Fred Hutch Cancer Center

Board Review - Ovarian Cancer

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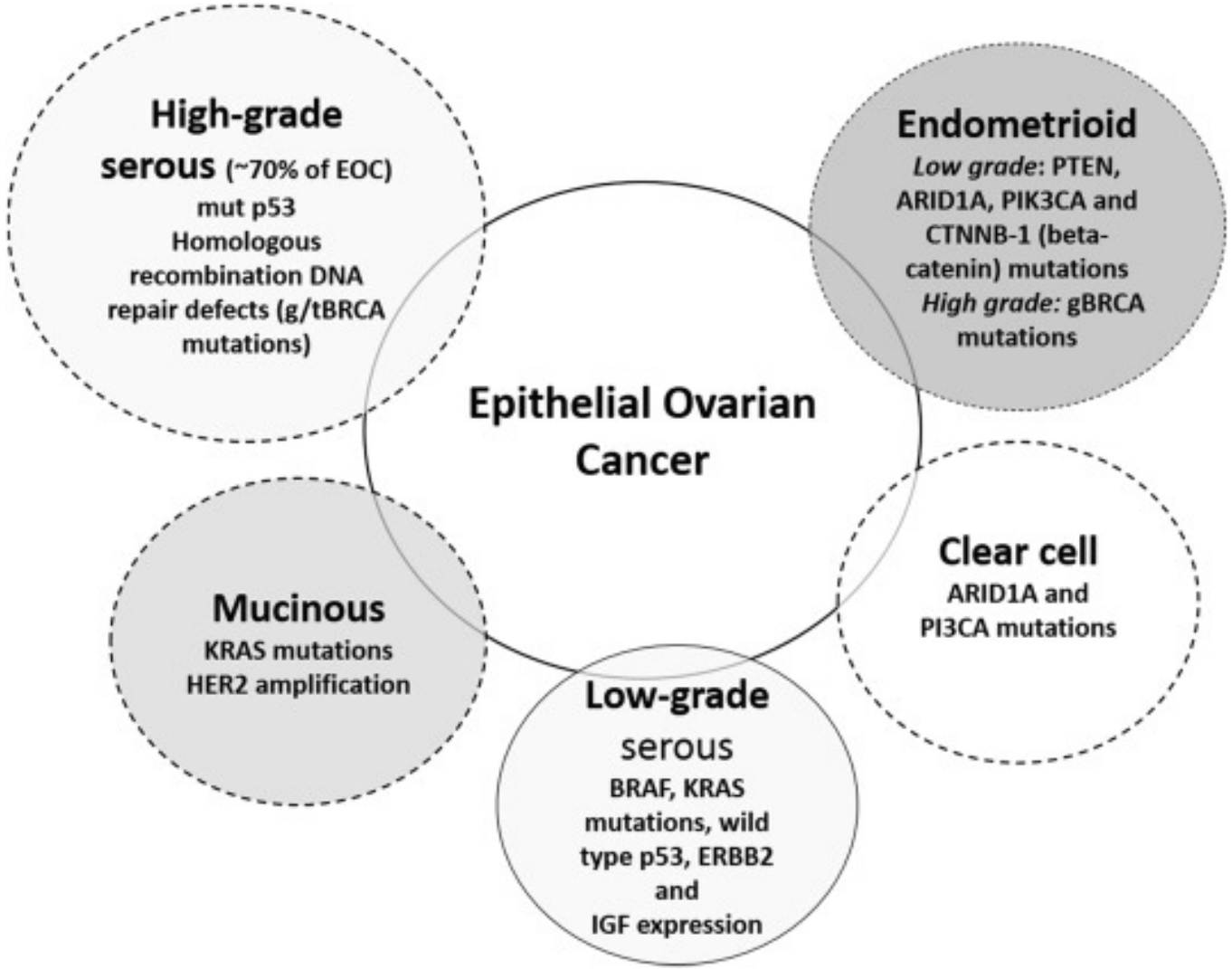
HISTOLOGICAL SUBTYPES



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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Treatment

Surgery

- Diagnosis
- Staging
- Cytoreduction

Systemic Therapy

Staging of disease via surgery especially important

Almost all patients get surgery and systemic therapy

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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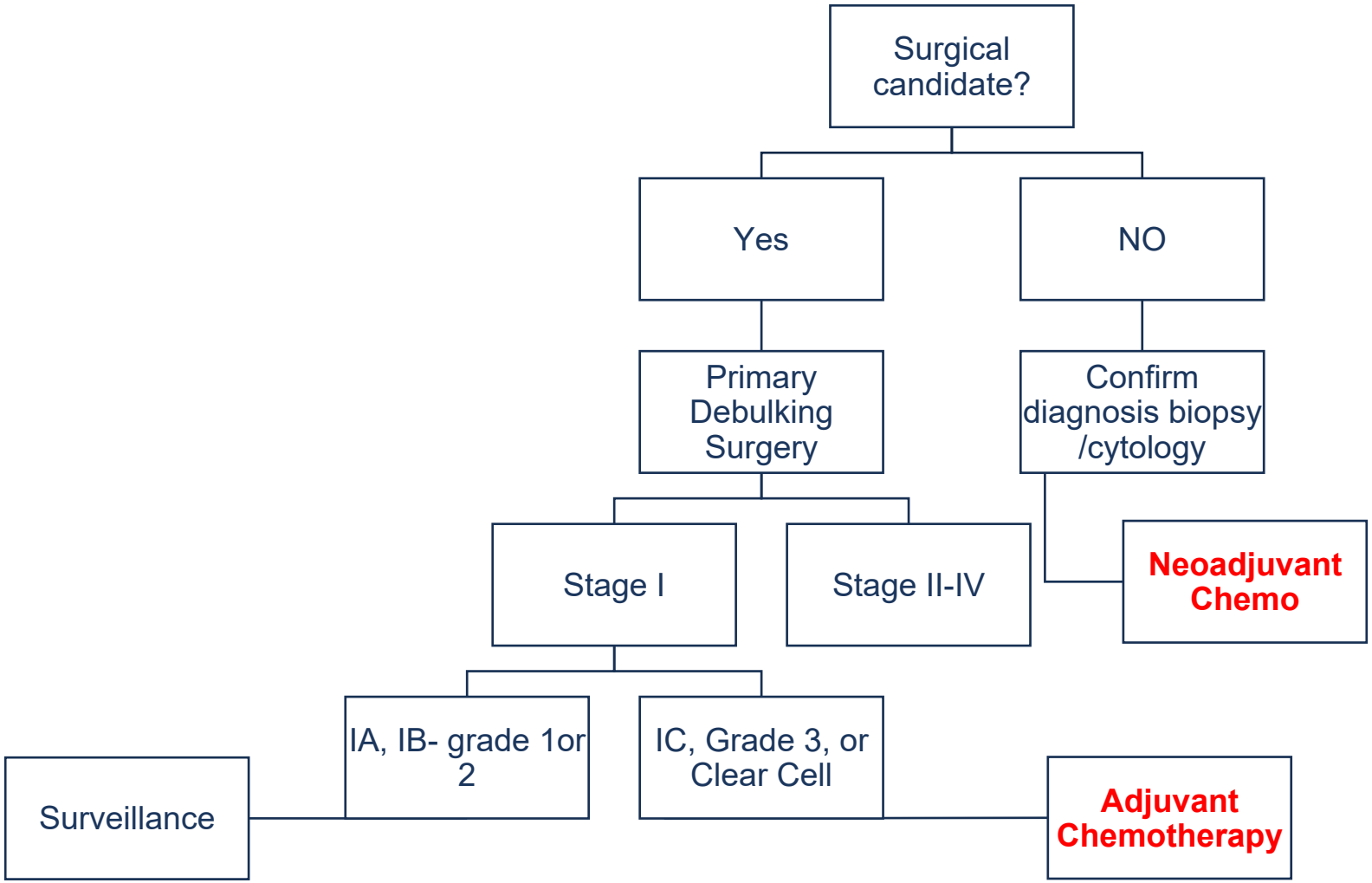
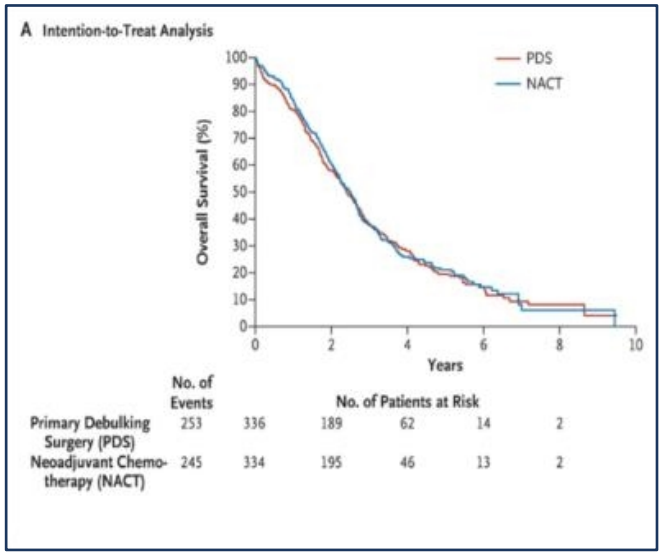
Upfront management- Suspected Ovarian Cancer



