

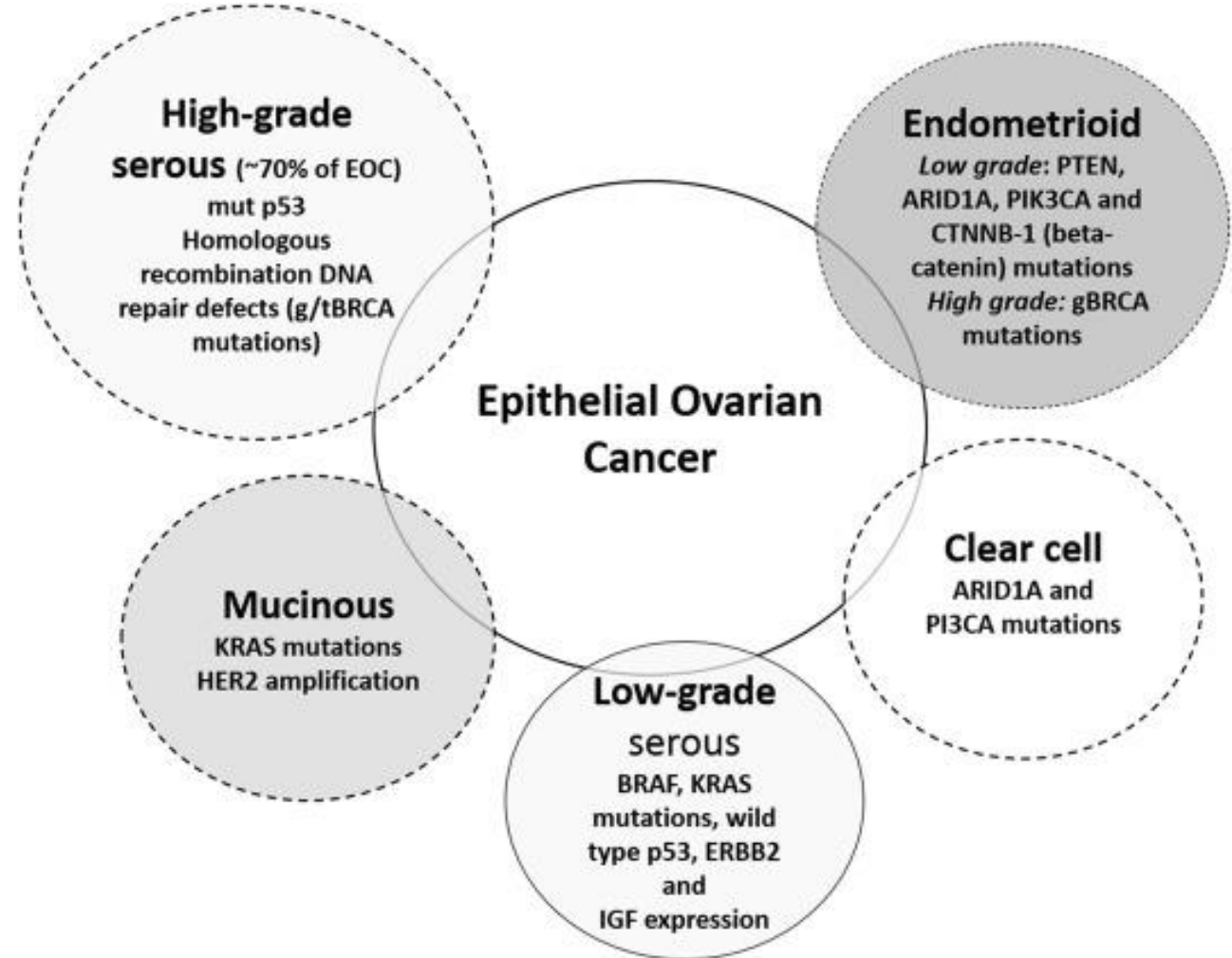


Board Review - Ovarian Cancer

Kalyan Banda
Assistant Professor, Clinical Research Division
September 2024

HISTOLOGICAL SUBTYPES

High grade serous and high grade endometrioid constitute the vast majority



Ledermann JA et al. Eur J Cancer 2016.

Question 1

- A 36-year-old woman presents to her gynecologist. Her sister was recently diagnosed with ovarian cancer, and she is concerned about her risk of developing this disease. The patient's sister underwent genetic counseling and tested negative for any known germline conditions associated with ovarian cancer. The patient had menarche at the age of 10. She is married and works as a social worker. She has taken oral contraceptive pills for the past 9 years and is G0P0. She exercises three times a week, and her BMI is 32. She follows a vegetarian diet.
- Which of the following factors is associated with a decreased risk of developing ovarian cancer?
 1. BMI of 32
 2. Prior oral contraceptive use
 3. Early menarche
 4. Nulliparity

Protective and risk factors

Protective

- OCPs
- Full term pregnancy
- Salpingo-oophorectomy
- Tubal ligation
- Hysterectomy
- Breast feeding

Risk

- Genetic mutations
- Family h/o
- Age
- White race
- Obesity
- Nulliparity, infertility
- 1st birth after 35
- Early menarche/late menopause
- Endometriosis
- Hormone therapy

Question 1

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 2. **Prior oral contraceptive use**
 3. Early menarche
 4. Nulliparity

Treatment

Surgery

- Diagnosis
- Staging
- Cytoreduction

Systemic Therapy

Recommended for nearly all patients

SURGICAL STAGING

Staging of disease
via surgery
especially
important

In an evaluation of 100 patients
believed to have
early-stage disease:

- 31% upstaged
- 77% were Stage III

Young RC et al. JAMA 1983.
Powless CA et al. Gynecol Oncol 2011.

