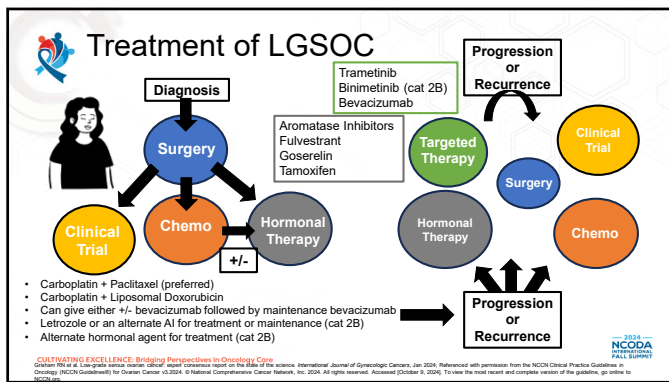
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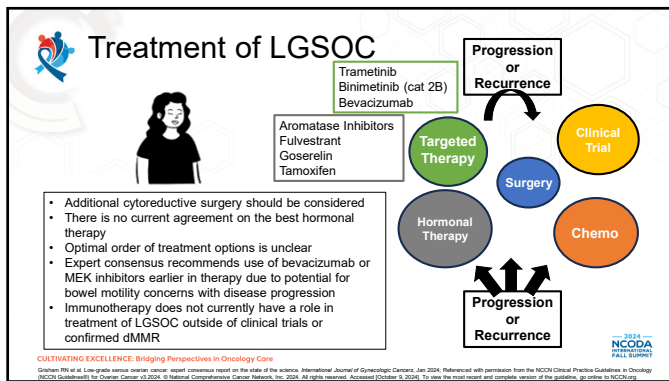
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Medications in LGSOC

- Chemo
- Targeted Therapy
- Hormonal Agents
- Clinical Trials

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Medications in LGSOC - Chemotherapy

- Chemotherapy regimens for use in LGSOC are similar those used in HGSOC
- First-line adjuvant therapy options include:
 - o Carboplatin + paclitaxel (preferred)
 - +/- bevacizumab
 - o Carboplatin + liposomal doxorubicin
 - o Carboplatin + docetaxel
- Therapies for recurrence could include single agent paclitaxel, liposomal doxorubicin, topotecan
- The concept of platinum-sensitivity does not apply to LGSOC

Chemo

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Adverse Events – Chemotherapy

Carboplatin	Paclitaxel
<ul style="list-style-type: none"> • Myelosuppression <ul style="list-style-type: none"> o Platelets • Nausea/Vomiting <ul style="list-style-type: none"> o Mod-highly emetogenic o 3-4 different antiemetics • Taste Changes • Nephrotoxicity • Allergic reactions 	<ul style="list-style-type: none"> • Myelosuppression • Neuropathy • Alopecia • Arthralgias/Myalgias • Hypersensitivity <ul style="list-style-type: none"> o Premed with antihistamines and corticosteroids

Chemo


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Medications in LGSOC – Targeted Agents

- Angiogenesis Inhibitors
 - Bevacizumab can be used with both primary treatment and recurrence
 - Data for use in LGSOC is based on trials including HGSOC and other subtypes
- MEK Inhibitors (oral therapy)
 - Trametinib
 - Can be given with dabrafenib in patients with BRAF V600E mutations
 - Binimetinib (cat 2B)

