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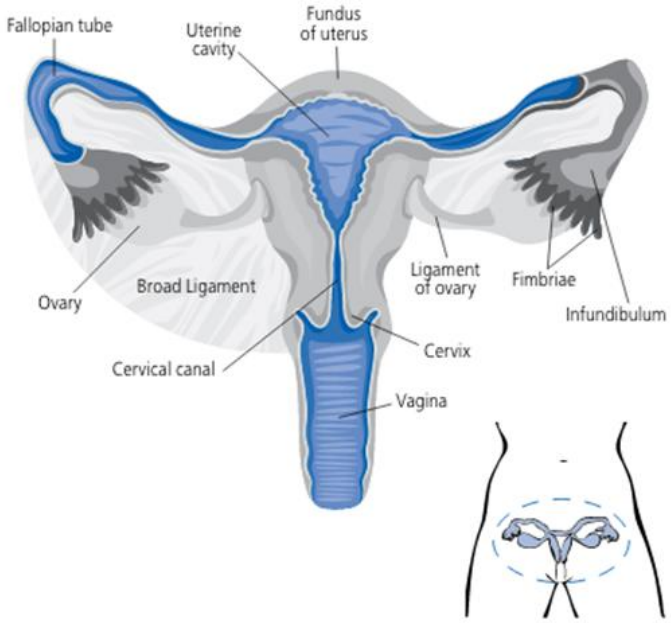
Overview of Ovarian Cancer Management for the GPO



Dr. Anna Tinker
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Vancouver Centre, BCCA
April 16, 2026

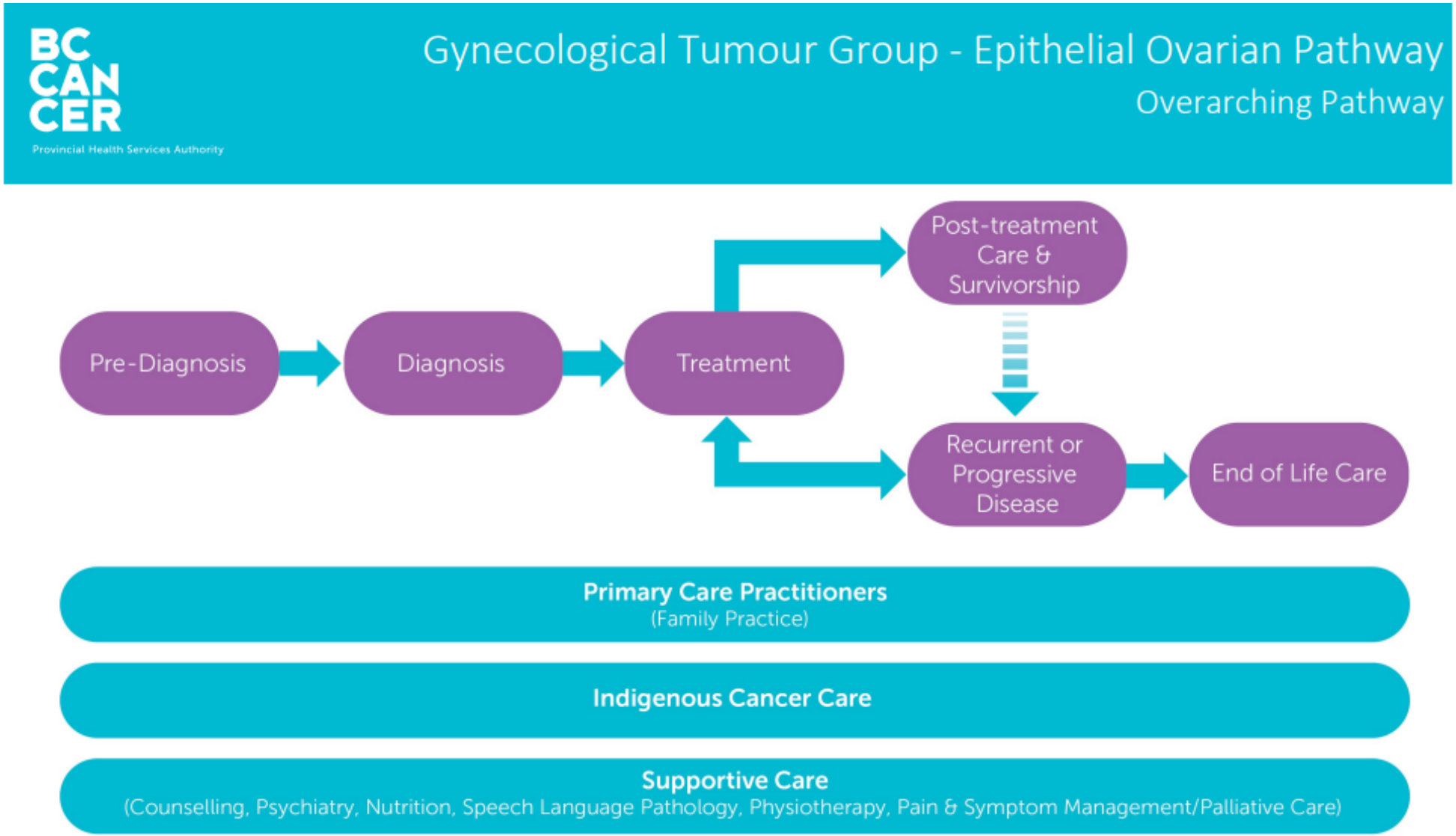
Disclosures

- I have received honoraria for work on advisory boards and speaker's fees from:
    - Merck
    - Abbvie
    - Bosch and Lomb
    - Eisai
    - GSK