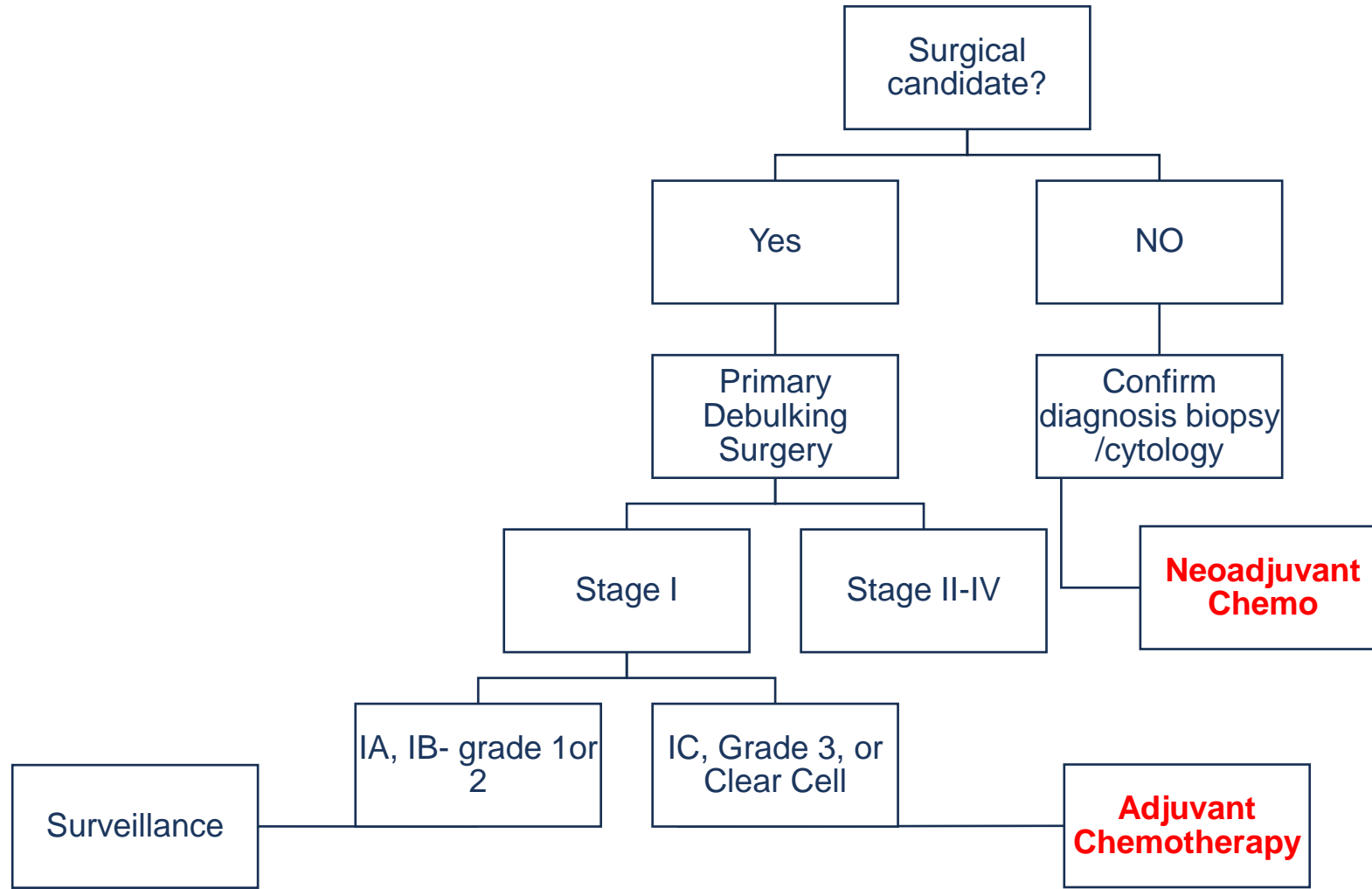
Question 2

- A 62-year-old G0P0 post-menopausal woman presents to her primary care physician with complaints of bloating and urinary frequency over the past 2 months. On examination, she is found to have a pelvic mass, and pelvic ultrasound shows a 6-cm mass in the left adnexa and trace fluid in the cul-de-sac. CT scan confirms the presence of a pelvic mass involving the left adnexa, demonstrates an atrophic right adnexa, and does not show other enlarged lymph nodes or intra-abdominal metastases. She is referred to her gynecologist, who performs a hysterectomy and left salpingo-oophorectomy. Pathology reveals a 7-cm, grade 3 endometrioid carcinoma involving the left ovary in a background of endometriosis. The endometrium is atrophic, a small fibroid is present, and the left fallopian tube is unaffected. She is referred for further management.
- What do you recommend?
 1. Observation
 2. Three cycles of chemotherapy with carboplatin and paclitaxel
 3. Six cycles of chemotherapy with carboplatin and paclitaxel
 4. Exploratory laparotomy, omentectomy, right salpingo-oophorectomy, lymphadenectomy, and peritoneal biopsies

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 3. Six cycles of chemotherapy with carboplatin and paclitaxel
 4. **Exploratory laparotomy, omentectomy, right salpingo-oophorectomy, lymphadenectomy, and peritoneal biopsies**

Upfront management- Suspected Ovarian Cancer



Chemotherapy Options

PRINCIPLES OF SYSTEMIC THERAPY

Primary Systemic Therapy Regimens^a - Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal

Primary Systemic Therapy Recommended Dosing

IV/IP Paclitaxel/cisplatin

- Paclitaxel 135 mg/m² IV continuous infusion⁹ Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m² IP Day 8
- Repeat every 21 days x 6 cycles

Paclitaxel 175/carboplatin^h

- Paclitaxel 175 mg/m² IV followed by carboplatinⁱ AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles^h

Paclitaxel weekly/carboplatin q3weeks

- Dose-dense paclitaxel 80 mg/m² IV Days 1, 8, and 15 followed by carboplatinⁱ AUC 5–6 IV Day 1
- Repeat every 21 days x 6 cycles

Paclitaxel weekly/carboplatin weekly

- Paclitaxel 60 mg/m² IV followed by carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)^f

Elderly Patients (age >70 years) and/or those with comorbidities

Paclitaxel 135/carboplatin¹

- Paclitaxel 135 mg/m² IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles^h

Paclitaxel weekly/carboplatin weekly

- Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)

Carboplatin¹

- Carboplatin AUC 5 IV given every 21 days

Docetaxel/carboplatin^h

- Docetaxel 60–75 mg/m² IV followed by carboplatin^c AUC 5–6 IV
- Repeat every 21 days x 3–6 cycles^h

Carboplatin/liposomal doxorubicin^h

- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m² IV
- Repeat every 28 days for 3–6 cycles^h

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab

- Paclitaxel 175 mg/m² IV followed by carboplatinⁱ AUC 5–6 IV, and bevacizumab 15 mg/kg IV Day 1
- Repeat every 21 days x 5–6 cycles
- Continue bevacizumab for up to 12 additional cycles

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab

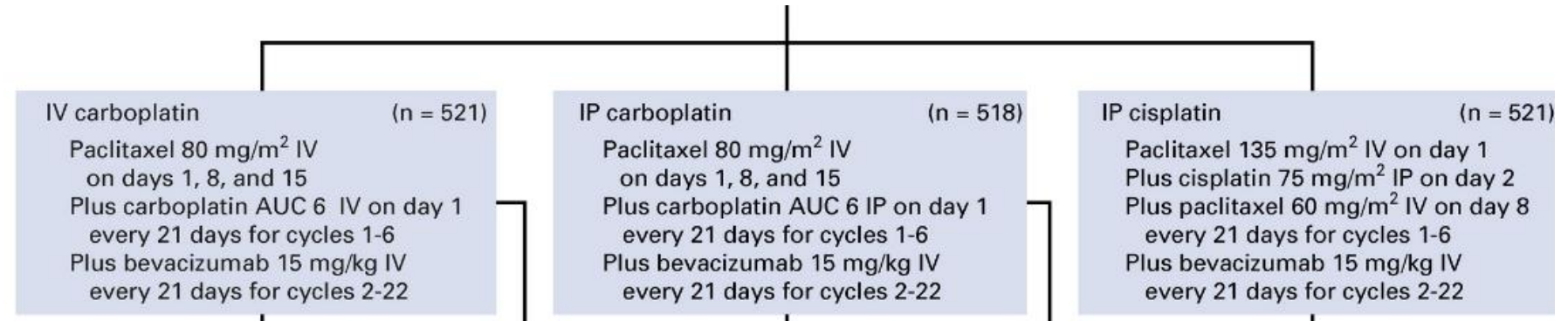
- Paclitaxel 175 mg/m² IV followed by carboplatinⁱ AUC 6 IV Day 1
- 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days x 22 cycles

NCCN

Intraperitoneal chemotherapy?

GOG 252

Stage II-IV ovarian cancer
Enrolled after primary surgery



Similar neurotoxicity scores for all arms

Worse FACT-TOI in IP cisplatin arm

Similar PFS and OS

Median OS 75.5 mos (IV C), 78.9 (IP C), 72.9 (IP cis)

Worse QOL, same outcomes – no really used today

Older patients?

MITO-7

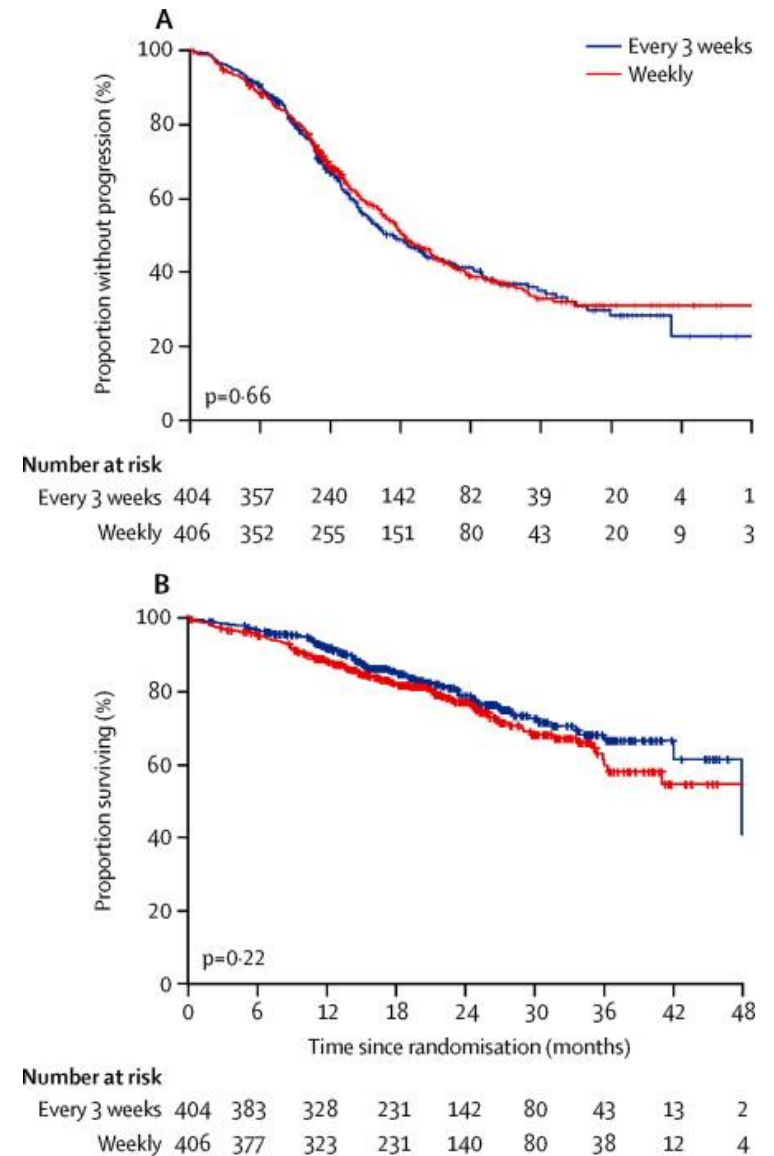
Stage IC-IV EOC
ECOG PS ≥ 2

Weekly Carbo (AUC 2)
and Taxol (60 mg/m²)

vs.