Neoadjuvant chemotherapy

EORTC & CHORUS

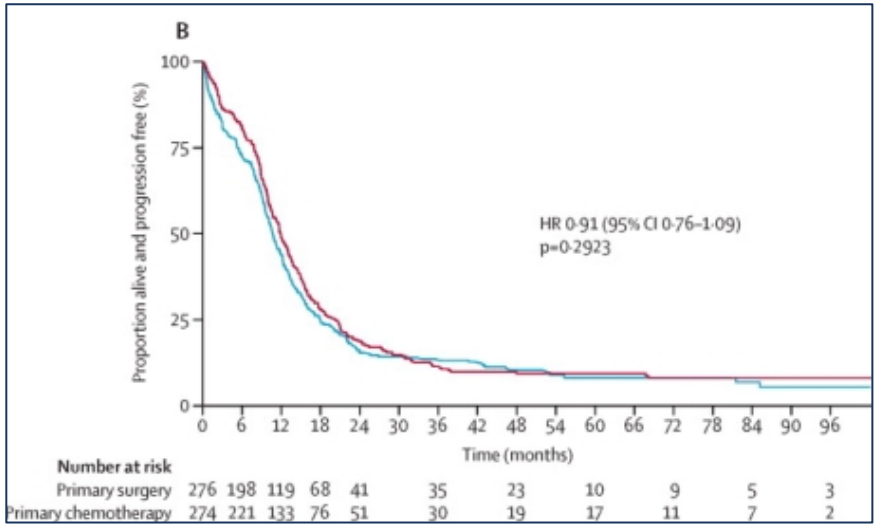
- Does not change PFS or OS
- Decreased surgical morbidity and mortality.
- Increase rates of successful cytoreduction



Consider NACT–

Poor operative candidates,

low likelihood of surgical cytoreduction



Vergote I et al. N Engl J Med 2010., Kehoe S et al. Lancet 2015.

Upfront management- Suspected Ovarian Cancer

Establish diagnosis with biopsy

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

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 infusion[g] 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 carboplatin[i] 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 carboplatin[i] 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]

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/
- Repeat every 28 days for 3–6 cycles[h]

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizur
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 5–6 IV, an 7.5 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 bevacizur
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 6 IV Day 1 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 2 22 cycles

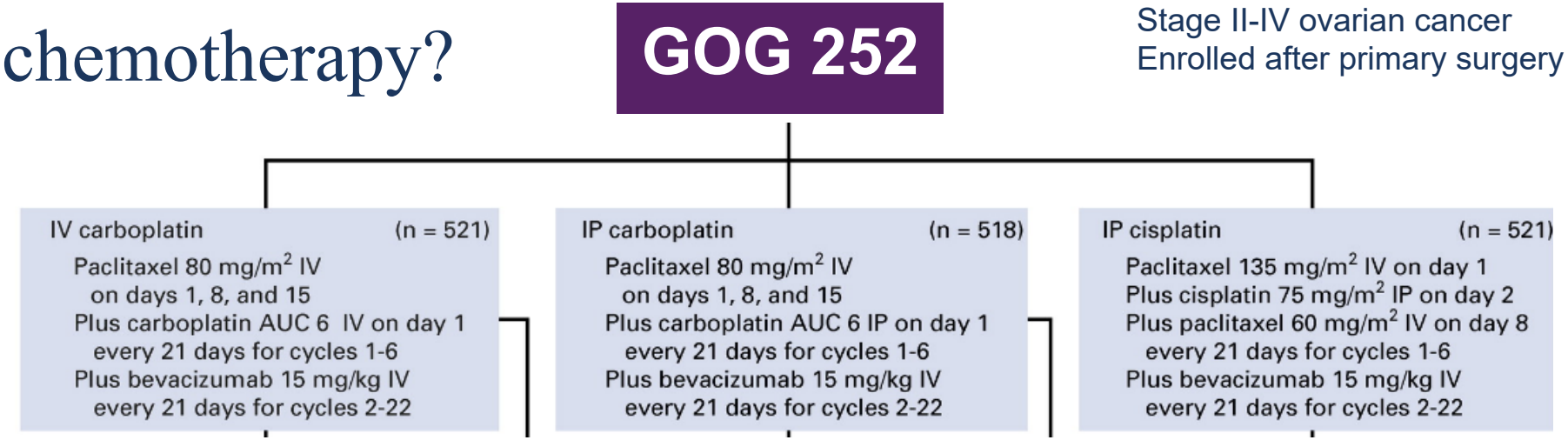
Elderly Patients (age >70 years) and/or those with comorbidities

Paclitaxel 135/carboplatin[1]
- 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)

Carboplatin[1]
- Carboplatin AUC 5 IV given every 21 days

Intraperitoneal chemotherapy?



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)

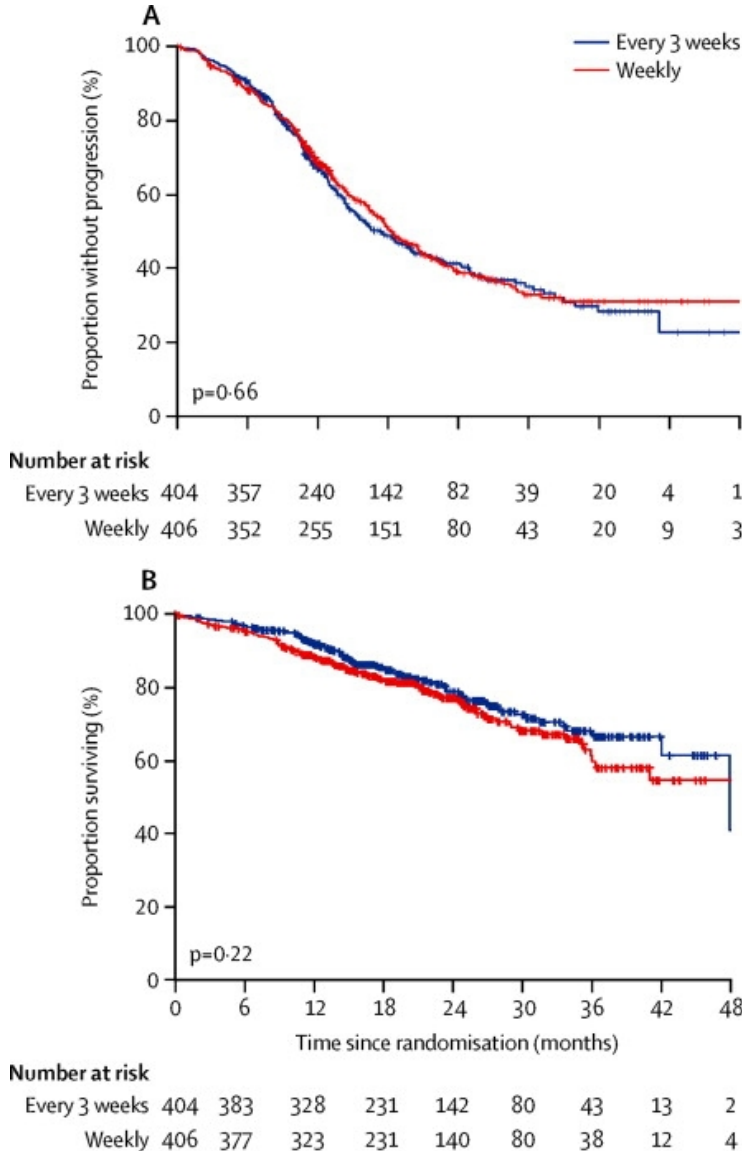
Worse QOL, same outcomes – no really used today

Older patients?