Learning Objectives:

- By the end of this session, participants will be able to:
  - Describe the **impact of histopathology and molecular testing on ovarian cancer management;**
  - Discuss **first-line ovarian cancer management**, including the role of surgical timing, chemotherapy and maintenance therapy;
  - Review **monitoring recommendations** during chemotherapy, maintenance therapy and after therapy completion; and
  - Summarize a **management approach to recurrent ovarian cancer**, including disease monitoring recommendations during treatment.

https://www.bccancer.bc.ca/health-professionals/clinical-resources/clinical-care-pathways/tumour-specific-pathwayshttps://www.bccancer.bc.ca/Documents/Epithelial%20Ovarian%20Clinical%20Pathway_Published.pdf



Histopathology and Molecular Testing

- Used to believe that different histology = morphological variants

- Histotype broadly defines **different diseases**

  - High grade serous
  - Clear Cell
  - Mucinous
  - Endometrioid
  - Low grade serous
  - Other very rare types…

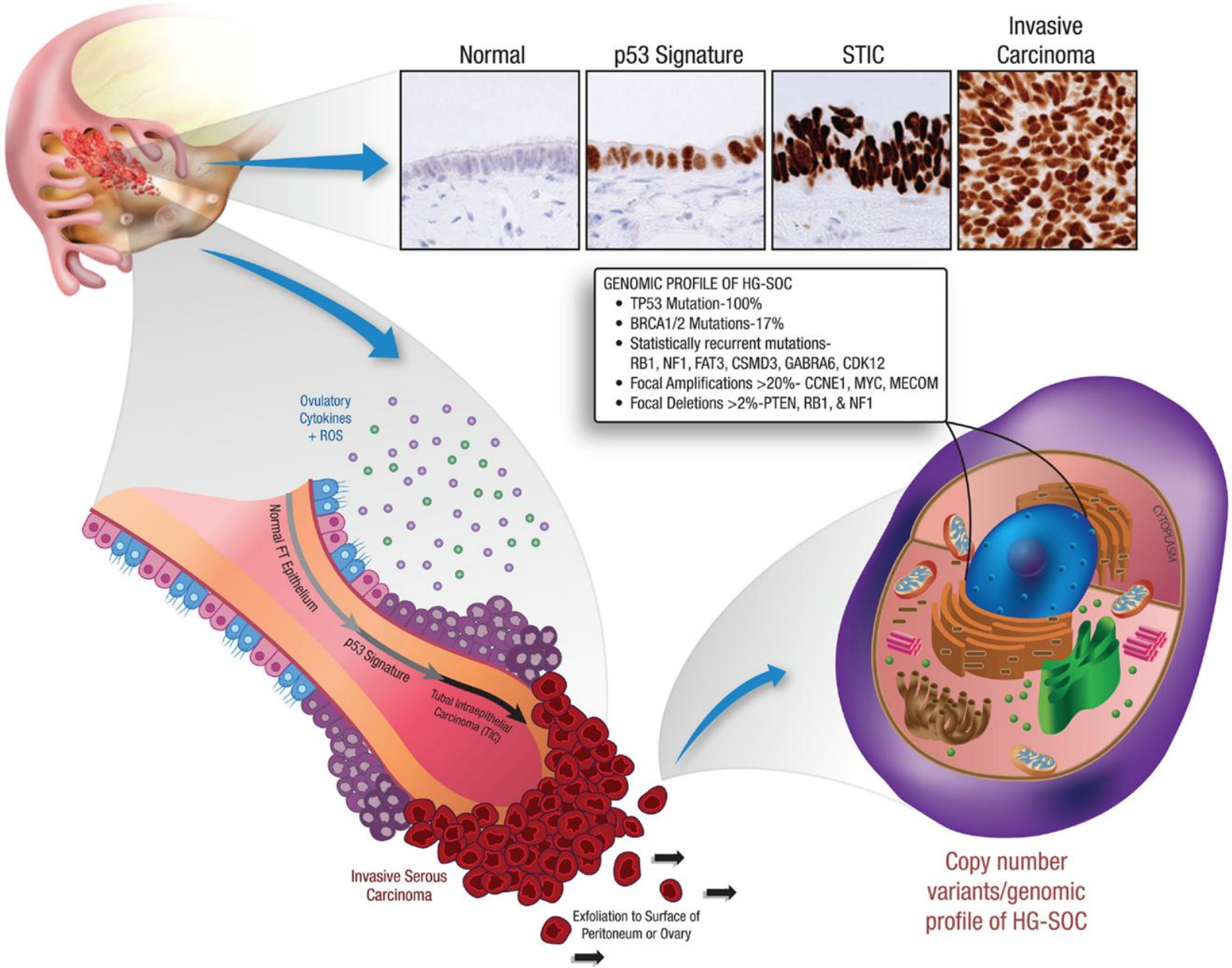
	HGSC	Clear Cell	Endometrioid	Mucinous	LGSC
Portion of cases	**70**	**12**	**11**	**3**	**3**
Genetic Risk Factors	BRCA1/2	Lynch Syndrome	Lynch Syndrome	none known	none known
Precursor Lesions/Cell of Origin	**STIC**, p53 signatures	**Endometriosis**	**Endometriosis**	not known	SBT/Fallopian tube
Common stage at presentation	advanced	early	early	early	advanced
Pattern of Spread	trans -coelomic	trans-coelomic/ hematogenous	trans-coelomic/ lymphatic	pseudomyxoma pertonei/ hematogenous	Trans-coelomic
Response to therapy	chemo-sensitive	chemo-resistant, radiosensitive ?immunotherapy	chemo- sensitive	chemo -resistant	chemo-resistant RAS pathway TKI
Molecular aberrations	**p53**, BRCA1, **BRCA2, HRD**	PI3K, ARID1A, MSI	PTEN, bcatenin, ARID1A, MSI	KRAS, HER2	BRAF, KRAS, NRAS **(p53 WT)**