Every 3 week Carbo (AUC 6)
and Taxol (175 mg/m²)

Similar PFS & OS – Use in older or poor PS



Neoadjuvant chemotherapy

EORTC & CHORUS

- Does not change PFS or OS
- Decreased surgical morbidity and mortality.
- Increase rates of successful cytoreduction

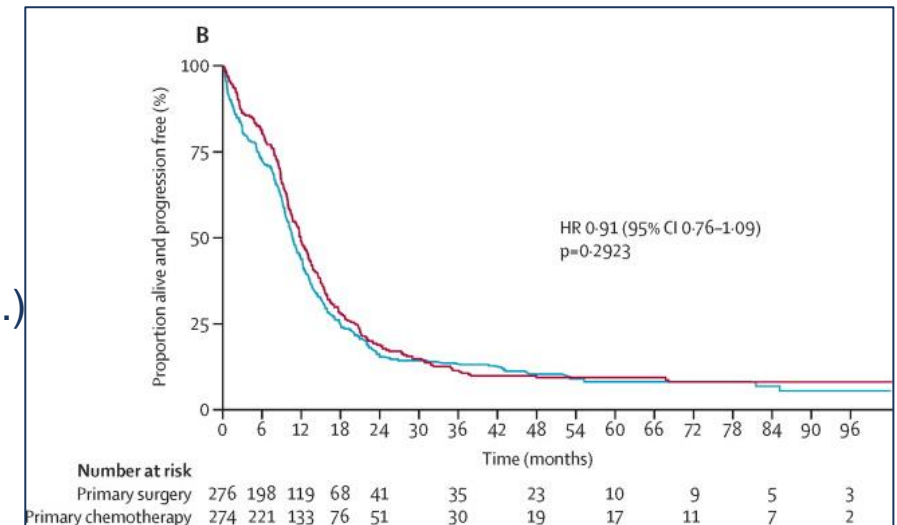
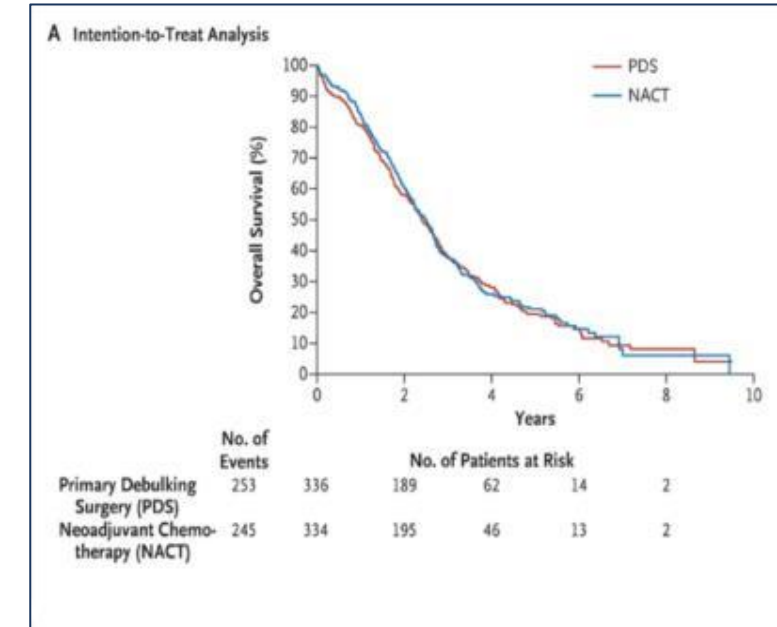
Establish diagnosis with biopsy

- If biopsy, not feasible cytology acceptable if:
- Presence of pelvic/ovarian mass.
- Presence of masses outside pelvis greater than 2 cm
- Lymph or metastasis or proof of stage IV (plural effusion/liver met, etc.)
- Ratio of CA 125: CEA > 200

Consider NACT– Poor operative candidates, low likelihood of

Surgical cytoreduction

Fred Hutch Cancer Center



Candidates for bevacizumab?

- **GOG – 218**
- Improve PFS, no OS difference.
- Stage IV – OS 42.8 months vs 32.6 months

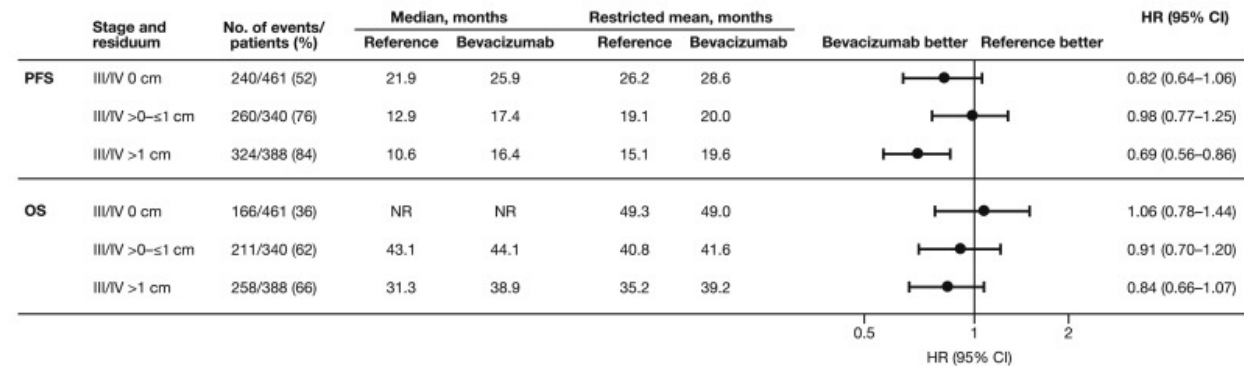
PFS benefit, no OS

Highest benefit in:

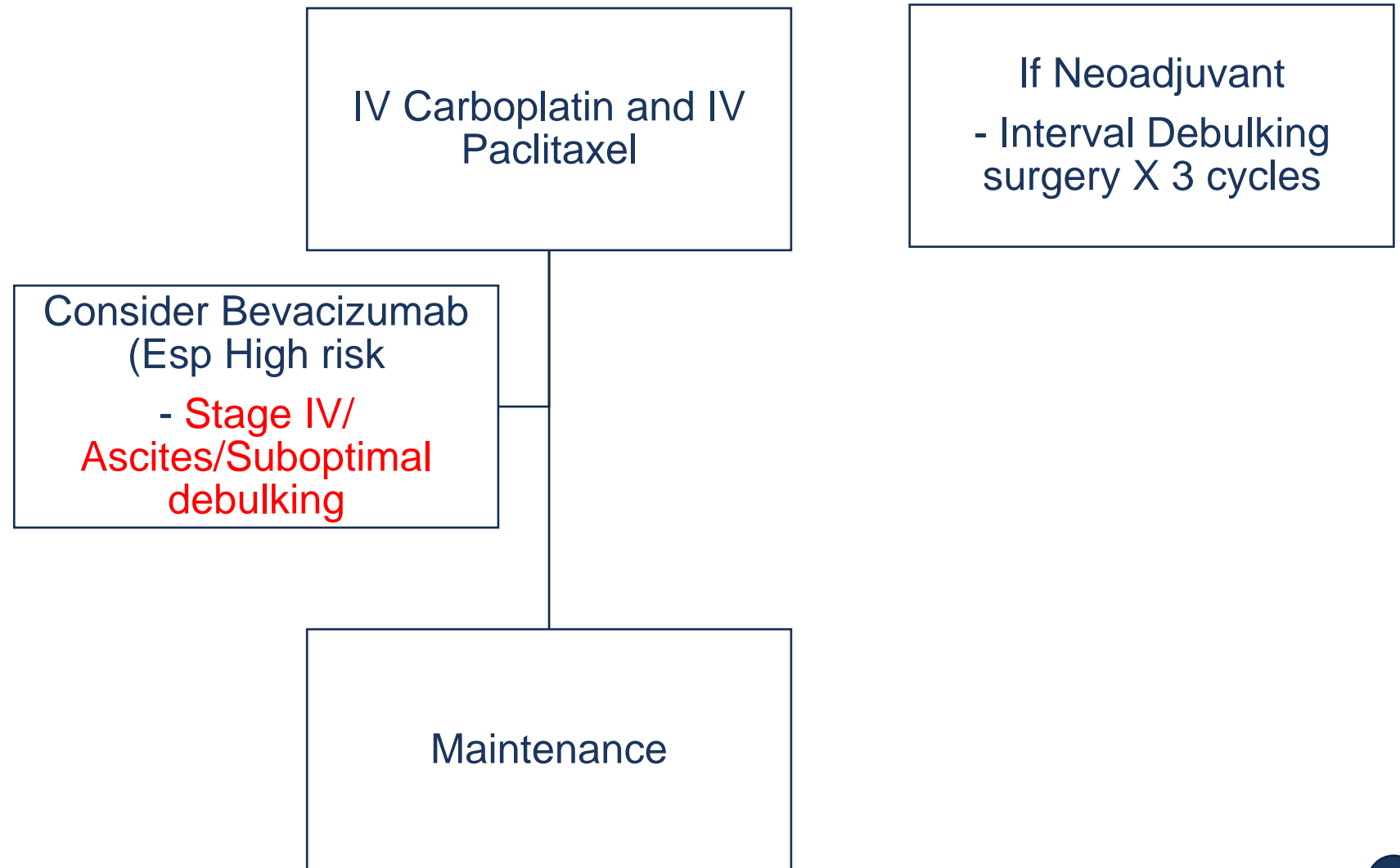
- **stage IV,**
- **>1 cm residual disease**
- **Ascites**