MITO-7

Stage IC-IV EOC
ECOG PS ≥ 2

Weekly Carbo (AUC 2)
and Taxol (60 mg/m^2)
vs.
Every 3 week Carbo (AUC 6)
and Taxol (175 mg/m^2)



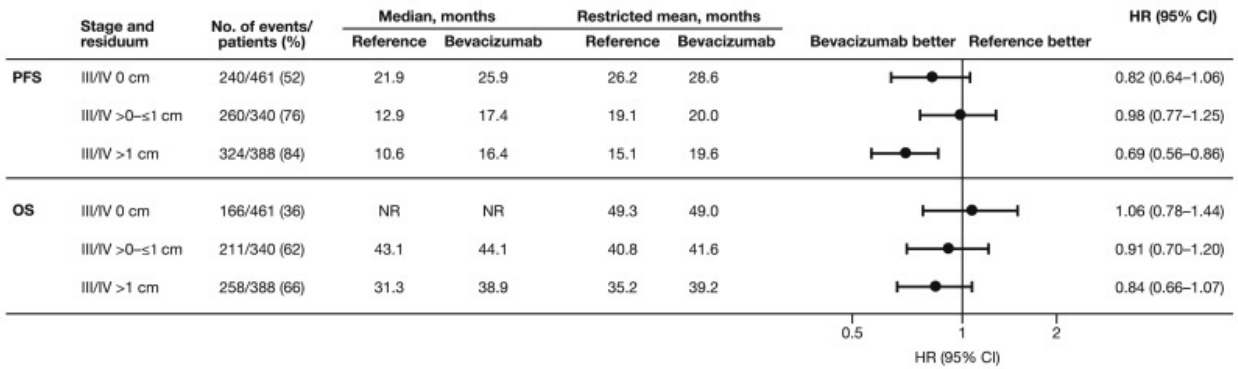
Similar PFS & OS – Use in older or poor PS

Pignata S et al. Lancet Oncol 2014.

Candidates for bevacizumab?

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

- **ICON-7**
- Improved PFS seen in "high risk" group (Stage IV disease, >1 cm residual disease at surgery)
- Trend towards improved OS



	Stage and residuum	No. of events/ patients (%)	Median, months		Restricted mean, months		HR (95% CI)
			Reference	Bevacizumab	Reference	Bevacizumab	
PFS	III/IV 0 cm	240/461 (52)	21.9	25.9	26.2	28.6	0.82 (0.64–1.06)
	III/IV >0–≤1 cm	260/340 (76)	12.9	17.4	19.1	20.0	0.98 (0.77–1.25)
	III/IV >1 cm	324/388 (84)	10.6	16.4	15.1	19.6	0.69 (0.56–0.86)
OS	III/IV 0 cm	166/461 (36)	NR	NR	49.3	49.0	1.06 (0.78–1.44)
	III/IV >0–≤1 cm	211/340 (62)	43.1	44.1	40.8	41.6	0.91 (0.70–1.20)
	III/IV >1 cm	258/388 (66)	31.3	38.9	35.2	39.2	0.84 (0.66–1.07)

PFS benefit, no OS

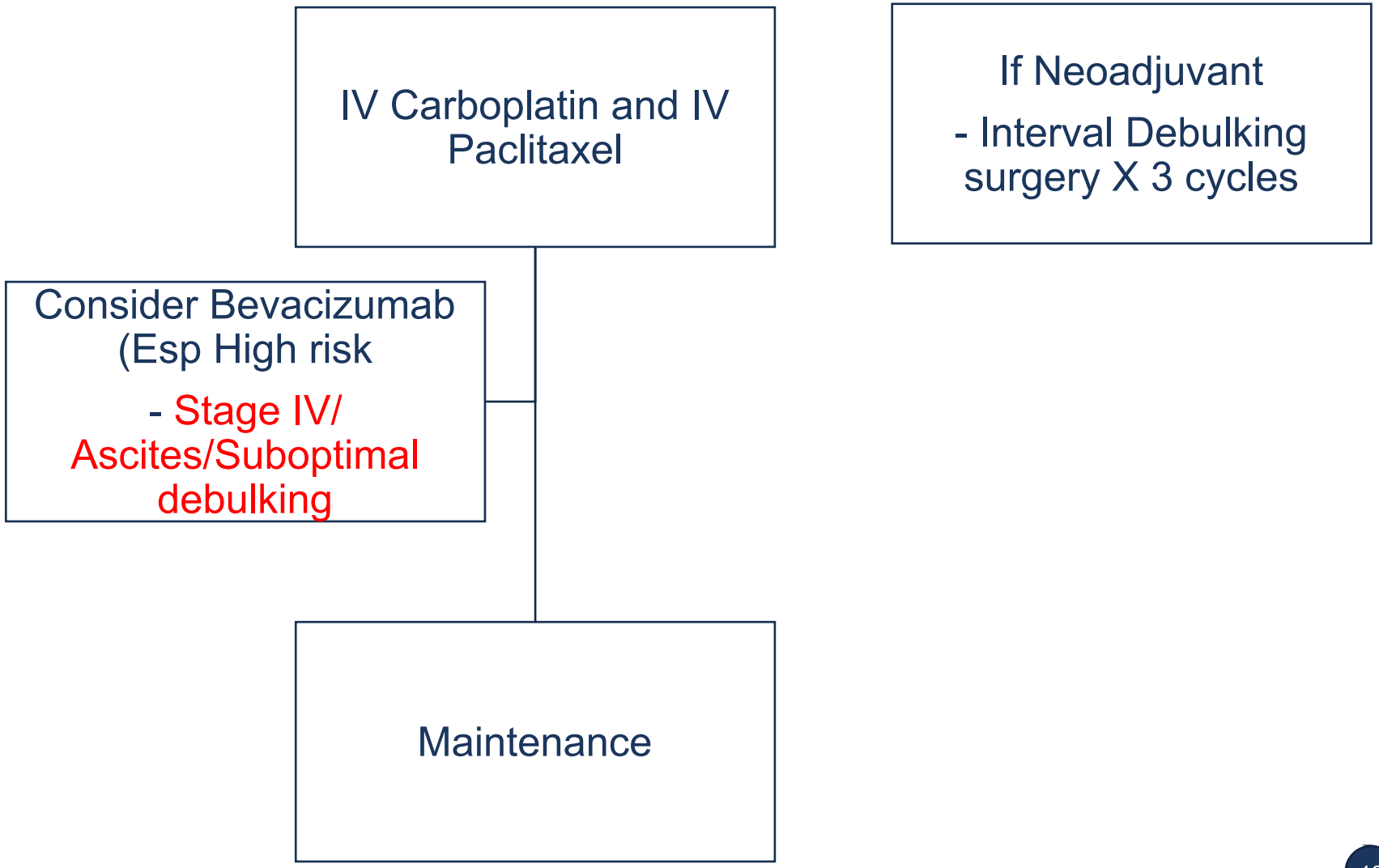
Highest benefit in:

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

Tewari KS et al. J Clin Oncol 2019.

Gonzalez Martin A et al. Gynecol Oncol 2019.