Hereditary Cancer

- Approximately 15-20% of all **high grade serous ovarian cancers** are caused by inherited predisposition
  - ***BRCA 1***
  - ***BRCA 2***
  - Less common: RAD51C, BRIP1..

- 50% of those who have a germline BRCA mutation do NOT have a positive family history

- In BC, all women with high grade ovarian cancer are eligible for BRCA testing
  - Tumour testing
  - Germline testing



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Jones and Drapkin Front. Oncol., 26 August 2013 | http://dx.doi.org/10.3389/fonc.2013.00217

Screening for Ovarian Cancer

- **No evidence to support screening for ovarian cancer in any population (low or high risk):**
  - U/S (TA and TV)
  - CA125, HE4 (human epididymis protein 4)
  - Ovarian cancer symptom index

- **NOT specific**
  - Leads to a high number of unnecessary surgeries/procedures
- Does not detect “early disease”
- Not proven to impact on survival

- Should not be done:
  - False reassurance
  - Risk of false positive

- **All major cancer groups discourage screening, even in high-risk women**

Prevention

- **BRCA mutation carriers (high risk)**
  - Bilateral salpingo-oopherectomy
    - Possible option: remove tubes early and consider oopherectomy closer to age of menopause

- **Non-BRCA (low risk)**
  - **Opportunistic salpingectomy**
    - tubal ligation, C-section, hysterectomy etc.
      - Society of Obstetricians and Gynecologists of Canada
      - American Congress of Obstetricians and Gynecologists (January 2015 – Committee Opinion)
  - No level 1 evidence
    - Population outcomes/complications - being tracked

JAMA Netw Open. 2022;5(2):e2147343. doi:10.1001/jamanetworkopen.2021.47343

Editorial > Gynecol Oncol Rep. 2025 Mar 13:58:101720. doi: 10.1016/j.gore.2025.101720. eCollection 2025 Apr.

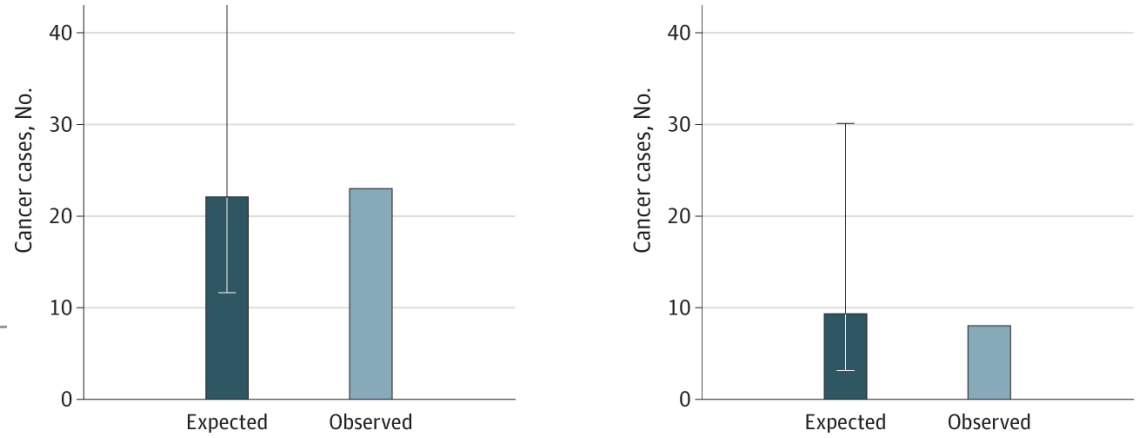
New opportunities for opportunistic salpingectomy: Leveraging non-gynecologic surgeries for ovarian cancer prevention

X Mona Guo [1], Katherine C Fuh [2], Rebecca Stone [3]

Figure Legend:

Numbers of Expected vs Observed Cancers in the Opportunistic Salpingectomy GroupError bars denote 95% CIs.