• **ICON-7**

- Improved PFS seen in "high risk" group (Stage IV disease, >1 cm residual disease at surgery)
- Trend towards improved OS



Systemic therapy



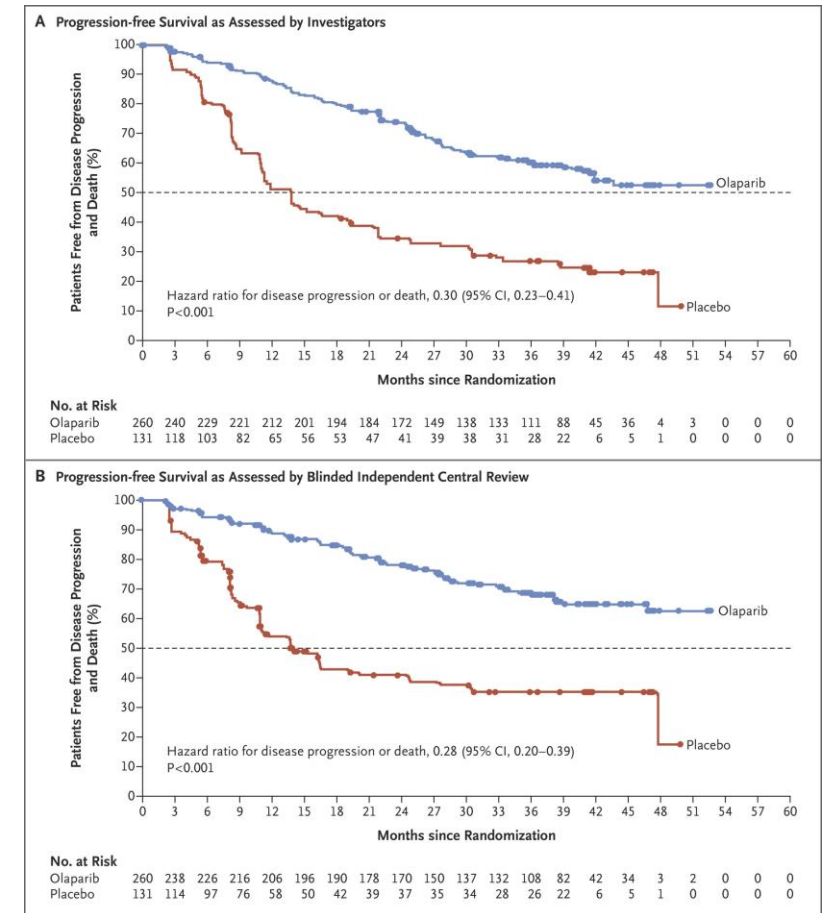
Maintenance Therapy

PARP inhibitors

In those with BRCA mutations – SOLO-1

- Randomized (2:1), placebo-controlled trial of **olaparib**
- Newly diagnosed stage III-IV high-grade serous or endometrioid ovarian cancer, *germline* BRCA 1 or 2 mutation
- After 5 years follow-up, median PFS 56 vs 14 months for olaparib vs placebo
- 1% patients on olaparib developed AML/MDS

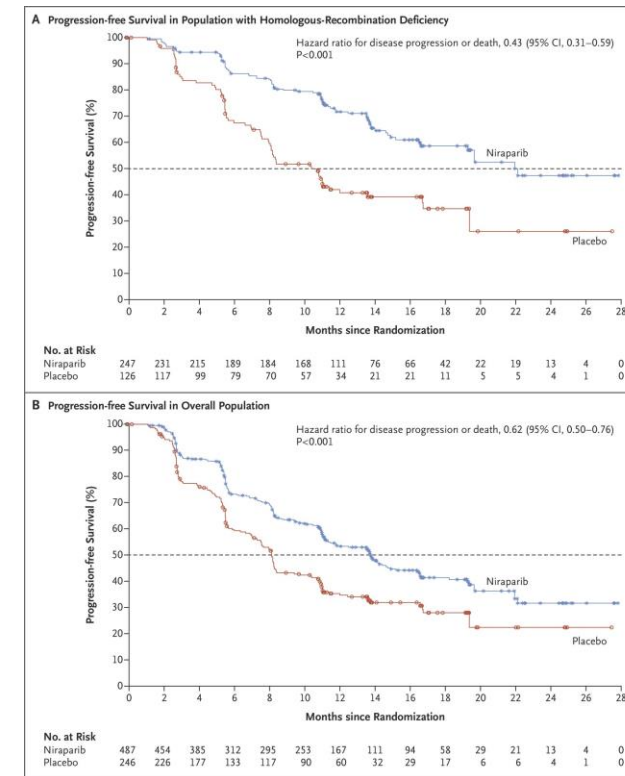
Marked benefit with two years of therapy



In all patients - PRIMA

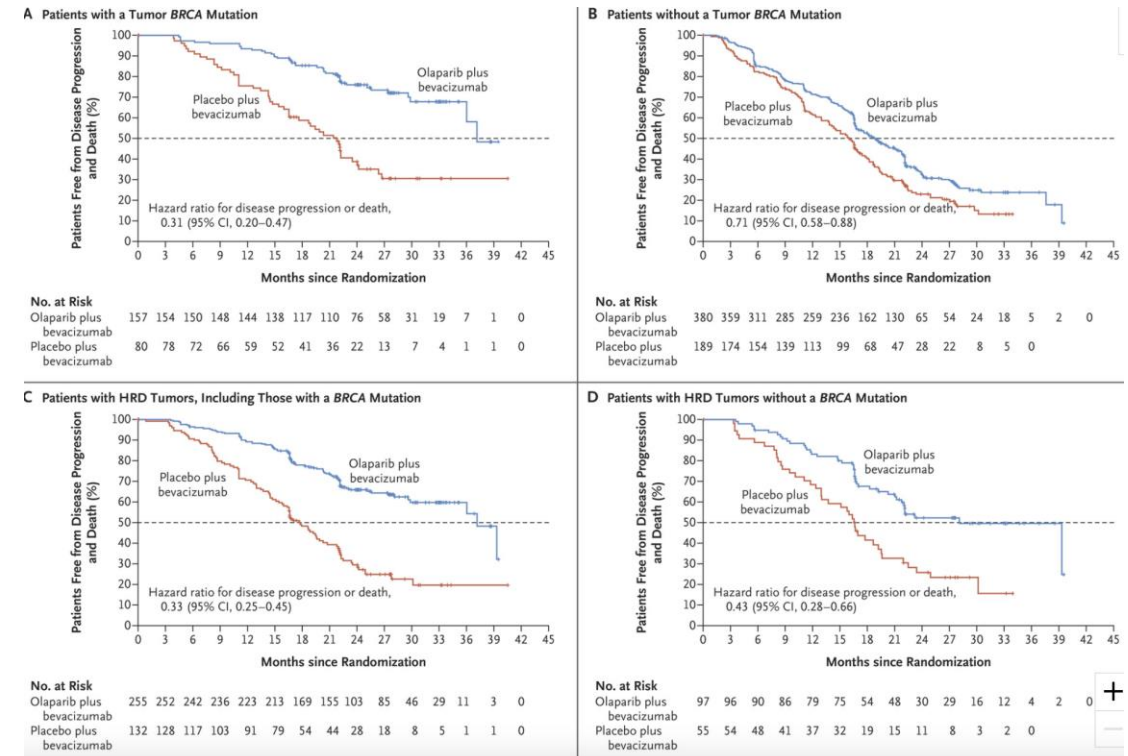
- **Niraparib**
- Newly diagnosed stage III-IV high-grade serous or endometrioid ovarian cancer, *with or without* mutations
- Median PFS in HR deficient - 21.9 months vs 10.4 months
- Median PFS in HR proficient - 8.1 months vs 5.4 months
- Median PFS in overall population 13.8 months vs 8.2 months
- Benefit in all patients regardless of HRD status