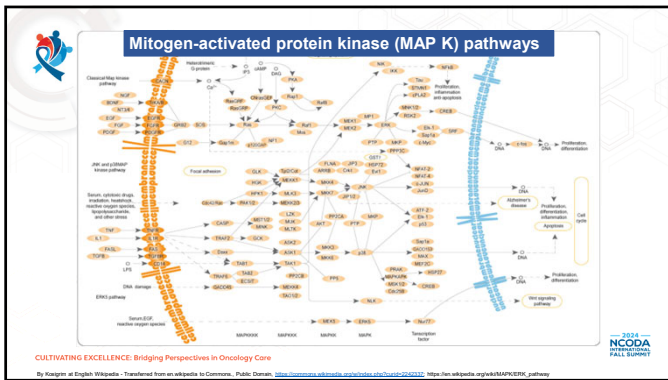


Targeted Therapy

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QUESTION 3

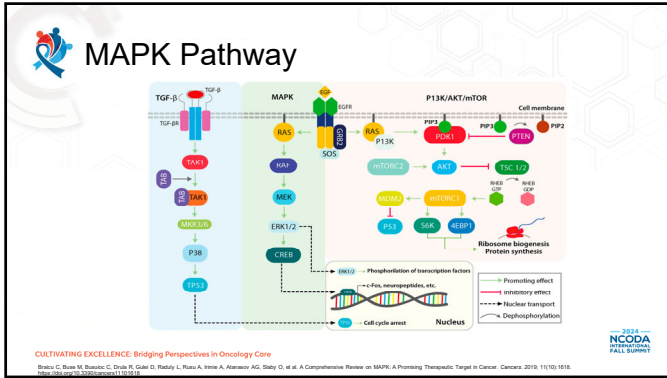
When considering the previous slide of mitogen-activated protein kinase (MAP K) pathways, please share your first reaction.

- I am somewhat familiar with the MAP K pathways, and I know that some medications take advantage of certain pathways to treat various diseases.
- I am a MAP K pathway expert and would love to make that slide my smart phone wallpaper.
- I just had a flashback from biology class of having to learn the Krebs cycle and my brain stopped working.
- I have no idea what was on the previous slide, but I bet I am going to find out.

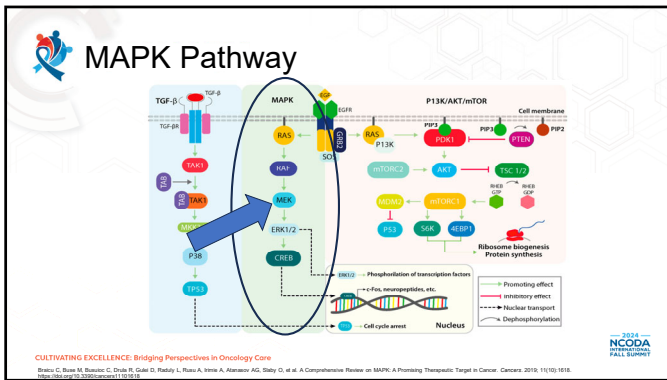
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Medications in LGSOC – Targeted Agents

- **Trametinib**
 - GOG-0281 → trametinib vs physicians choice (paclitaxel, PLD, topotecan, letrozole, tamoxifen)
 - Median PFS was greater in the trametinib group
 - 13 months trametinib vs 7.2 months
- **Binimetinib (cat 2B)**
 - MILO Study → binimetinib vs physicians choice (paclitaxel, PLD, topotecan)
 - Median PFS was greater in chemotherapy group
 - 9.1 months binimetinib vs 10.6 months
 - Overall survival greater in binimetinib group
 - 25.3 months binimetinib vs 20.8 months

Targeted Therapy

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
 Brady C, Bose M, Basovic C, Drake H, Glick D, Kelly L, Raza A, Srinivasan AG, Staley D, et al. A Comprehensive Review on MAPK: A Promising Therapeutic Target in Cancer. *Cancers*. 2019; 11(10):1618. <https://doi.org/10.3390/cancers11101618>

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Adverse Events - Bevacizumab

- Vascular endothelial growth factor (VEGF) inhibitor
- Hypertension
 - Patients should monitor blood pressure regularly
- Proteinuria/Nephrotic Syndrome
- Wound healing complications
- Arthralgias
- GI perforation/Fistula formation
- Hemorrhage
- Thromboembolism

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Astellor package insert, Genentech, 2022

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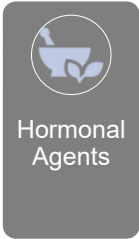
Adverse Events – MEK Inhibitors

Trametinib	Binimetinib
<ul style="list-style-type: none"> • Skin Rash (acneiform) <ul style="list-style-type: none"> ◦ Counsel on sun avoidance, SPF 30 • Moisturize skin • Diarrhea • Edema • Anemia • Fatigue • Hypertension • Cardiomyopathy <ul style="list-style-type: none"> ◦ Monitor LVEF • Ocular toxicity- Eye exams periodically • Hemorrhage or VTE • Pneumonitis 	<ul style="list-style-type: none"> • Mod-highly emetogenic • Skin Rash • CPK elevations • Diarrhea • Edema • Hypertension • Anemia • Ocular toxicity <ul style="list-style-type: none"> ◦ Eye exams periodically • VTE or hemorrhage • Fatigue • Cardiomyopathy <ul style="list-style-type: none"> ◦ Monitor LVEF