Systemic therapy



Fred Hutch Cancer Center

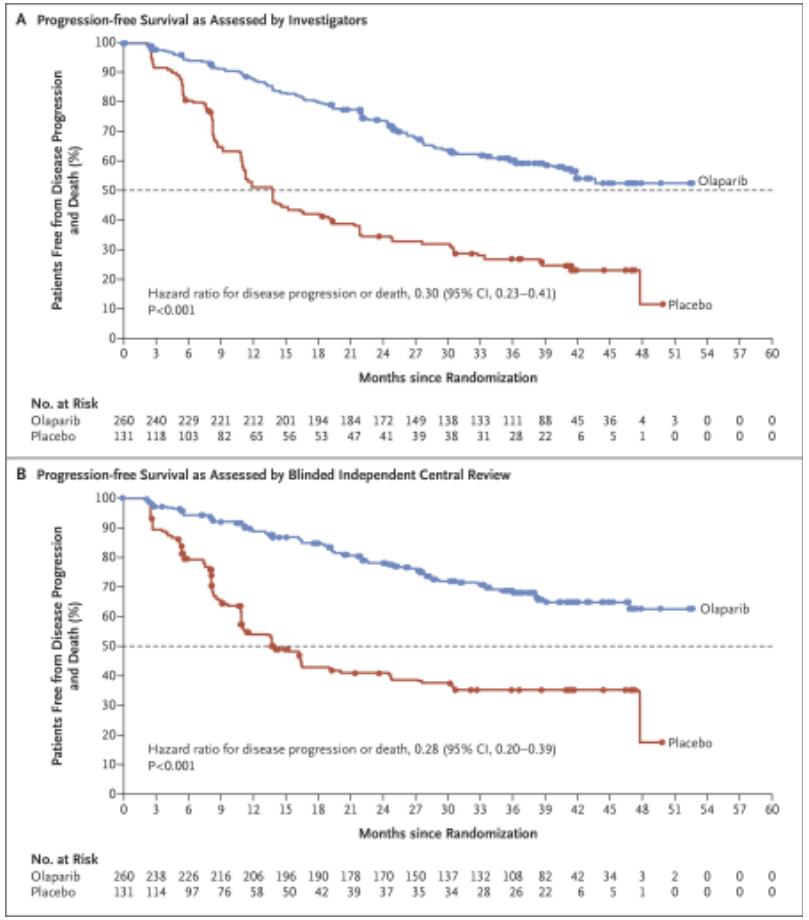
Maintenance Therapy

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

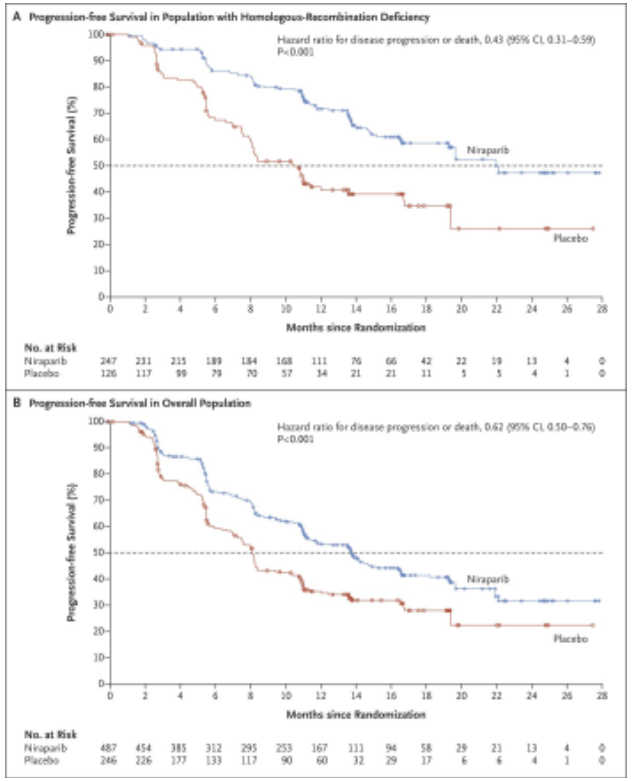
Marked benefit with two years of therapy



Moore K et al, N Engl J Med 2018

In all patients - PRIMA

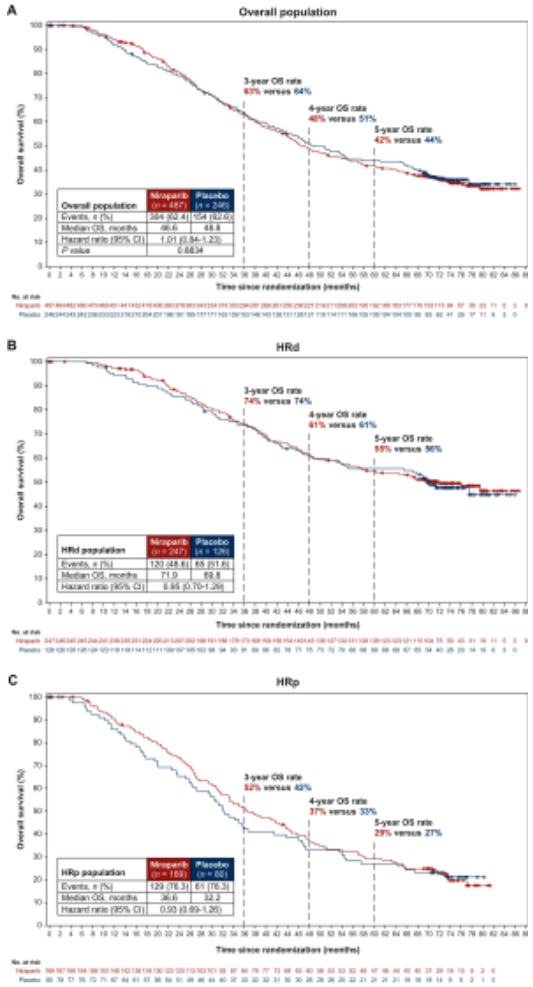
- **Niraparib**
- Newly diagnosed stage III-IV high-grade serous or endometrioid ovarian cancer, *with or without* mutations
- Median PFS in HR deficient - 21.9 months vs 10.4 months
- Median PFS in HR proficient - 8.1 months vs 5.4 months
- Median PFS in overall population 13.8 months vs 8.2 months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