FDA approved for all patients



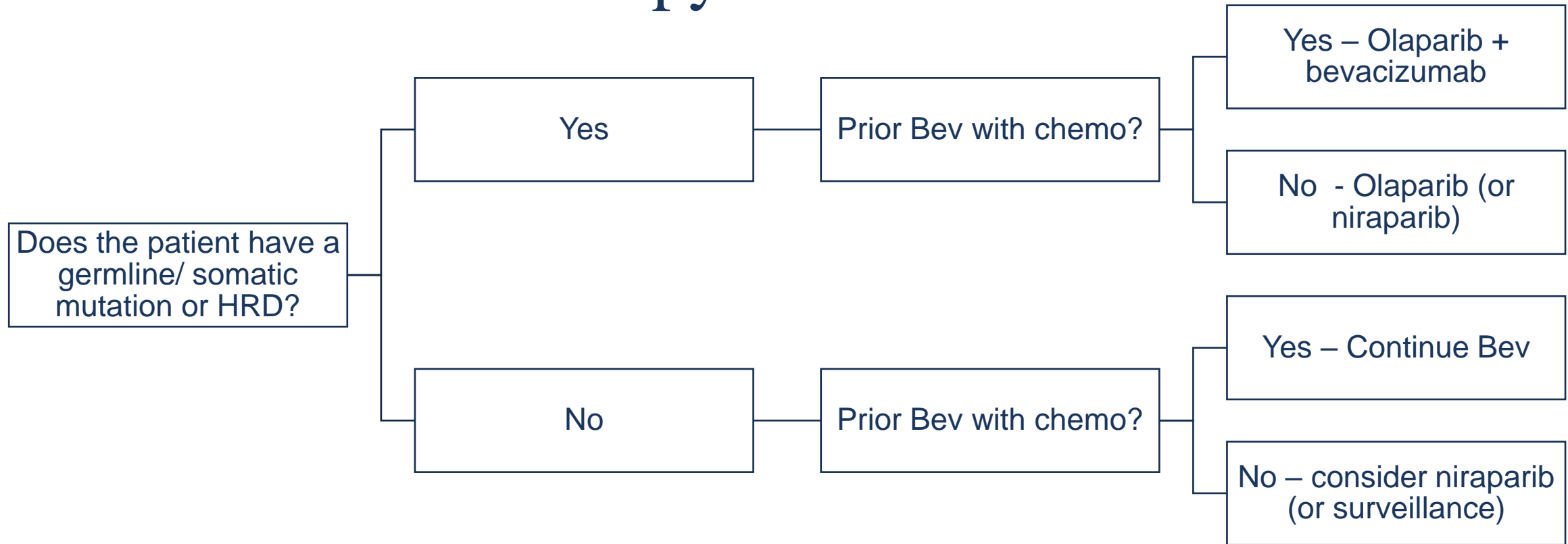
In those with HRD, combination with bevacizumab: PAOLA -1

- Maintenance Olaparib + Bevacizumab in patients with HRD
- N Engl J Med. 2019 Dec 19;381(25):2416-2428.



Combination FDA approved in patients with HRD

Maintenance Therapy



ALL OvCa patients must get germline testing

If germline negative, all patients eligible for maintenance therapy should get somatic HRD testing

Question 3

- A 66-year-old woman presented with right lower quadrant pain and general abdominal discomfort. The patient underwent CT of the abdomen and pelvis with contrast, which showed a large cystic mass about the central pelvis extending slightly to the left, measuring 10.7 x 12.0 x 11-cm in size. A smaller cystic lesion in the right adnexa measuring 5.6 x 3.6-cm. The patient underwent staging laparotomy with bilateral salpingo-oophorectomy, pelvic washings, omentectomy, sigmoid colectomy with colostomy placement, and appendectomy. She underwent optimal cytoreduction. Postsurgical pathology was positive for high-grade serous ovarian cancer of the left ovary with adjacent organ involvement into the right ovary, omentum, urinary bladder, and sigmoid colon with peritoneal ascitic fluid positive for malignancy. The patient is negative for somatic or germline BRCA 1 and BRCA2 mutations. She is homozygous recombinant deficiency negative. *The patient does not carry a BRCA1 or BRCA2 mutation, and her tumor is negative for these mutations and homologous recombination deficiency.* The patient had a complete response following six cycles of carboplatin, paclitaxel, and bevacizumab.
- Which of the following is the most appropriate regimen for the management of this patient?
 1. Maintenance bevacizumab
 2. Maintenance bevacizumab and Olaparib
 3. Maintenance bevacizumab and niraparib
 4. Maintenance olaparib

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Question 4

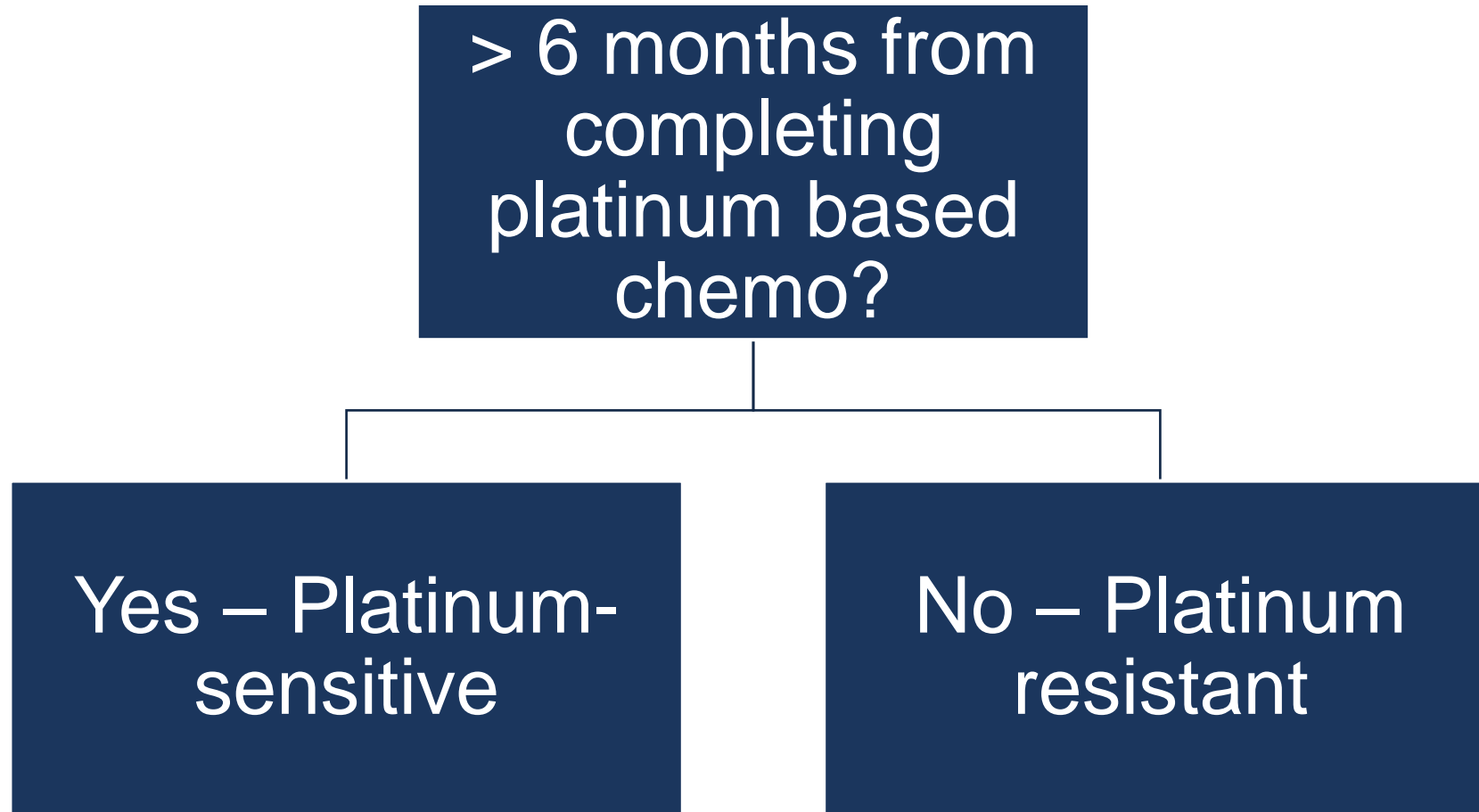
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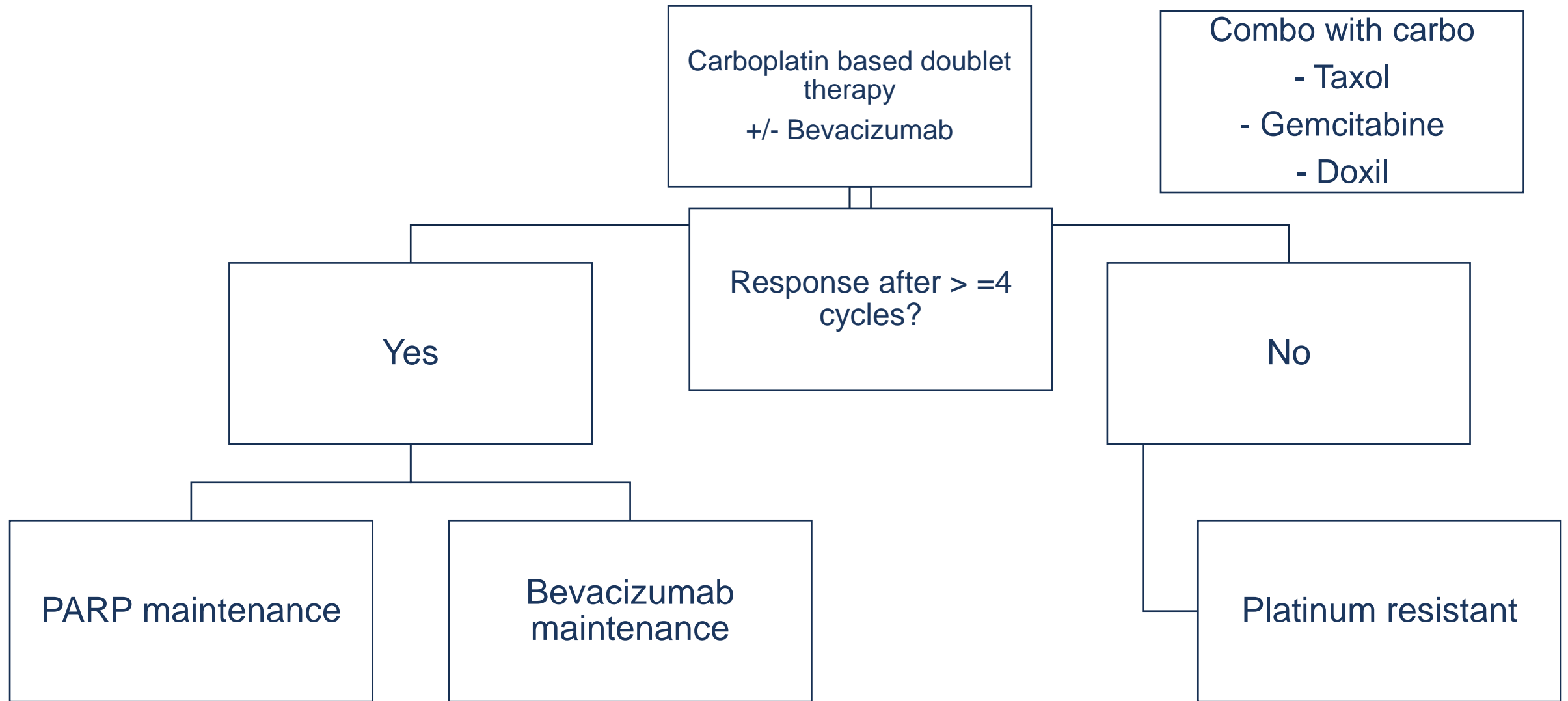
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Recurrence