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Mekinist package insert, Novartis Pharmaceuticals Corporation, July 2024; Mekinist package insert, Array BioPharma Inc., June 2018

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Medications in LGSOC

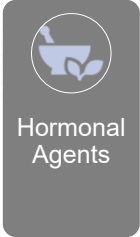
- Because the majority of LGSOCs are ER/PR positive, hormonal based therapies can be effective
- **Aromatase Inhibitors (AI)**
 - Anastrozole, exemestane, letrozole
- **Estrogen Receptor Antagonists**
 - Fulvestrant IM injection
- **Selective Estrogen Receptor Modulators**
 - Tamoxifen
- **Gonadotropin Releasing Hormone Agonist**
 - Goserelin
 - Leuprolide

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References: 1. American Society of Clinical Oncology. 2022. ASCO Guidelines for the Management of Low-Grade Serous Ovarian Cancer. 2022. 2. National Cancer Institute. 2023. 3. ASCO. 2023. 4. ASCO. 2023. 5. ASCO. 2023. 6. ASCO. 2023. 7. ASCO. 2023. 8. ASCO. 2023. 9. ASCO. 2023. 10. ASCO. 2023. 11. ASCO. 2023. 12. ASCO. 2023. 13. ASCO. 2023. 14. ASCO. 2023. 15. ASCO. 2023. 16. ASCO. 2023. 17. ASCO. 2023. 18. ASCO. 2023. 19. ASCO. 2023. 20. ASCO. 2023. 21. ASCO. 2023. 22. ASCO. 2023. 23. ASCO. 2023. 24. ASCO. 2023. 25. ASCO. 2023. 26. ASCO. 2023. 27. ASCO. 2023. 28. ASCO. 2023. 29. ASCO. 2023. 30. ASCO. 2023. 31. ASCO. 2023. 32. ASCO. 2023. 33. ASCO. 2023. 34. ASCO. 2023. 35. ASCO. 2023. 36. ASCO. 2023. 37. ASCO. 2023. 38. ASCO. 2023. 39. ASCO. 2023. 40. ASCO. 2023. 41. ASCO. 2023. 42. ASCO. 2023. 43. ASCO. 2023. 44. ASCO. 2023. 45. ASCO. 2023. 46. ASCO. 2023. 47. ASCO. 2023. 48. ASCO. 2023. 49. ASCO. 2023. 50. ASCO. 2023. 51. ASCO. 2023. 52. ASCO. 2023. 53. ASCO. 2023. 54. 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Medications in LGSOC

- Retrospective trial for use of hormonal agents for **maintenance** therapy in LGSOC (Gershenson DM, et al. 2017)
- Patient group → Stage II-IV, primary surgery followed by platinum-based chemotherapy, n = 203
- Hormonal therapy vs observation
 - AI (57%), tamoxifen (29%), leuprolide, leuprolide + letrozole or tamoxifen

	Progression Free Survival	Overall Survival
Observation n = 133	26.4 months	115.7 months
Hormonal Therapy n = 70	64.9 months	102.7 months



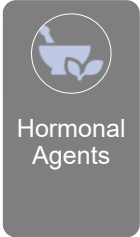
Hormonal Agents

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Gershenson DM, et al. 2017. Retrospective Trial of Hormonal Therapy in Low-Grade Serous Ovarian Cancer. *Curr Treat Options Oncol*. 2017;17(7):854-865. doi: 10.1007/s11804-017-0104-4

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Medications in LGSOC

- Retrospective trial for use of hormonal agents for **treatment after recurrence** in LGSOC (Gershenson DM, et al. 2012)
- Included single agent and combination hormonal agents
 - Time to progression = 7.4 months
 - Overall survival = 78.2 months
- PARAGON trial** → prospective, single arm, Phase II study of anastrozole after recurrence of ER/PR+ LGSOC
 - Response rate = 14%
 - Duration of benefit = 9.5 months



Hormonal Agents

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Gershenson DM, et al. 2012. Retrospective Trial of Hormonal Therapy in Low-Grade Serous Ovarian Cancer. *Curr Treat Options Oncol*. 2012;12(5):651-665. doi: 10.1007/s11804-012-0057-7

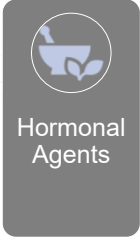
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Medications in LGSOC

GOG 281 → trametinib vs chemotherapy or hormonal agents for **treatment after recurrence** in LGSOC