[a]Denotes a cell size of less than or equal to 5, not an exact number.

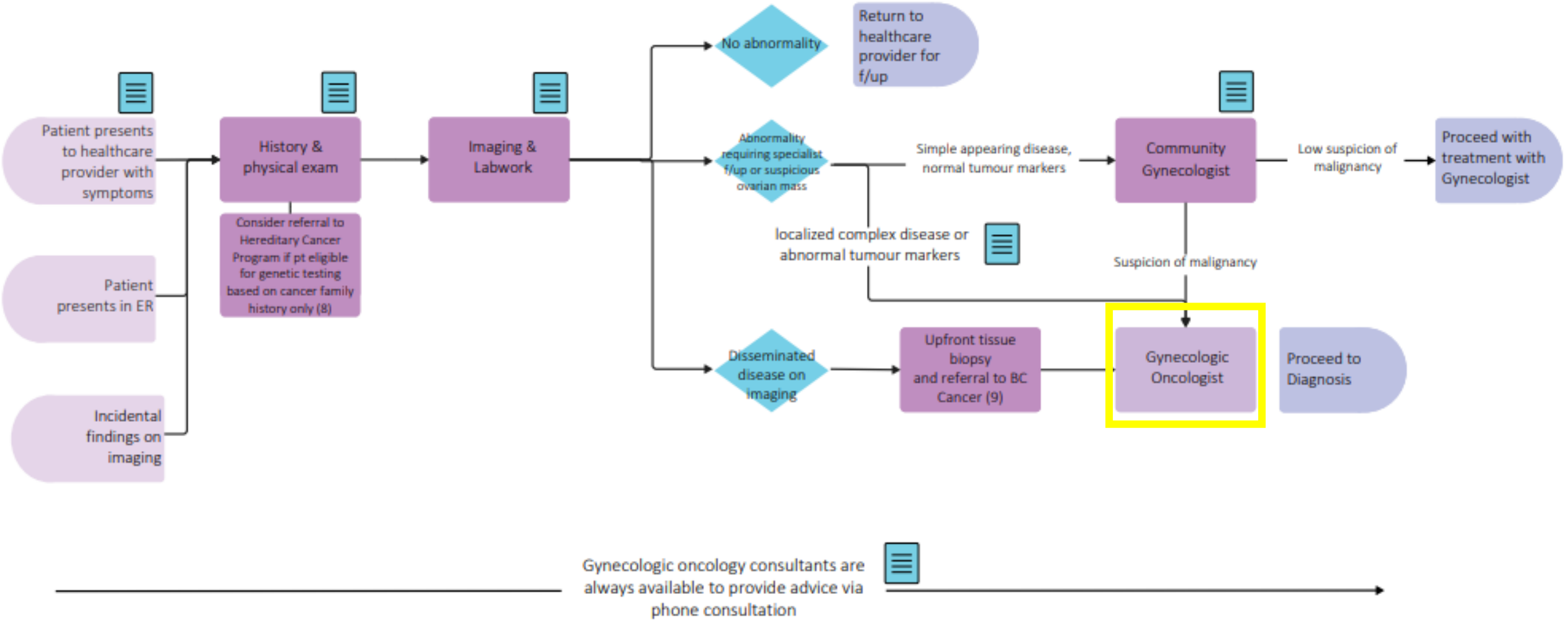


Biopsy

- Biopsies
  - Always correct to consider a biopsy of disseminated disease
    - Omental masses
    - Palpable lymphadenopathy (supraclav, inguinal)
    - In some cases, visceral mets (liver)
  - **Core biopsy always preferable to FNA**
    - Allows better architectural definition of the disease
    - Helps with disease subtyping
      - More material for IHC (can be essential in some cases)
    - Requires image guidance

New Presentation/Diagnosis Work Up

https://www.bccancer.bc.ca/Documents/Epithelial%20Ovarian%20Clinical%20Pathway_Published.pdf