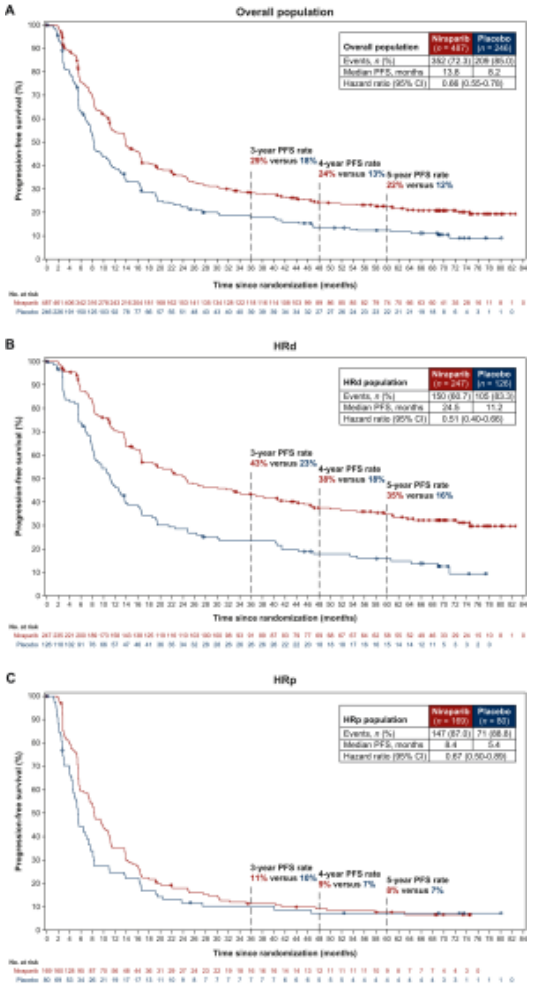


FDA approved for all patients

Gonzalez-Martin A N Engl J Med.2019

PRIMA - Update

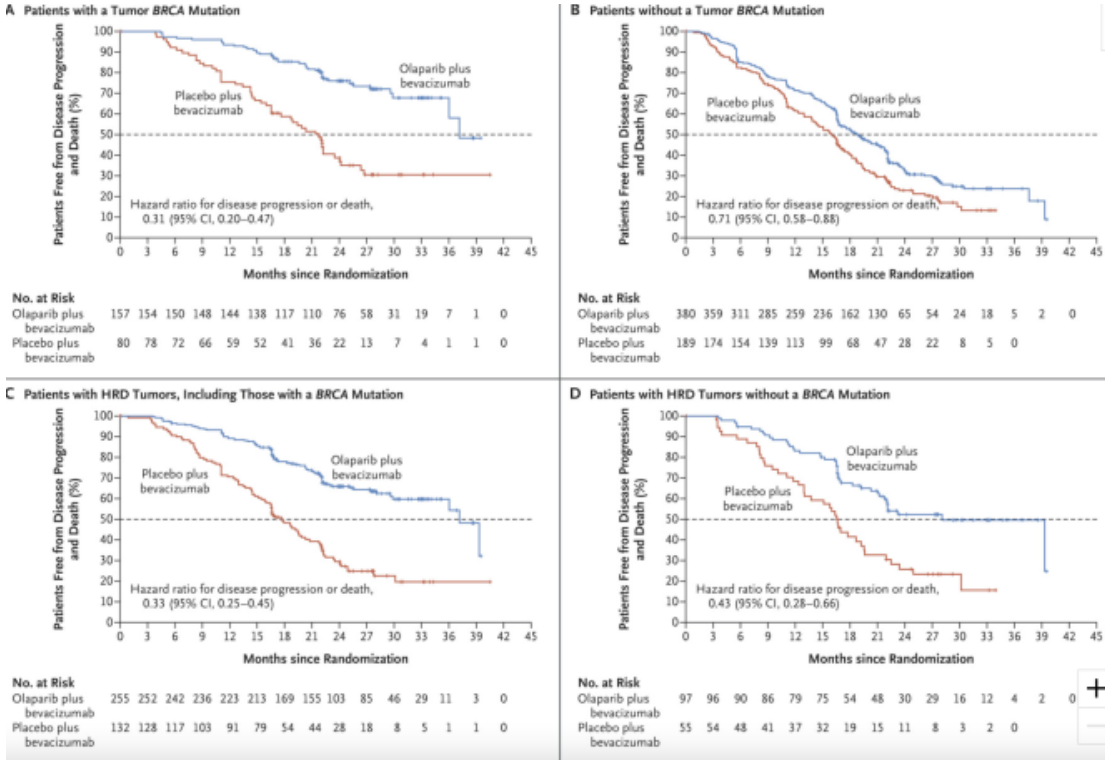




No Overall Survival benefit!

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

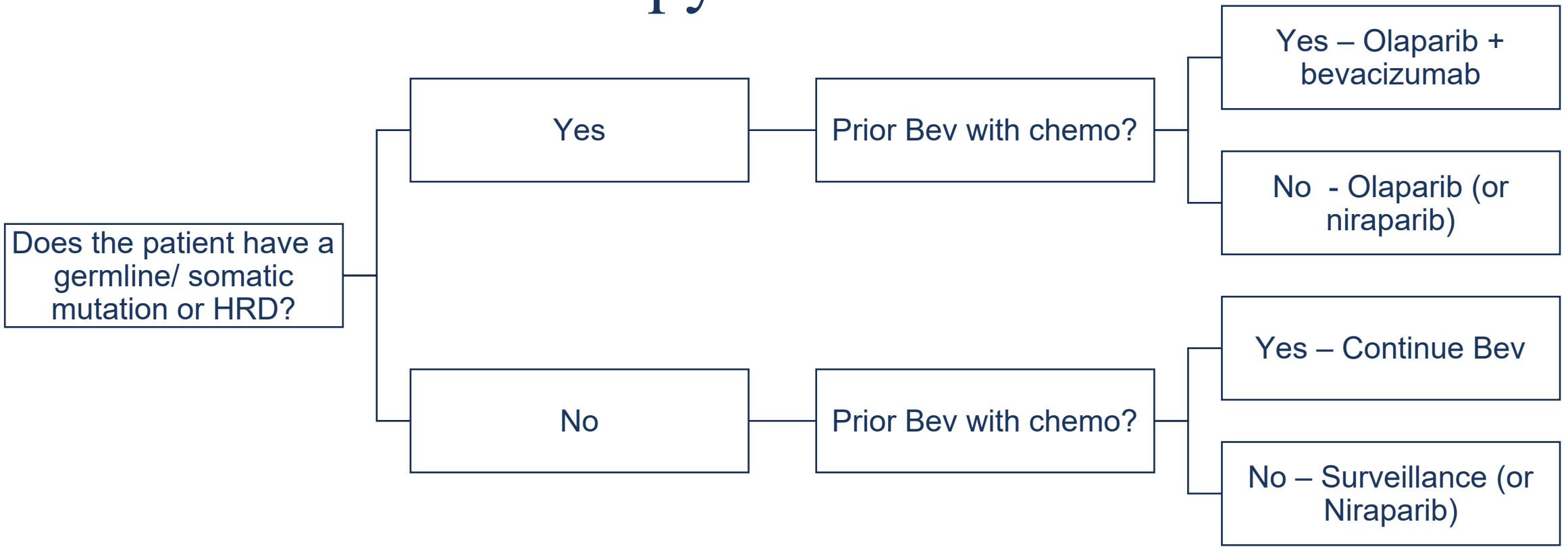