	Progression Free Survival	Response Rate
Trametinib	15 months	26%
Letrozole	10.6 months	14%

	Progression Free Survival	Overall Response Rate
Trametinib	19.1 months	26%
Tamoxifen	3.7 months	0%



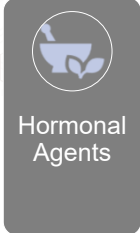
Hormonal Agents

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
GOG 281. Gershenson DM, et al. 2017. Retrospective Trial of Hormonal Therapy in Low-Grade Serous Ovarian Cancer. *Curr Treat Options Oncol*. 2017;17(7):854-865. doi: 10.1007/s11804-017-0104-4

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Adverse Events – Hormonal Therapy

Medication	Administration	Side Effects
Aromatase Inhibitors Anastrozole Exemestane Letrozole	Oral Tablets Daily administration	Hot flashes, arthralgias, myalgias, decreased bone mineral density, elevated cholesterol
Fulvestrant	Intramuscular (IM) Loading doses then monthly injections	Injection site pain, nausea, hot flashes, increased LFTs, fatigue
Tamoxifen	Oral Tablets Daily administration	Hot flashes, edema, increased risk of VTE, uterine cancer, drug interactions CYP2D6
Goserelin Leuprolide	Subcutaneous or IM Injection Monthly injections	Hot flashes, acne, edema, decreased libido, depression, decreased bone mineral density, increased heart disease




Hormonal Agents

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Anastrozole prescribing info: https://www.accessdata.fda.gov/drugsatfda_docs/nda/020122Orig1s001.pdf, website accessed Sept 17, 2024. Arimidex package insert, Phase 1/2021. Femara package insert, Novartis 1/2016. Fulvestrant package insert: https://www.accessdata.fda.gov/drugsatfda_docs/nda/020122Orig1s001.pdf, website accessed Sept 17, 2024. Exemestane package insert, Phase 1/2021. Femara package insert, Novartis 1/2016. Fulvestrant package insert: https://www.accessdata.fda.gov/drugsatfda_docs/nda/020122Orig1s001.pdf, website accessed Sept 17, 2024. Zoladex package insert, AstraZeneca, March 2002. Lutera Sheet, package insert, Novartis 2019.

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Medications in LGSOC - Trials

- **NRG-GY019** (NCT04095364)
 - o Phase III adjuvant treatment – Stage II-IV
 - o Carboplatin/paclitaxel x6 cycles followed by letrozole maintenance vs letrozole maintenance
 - o Estimated primary completion – Feb 2027
- **MATAO** (NCT04111978)
 - o Phase III adjuvant treatment – Stage II-IV
 - o Low-grade, high-grade, endometrioid EOC
 - o Carboplatin/paclitaxel followed by letrozole maintenance vs placebo
 - o Estimated primary completion – Oct 2025




Clinical Trials
Adjuvant Treatment

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Gruber, BB, et al. Low-grade versus ovarian cancer: novel concepts report on the state of the science. International Journal of Gynecologic Cancer. Jan 2024. 34(1):16-24. doi:10.1097/GIG.0000000000000000. website accessed 9/14/2024.
Gruber, BB, et al. Low-grade versus ovarian cancer: novel concepts report on the state of the science. International Journal of Gynecologic Cancer. Jan 2024. 34(1):16-24. doi:10.1097/GIG.0000000000000000. website accessed 9/14/2024.

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Medications in LGSOC - Trials

- **GOG-3026** (NCT03673124)
 - o Letrozole + ribociclib for recurrent LGSOC
 - o Initial data presented March 2023
 - 37 patients evaluated for response
 - Overall response rate 24%
 - 9 out of 37 had a partial response
- Ribociclib – CDK 4/6 inhibitor (cyclin-dependent kinase)
 - o Currently FDA-approved for HR+, HER2- breast cancer in conjunction with AI or fulvestrant



Clinical Trials
Recurrent Treatment

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Abstracts of 2023 GOG annual meeting: <https://www.goc.org/2023-annual-meeting>, website accessed 9/14/2024. KRSN21 package insert, Novartis, Oct 2022.


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QUESTION & ANSWERS

Low Grade Serous Ovarian Cancer Overview and Patient Management

Sarah Hayward, PharmD, BCOP
Clinical Pharmacy Specialist,
Gynecologic Oncology

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care




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CE CODE

Low Grade Serous Ovarian Cancer Overview and Patient Management


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CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care



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