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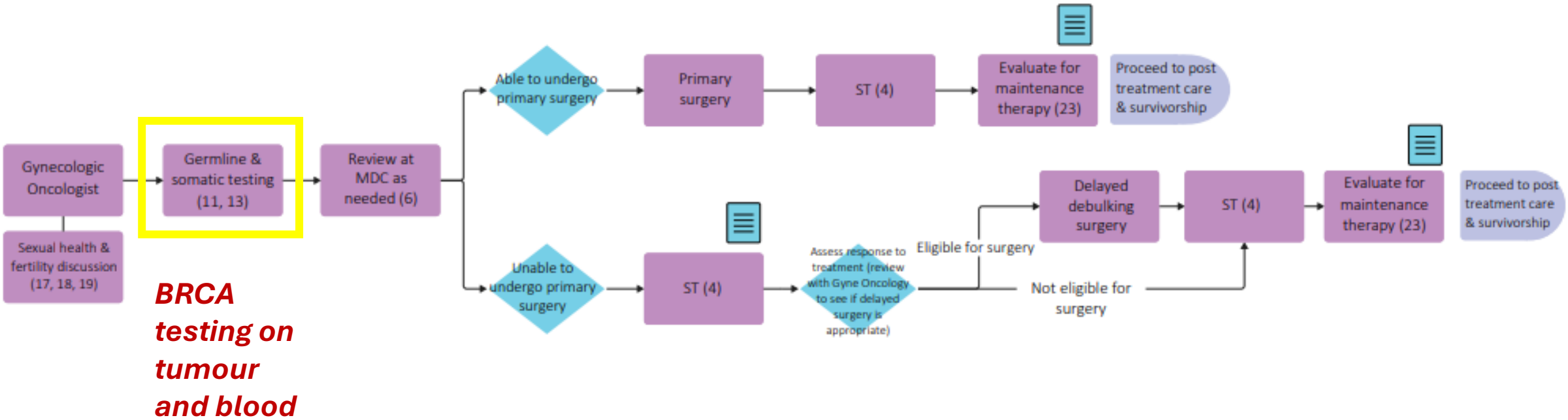
First-Line Treatment of Advanced Ovarian Cancer

"Neoadjuvant" or Pre-Operative

OR

"Adjuvant" or Post-Operative

Treatment - High Grade Serous Ovarian Cancer (22)



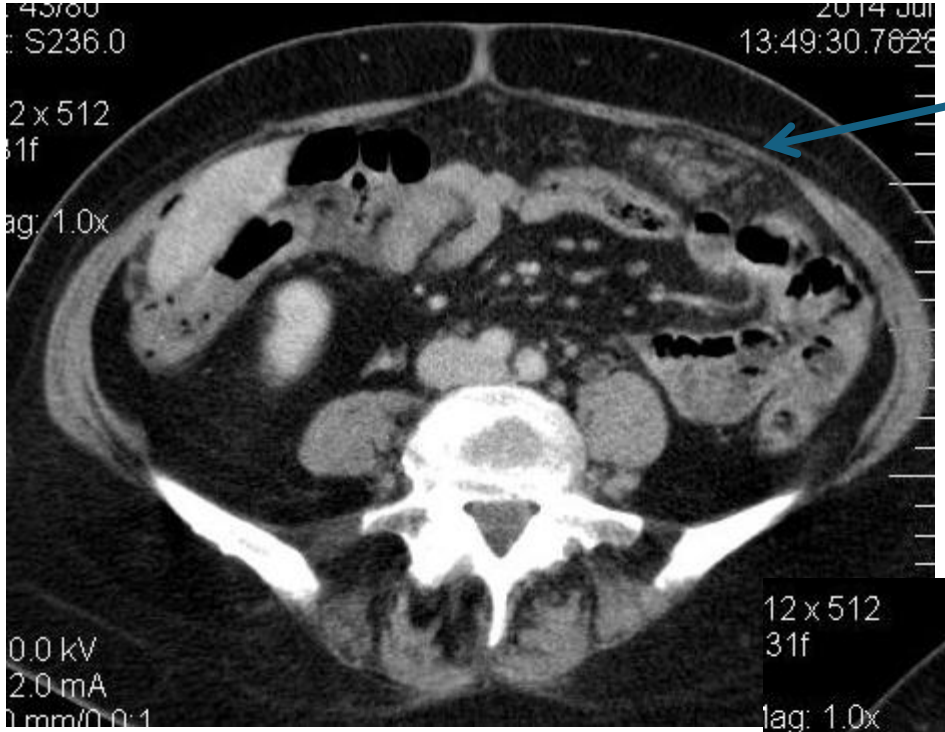
BRCA testing on tumour and blood

Surgery: Gynecologic Oncologist

- Outcomes are generally the same whether surgery first or chemo first
  - Pts with **stage III or IV ovarian cancer**
  - 4 randomized phase III trials
  - Otherwise fit for surgery (no PE/DVT, or serious commorbidity)