- Maintenance Olaparib + Bevacizumab in patients with HRD



Combination FDA approved in patients with HRD

N Engl J Med. 2019 Dec 19;381(25):2416-2428

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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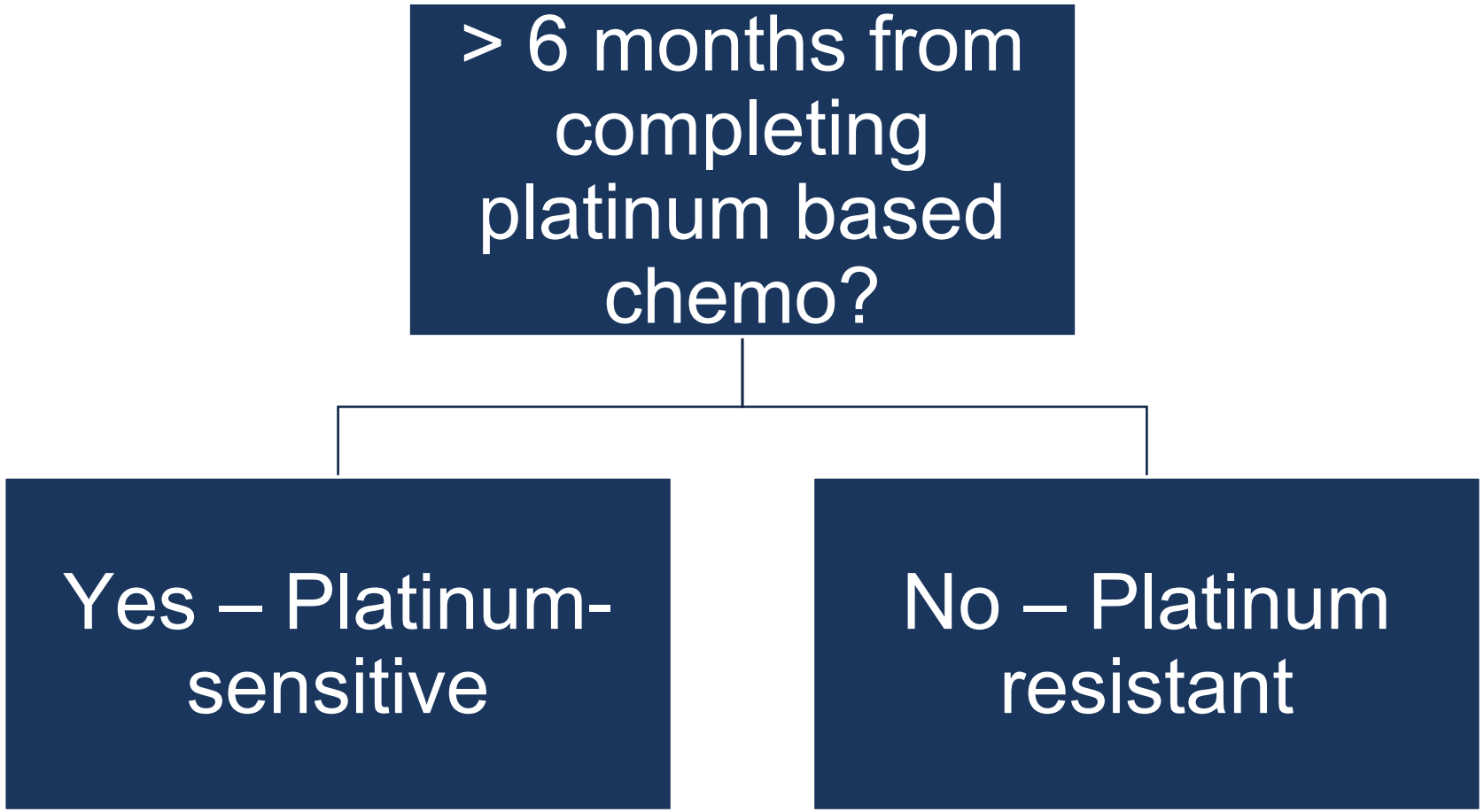
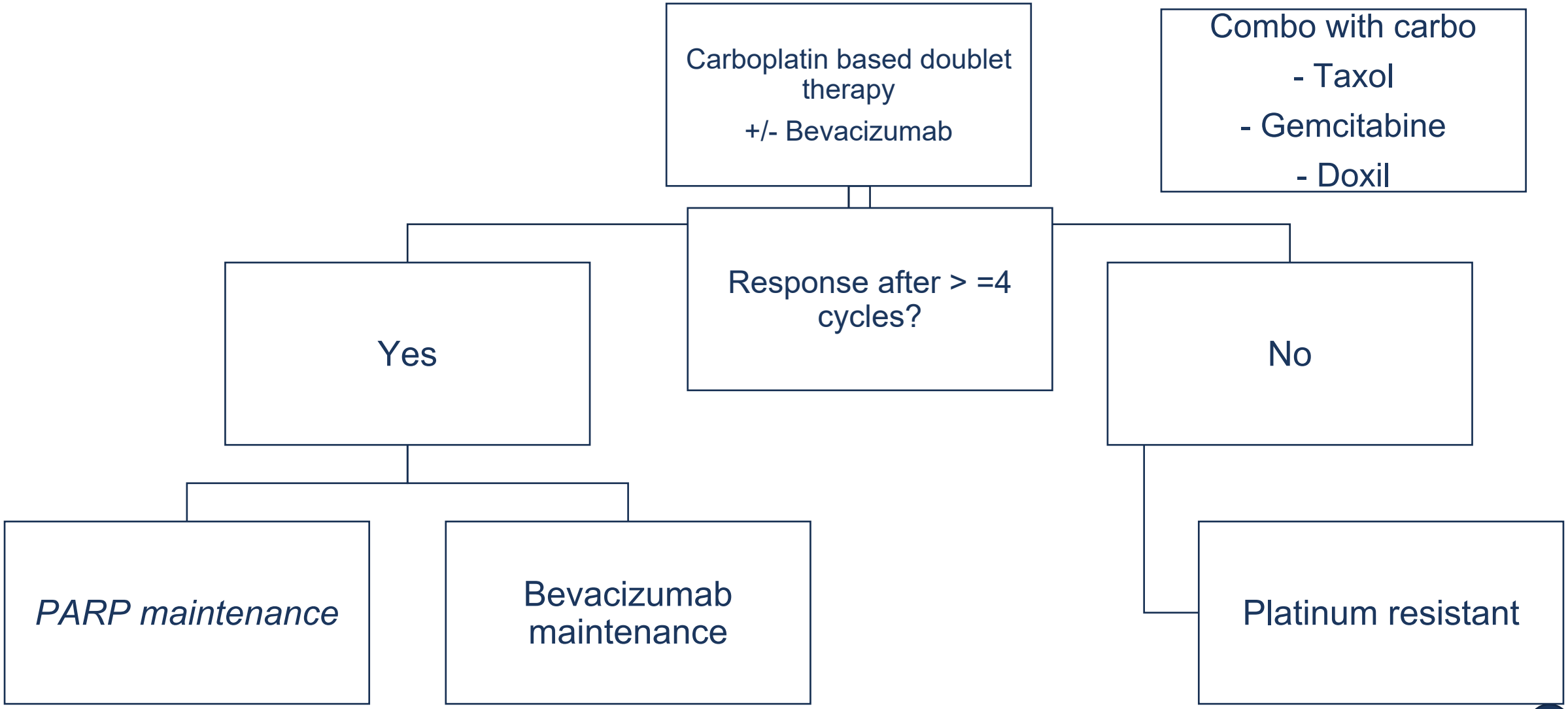
Recurrence