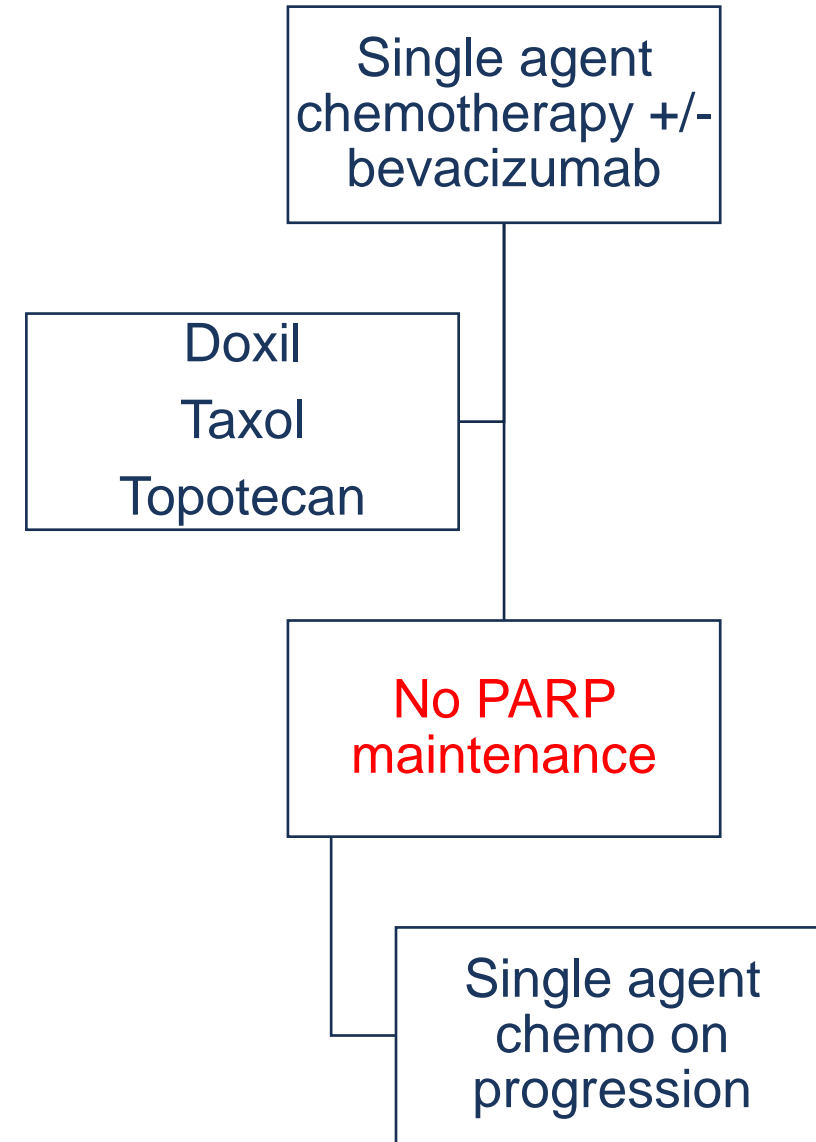
Recurrence- Treatment free interval



Platinum-sensitive recurrence



Platinum-Resistant recurrence



Question 5

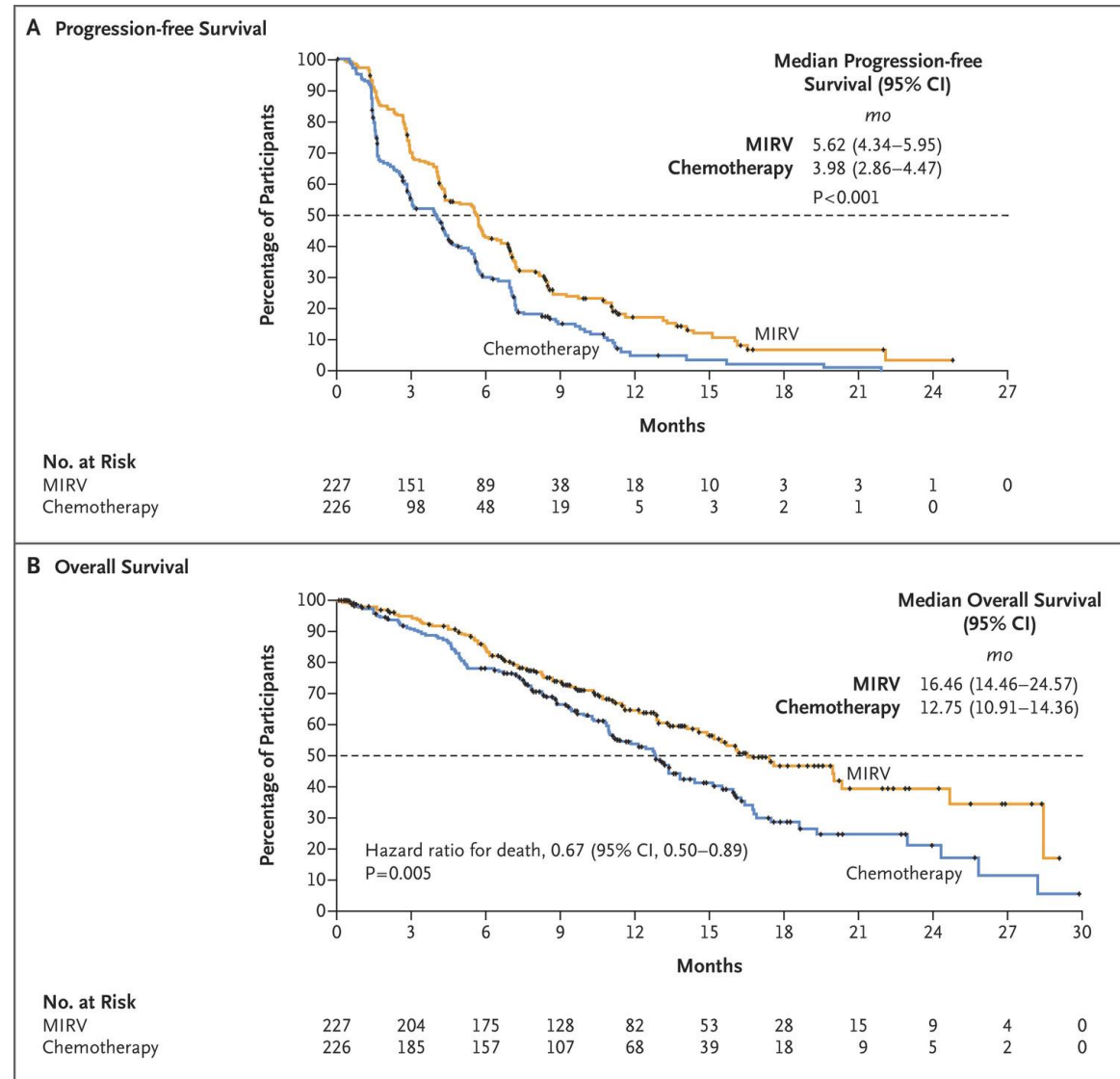
- A 43-year-old woman is diagnosed with Stage IIIC recurrent ovarian cancer. She undergoes a complete gross resection of disease and treatment with 6 cycles of carboplatin and paclitaxel chemotherapy. She is BRCA wild-type. CT chest, abdomen, and pelvis scan at the end of treatment show she is in remission. Three months later, she is found to have recurrent disease.
 - Which of the following is the most appropriate treatment at this time?
1. Bevacizumab in combination with carboplatin and gemcitabine
 2. Cediranib in combination with carboplatin and paclitaxel
 3. Bevacizumab in combination with liposomal doxorubicin
 4. Bevacizumab in combination with gemcitabine