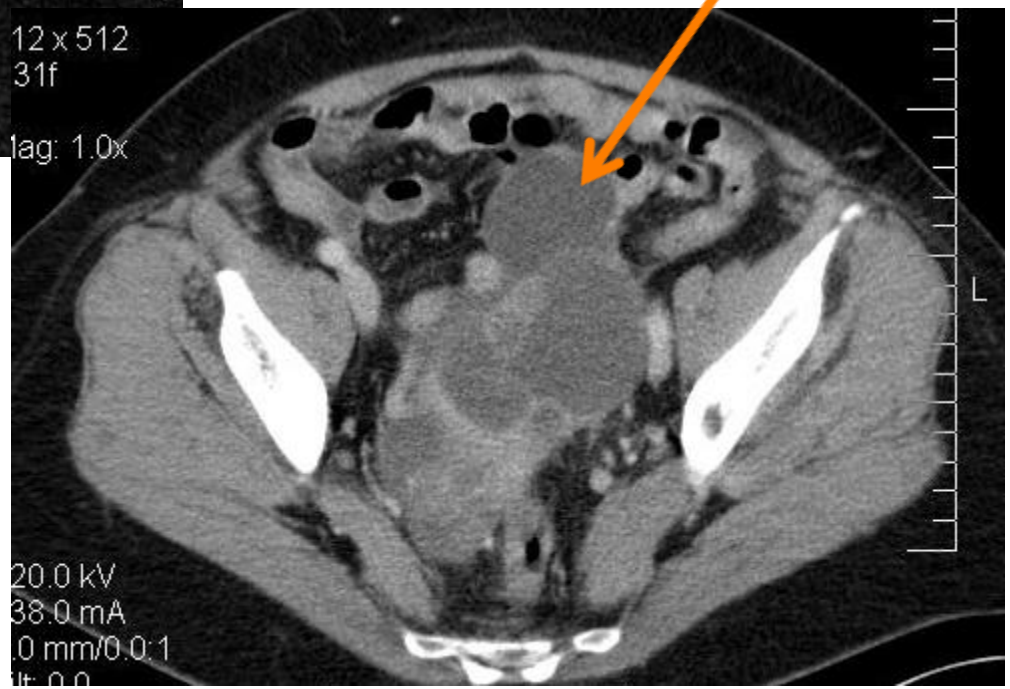
- Usually suitable for surgery if:
  - Pelvic mass/Omental cake/All disease felt to be removable by a gynecologic oncologist

- Usually delay surgery if:
  - Diffuse peritoneal disease/disease under the diaphragms/Massive ascites/Large retroperitoneal LNs/
  - Acute medical problem – MI/unstable angina, acute PE/DVT



Omental mass

Pelvic Mass



This case had upfront surgery

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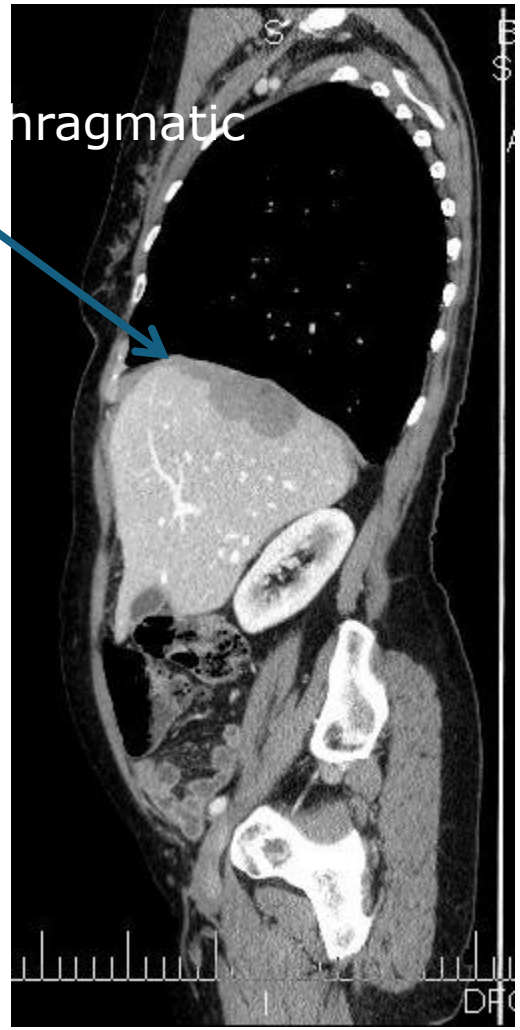
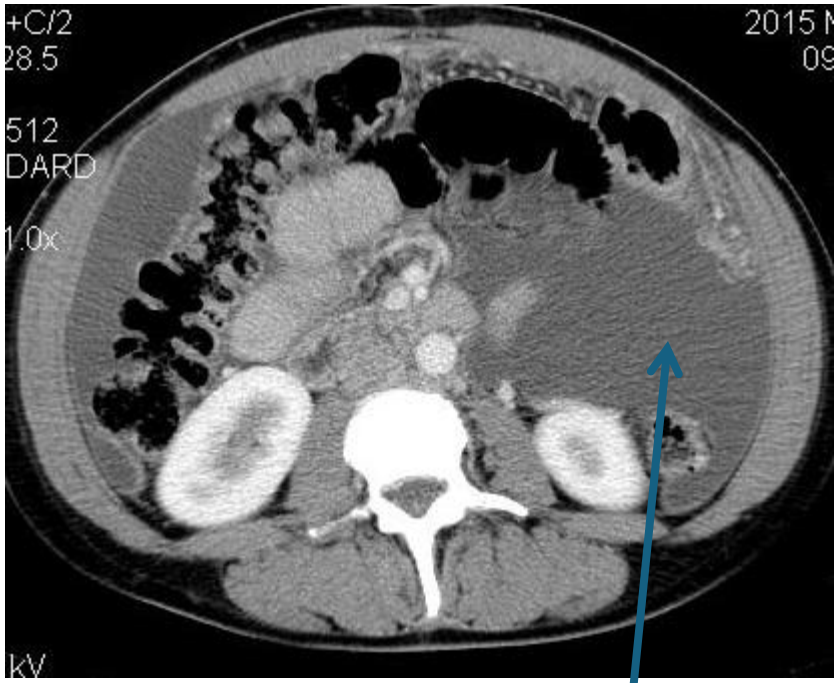
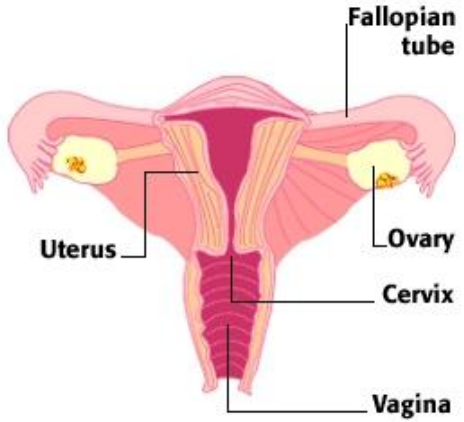