Recurrence- Treatment free interval



Platinum-sensitive 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

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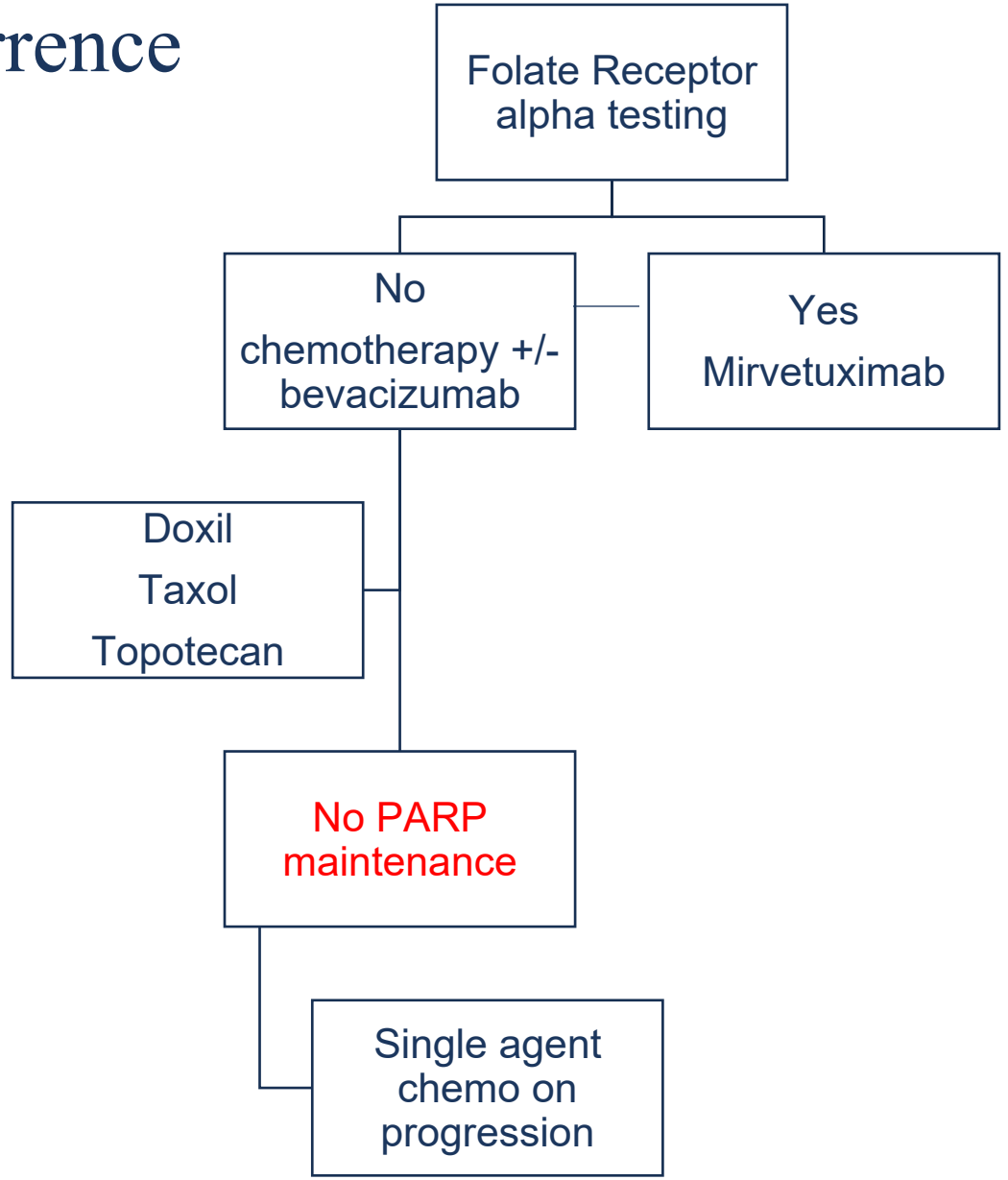
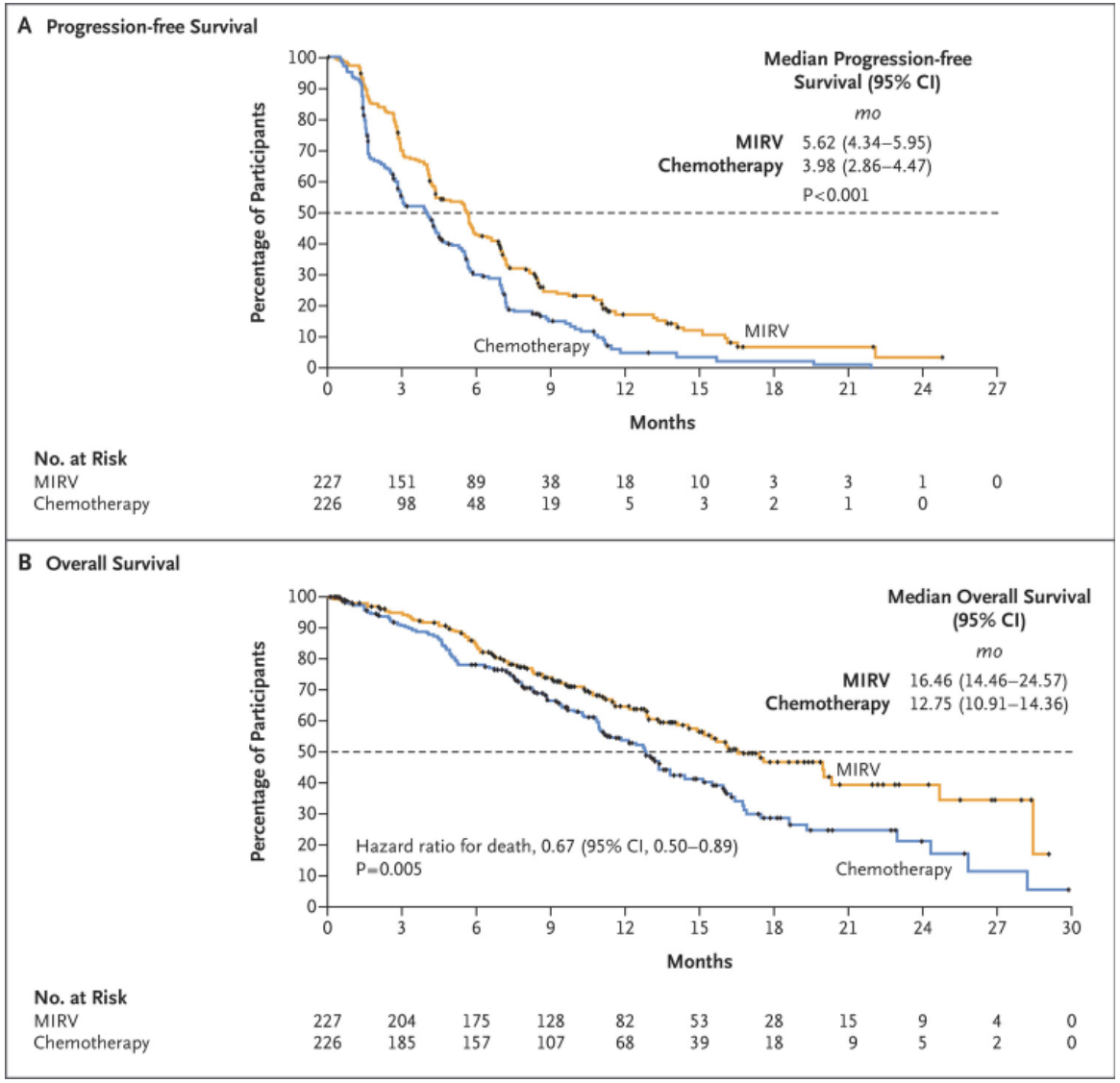
Platinum-Resistant recurrence