Question 5

- A 43-year-old woman is diagnosed with Stage IIIC recurrent ovarian cancer. She undergoes a complete gross resection of disease and treatment with 6 cycles of carboplatin and paclitaxel chemotherapy. She is BRCA wild-type. CT chest, abdomen, and pelvis scan at the end of treatment show she is in remission. Three months later, she is found to have recurrent disease.
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Platinum-Resistant recurrence- Antibody Drug Conjugates

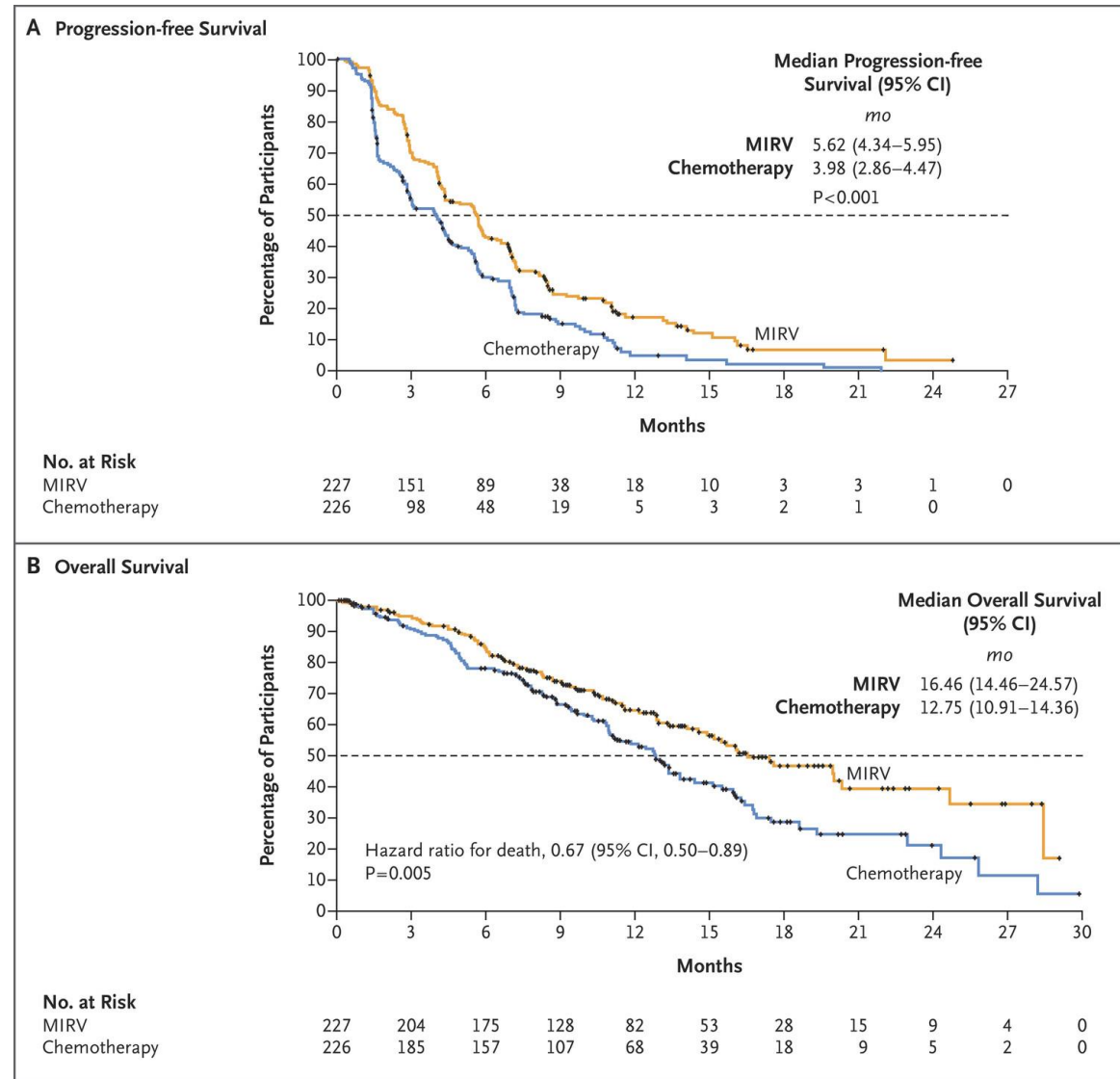
- Phase 3 , RCT
- 1:1 Mirvetuximab Soravtansine vs physician of chemotherapy (Taxol/ Doxil/ Topotecan)
- Key eligibility:
- Folate receptor alpha (FR α)-Positive- ($\geq 75\%$ of cells with $\geq 2+$ staining intensity)
- Prior 1-3 lines of chemotherapy



Platinum-Resistant recurrence- Antibody Drug Conjugates

- Median PFS -5.62 months vs 3.98 months
- ORR - 42.3% vs 15.9%
- Overall survival - 16.46 months vs. 12.75 months
- **First and only treatment with OS benefit in PROC**

**FDA approved in PROC
after 1-3 lines of chemo**



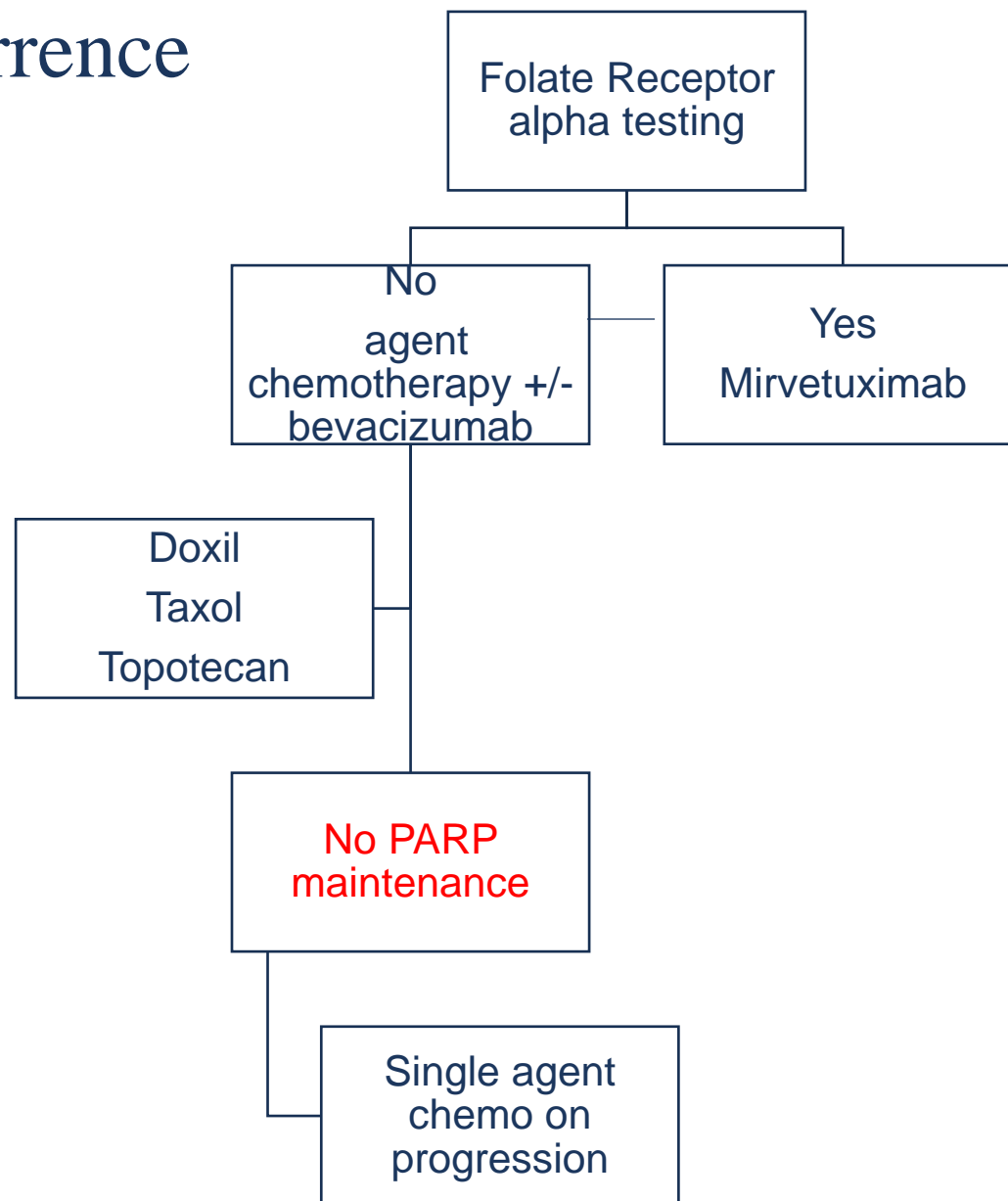
Platinum-Resistant recurrence- Antibody Drug Conjugates