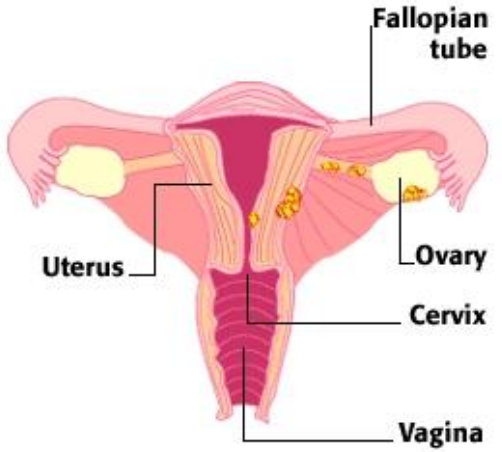
Massive ascites

These cases had pre-operative chemotherapy



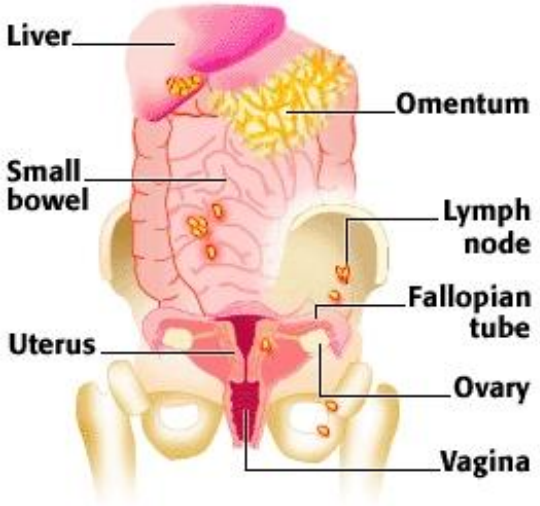
Stage 1
Tumor limited to one or both ovaries. Tumor may be found on ovarian surface.

- IA unilateral
- IB bilateral
- IC any of:
  - cyst rupture
  - positive peritoneal cytology
  - surface involvement



Stage 2
Tumor invades one or both ovaries, with extension into the pelvic region, but without spread to the abdomen.

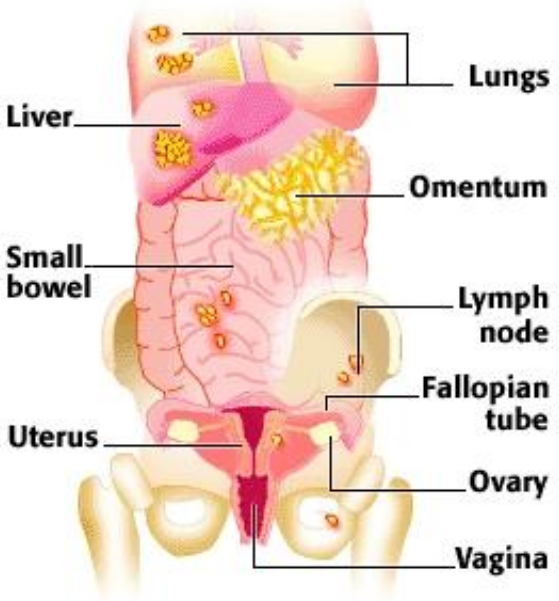
- 2A involvement of fallopian tubes or uterus
- 2B extention to other pelvic structures (bladder, rectum)
- 2C like 2B but with positive peritoneal washings



Stage 3
Tumor extends beyond pelvis into the abdominal organs.