10/7/25

Platinum-Resistant recurrence- Antibody Drug Conjugates

- Phase 3 , RCT
- 1:1 Mirvetuximab Soravtansine vs chemotherapy
-
- Key eligibility:
- Folate receptor alpha (FRα)-Positive- (≥75% of cells with ≥2+ staining intensity)
- Prior 1-3 lines of chemotherapy

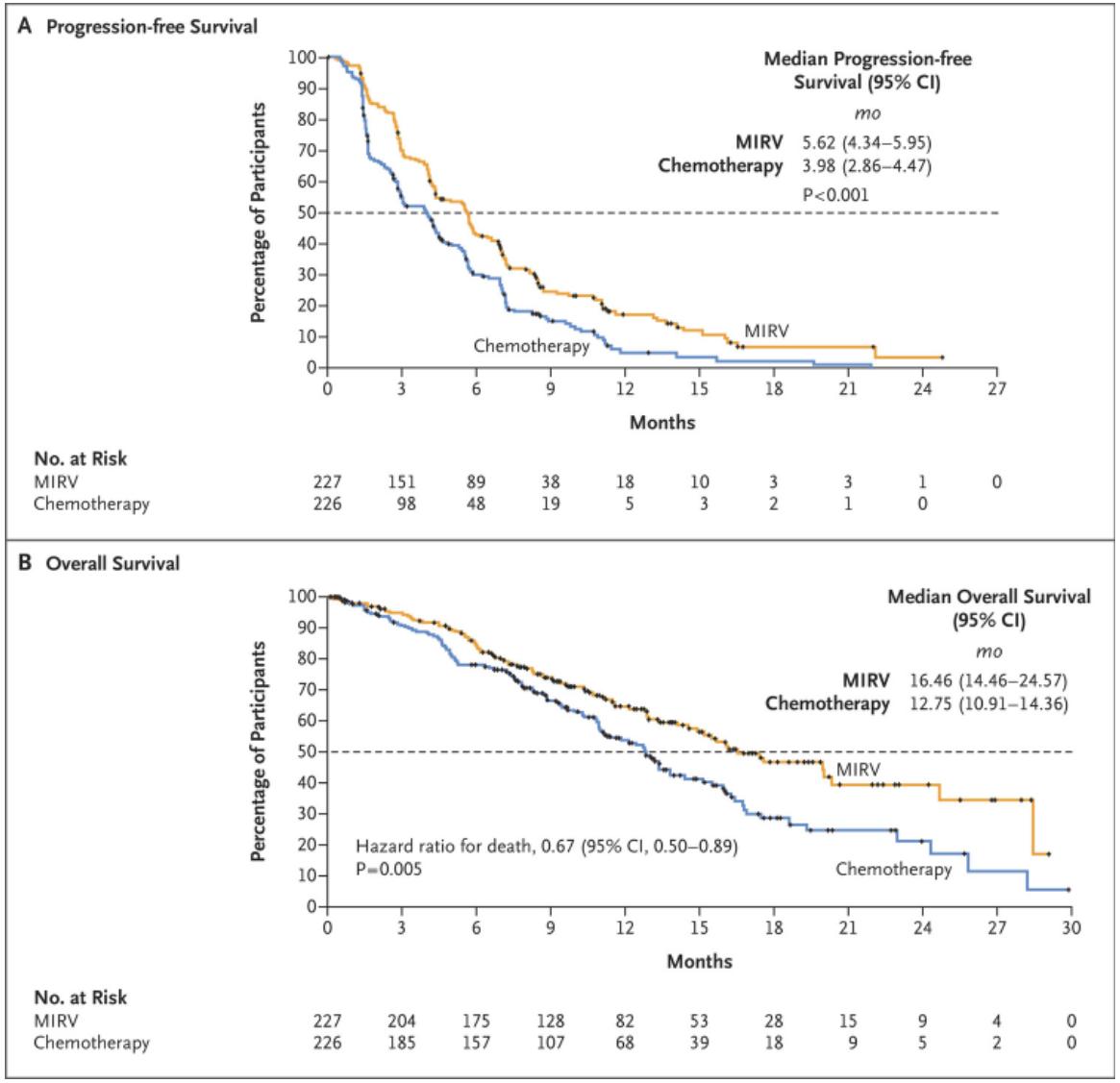


Platinum-Resistant recurrence- Antibody Drug Conjugates

- 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**

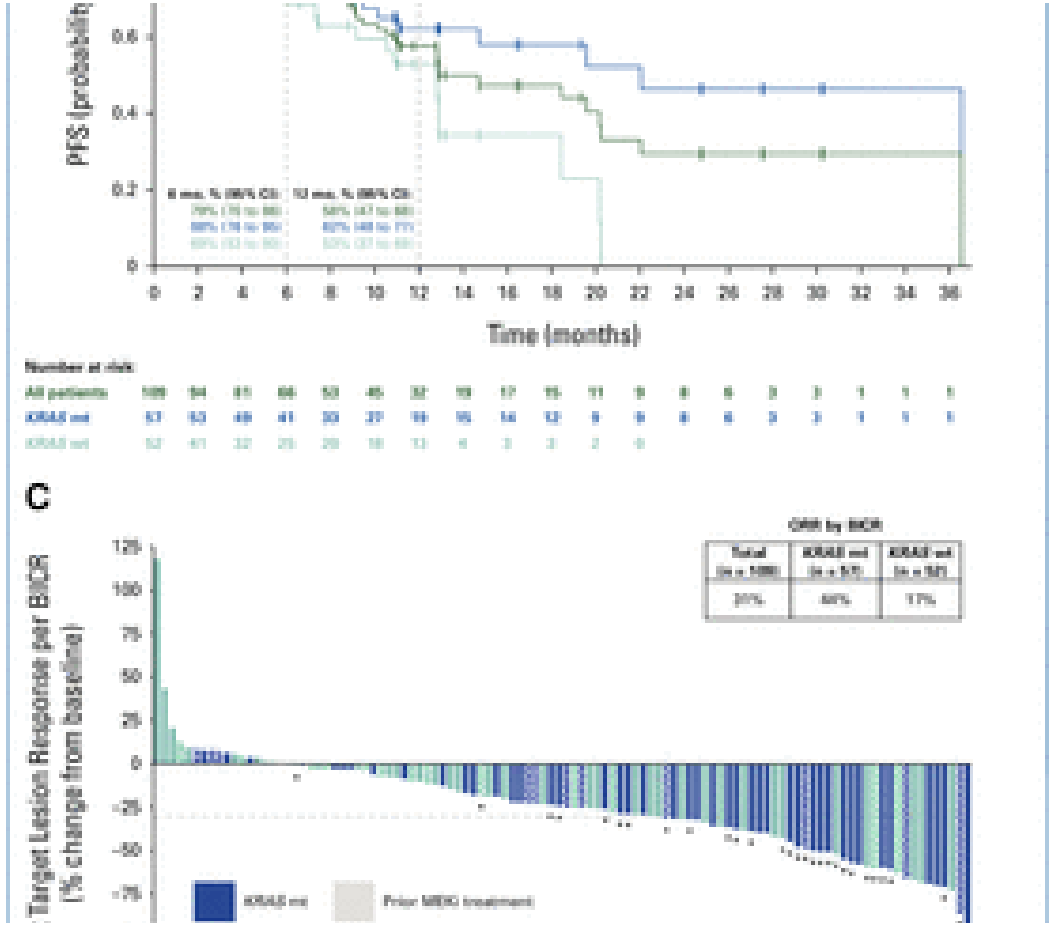
Adverse Event	MIRV (N=218)		Chemotherapy (N=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of participants (percent)			
Any adverse event	210 (96.3)	91 (41.7)	194 (93.7)	112 (54.1)
Any treatment-related adverse event	188 (86.2)	53 (24.3)	167 (80.7)	77 (37.2)
Serious adverse event	52 (23.9)	44 (20.2)	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)

[a] 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.

Rare Histologies

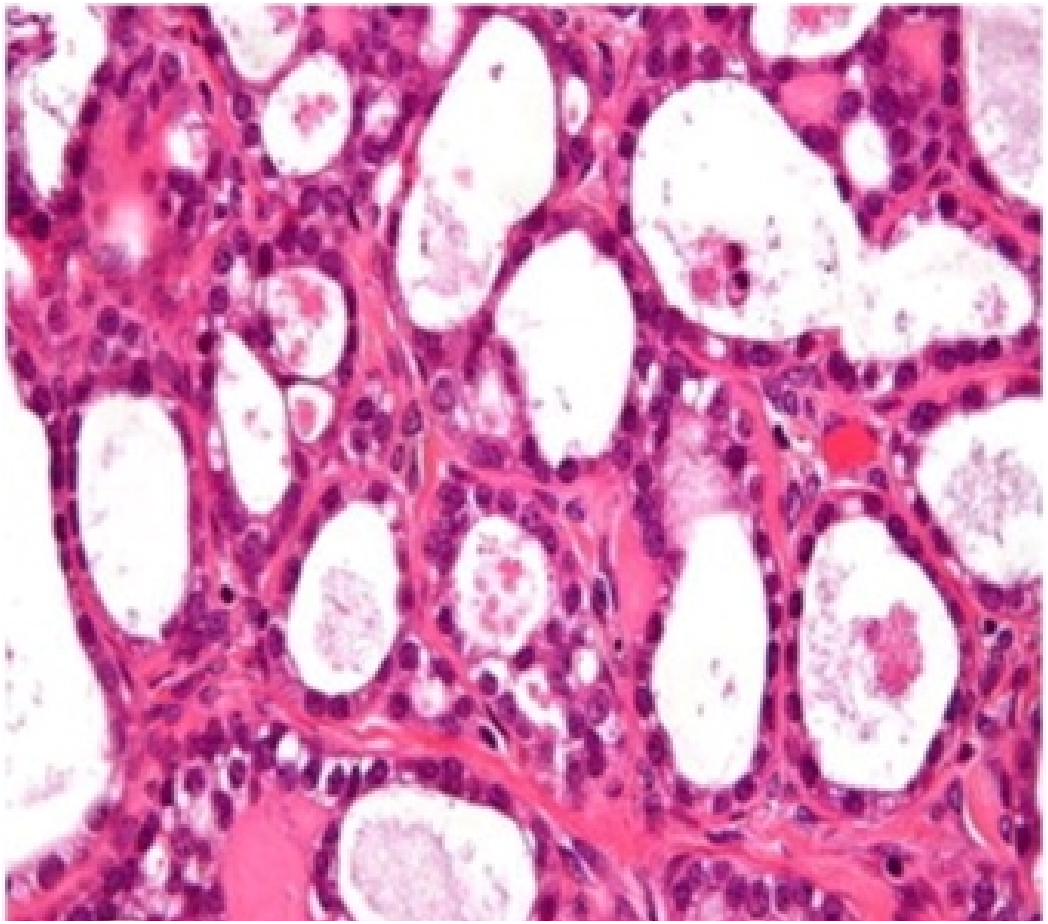
Low Grade Serous (LGS) - < 5%

- Indolent ER+ve
- KRAS, BRAF mutations
- Poor response to chemo
- Treatment – surgery + Carbo/taxol + Aromatase inhibitors
- Metastatic disease - BRAF/MEK inhibitors
- **RAMP 201 - Avutometinib ± Defactinib**
- FDA approval for KRAS-mutated



J Clin Oncol. 2025 Sep;43(25):2782-2792.

Clear Cell Carcinoma - ~ 10%



- Chemoresistant
- ARID1A, PIK3CA mutated
- 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 ~ 3%

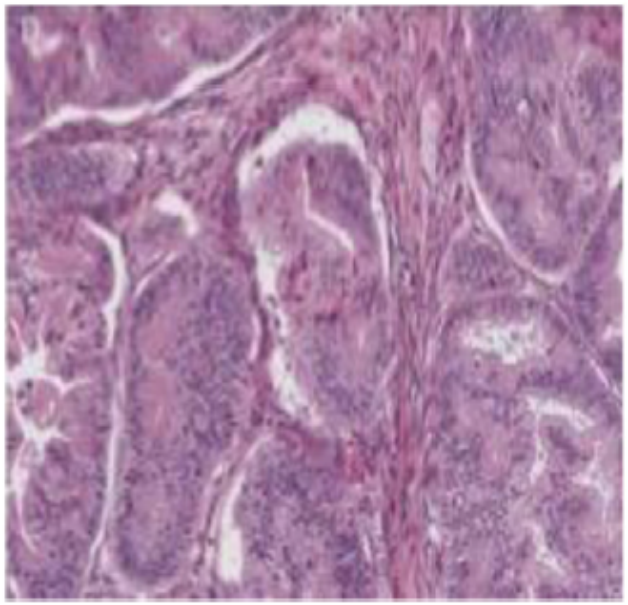


Fig. 4. Mucinous carcinoma exhibiting an expansive pattern with few mitotic figures. All figures were borrowed with permission from David M. Gershenson and Anais Malpica, MD Anderson Cancer Center.

- KRAS, HER2
- **Rule of GI primary**
- May be low- or high-grade
- In advanced stages, significantly worse prognosis than high-grade serous cancers
- Consideration of “GI-type” chemotherapy regimens – FOLFOX

Zaino RJ et al. Cancer 2011.

Ledermann JA et al. Int J Gynecol CA 2014.

Kurnit KC et al. Obstet Gynecol 2019.

Gore M et al. Gynecol Oncol 2019.

Please consider clinical trials for your patients!

Fred Hutch Cancer Center

Thank you