- **Almost 10% have grade 3 keratopathy!**
- **Slit lamp exam every other cycle for the first 8 cycles**

Adverse Event	MIRV (N=218)		Chemotherapy (N=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of participants (percent)</i>			
Any adverse event	210 (96.3)	91 (41.7)	194 (93.7)	112 (54.1)
Any treatment-related adverse event	188 (86.2)	53 (24.3)	167 (80.7)	77 (37.2)
Serious adverse event	52 (23.9)	44 (20.2)	68 (32.9)	59 (28.5)
Serious treatment-related adverse event	20 (9.2)	16 (7.3)	16 (7.7)	16 (7.7)
Adverse event leading to dose reduction	74 (33.9)	—	50 (24.2)	—
Adverse event leading to dose delay or hold	117 (53.7)	—	111 (53.6)	—
Adverse event leading to dose discontinuation	20 (9.2)	—	33 (15.9)	—
Adverse event leading to death	5 (2.3)	—	5 (2.4)	—
Treatment-related adverse event leading to death	1 (0.5)	—	1 (0.5)	—
Adverse events occurring in ≥20% of participants in a trial group				
Blurred vision	89 (40.8)	17 (7.8)	5 (2.4)	0
Keratopathy	70 (32.1)	20 (9.2)	0	0
Abdominal pain	66 (30.3)	6 (2.8)	31 (15.0)	3 (1.4)
Fatigue	66 (30.3)	5 (2.3)	52 (25.1)	11 (5.3)
Diarrhea	64 (29.4)	3 (1.4)	36 (17.4)	1 (0.5)
Dry eye	61 (28.0)	7 (3.2)	5 (2.4)	0
Constipation	59 (27.1)	0	40 (19.3)	2 (1.0)
Nausea	58 (26.6)	4 (1.8)	60 (29.0)	4 (1.9)
Peripheral neuropathy	47 (21.6)	3 (1.4)	30 (14.5)	4 (1.9)
Neutropenia	24 (11.0)	2 (0.9)	59 (28.5)	36 (17.4)
Anemia	21 (9.6)	2 (0.9)	71 (34.3)	21 (10.1)

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The relatedness of adverse events to treatment was determined by the investigator.

Platinum-Resistant recurrence



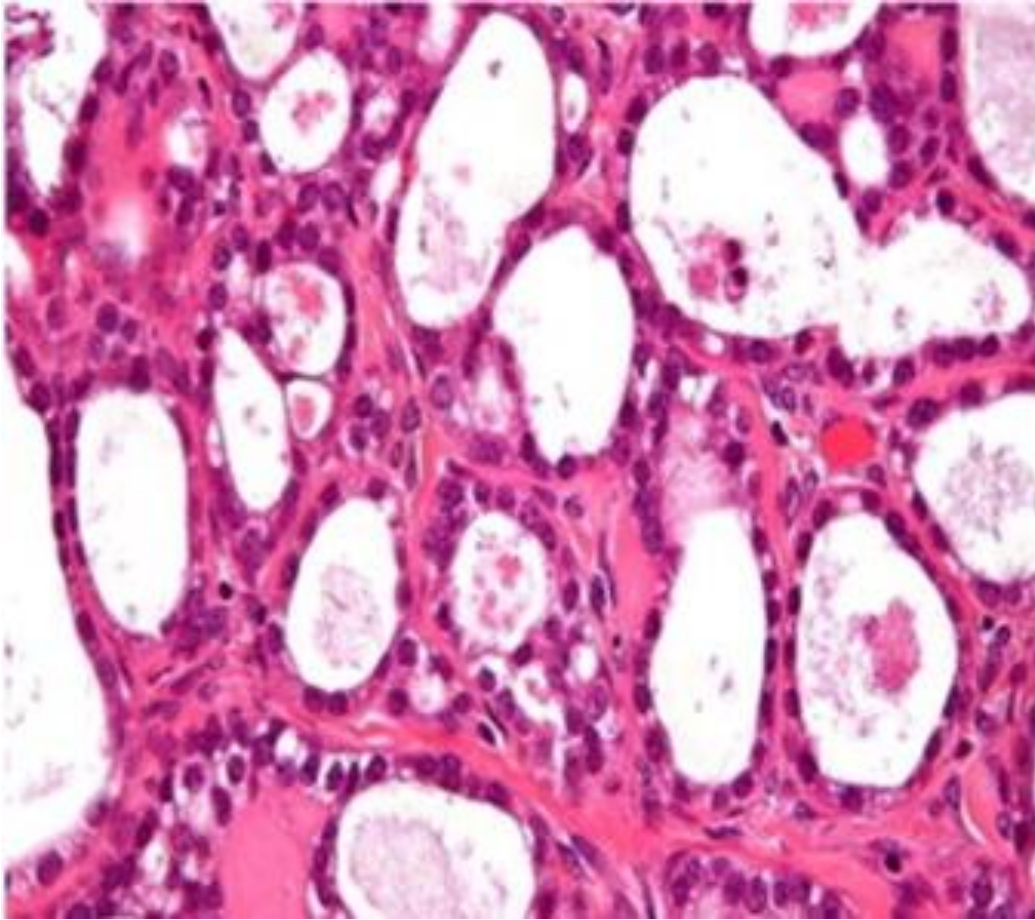
Rare Histologies

Low Grade Serous (LGS)

Indolent ER+ve

- PTEN, KRAS, BRAF, PI3KCA
- Poor response to chemo
- Treatment – surgery + Carbo/taxol + Aromatase inhibitors
- Metastatic disease - MEK inhibitors, BRAF inhibitors, SERM/SERD/AI, CDK4/6inhibitors

Clear Cell Carcinoma



- 3-12% of all ovarian cancers, higher prevalence in Asian patients
- Lower response to platinum-based chemotherapy compared to high-grade serous cancers
- Use of antiangiogenic agents
 - Used in renal clear cell carcinoma
 - Such cancers have very high VEGF expression
- Respond to immunotherapy – like renal

Mabuchi S et al. Mol Cancer Ther 2010.
Hoskins PJ et al. J Clin Oncol 2012.
Brown AP et al. Gynecol Oncol 2013.

Mucinous Ovarian Cancer

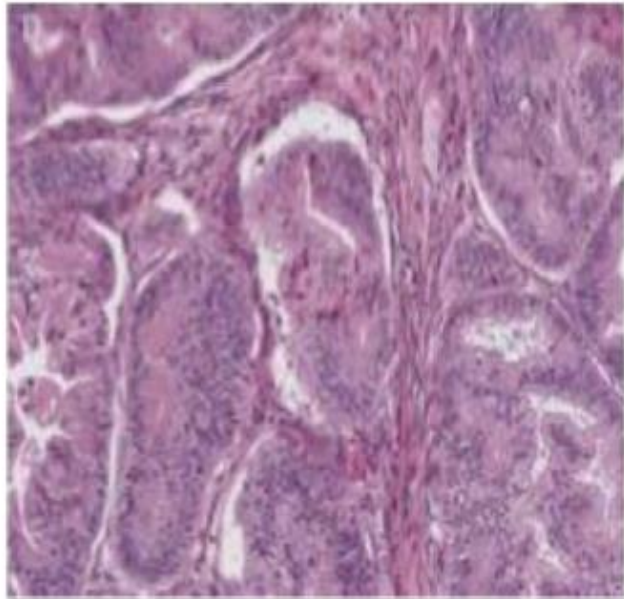


Fig. 4. Mucinous carcinoma exhibiting an expansive pattern with few mitotic figures. All figures were borrowed with permission from David M. Gershenson and Anaïs Malpica, MD Anderson Cancer Center.

- 3–5% of ovarian cancers
- Incidence hard to estimate given overlap with primary GI sites
- May be low- or high-grade
- In advanced stages, significantly worse prognosis than high-grade serous cancers
- Consideration of “GI-type” chemotherapy regimens – FOLFOX

Please consider clinical trials for your patients!



Thank you