- 3A microscopic **involvement of the peritoneum or the omentum**
- 3B abdomin-peritoneal implants <2cm
- 3C abdomin-peritoneal implants >2cm

- Disease within **visceral organs** or **above the diaphragm** (if a plural effusion must be confirmed cytologically to be considered stage 4).



Stage 4
Distant metastasis to the lung, liver, or lymph nodes in the neck.

Prognosis by Stage

SEER* stage	5-year relative survival rate
Localized	92%
Regional	71%
Distant (III/IV)	32%
BRCA (III/IV)	~75%

Stage III and IV **BRCA mutated ovarian cancer – improved longer term prognosis**

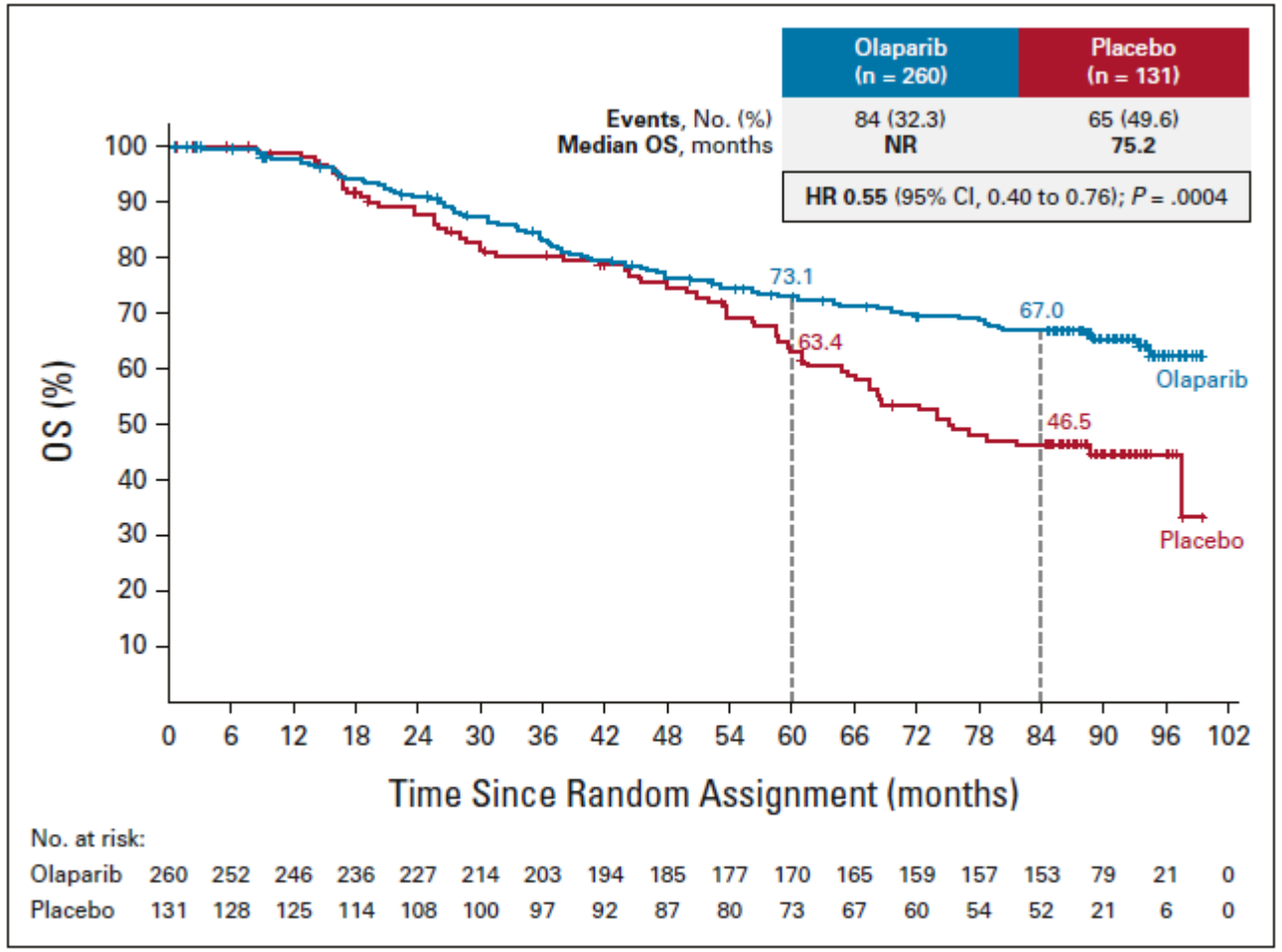


FIG 2. Kaplan-Meier estimates of OS. HR, hazard ratio; NR, not reached; OS, overall survival.

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First Line Systemic Therapy

- **<u>Carboplatin and Paclitaxel</u>**

  Q 3 weekly

  Goal – 6 cycles

- **<u>Monitoring:</u>**
  - For women with delayed surgery – in addition to monitoring for toxicity, need to monitor for disease response
    - Clinical – improving symptoms related to the advanced cancer?
    - CA125 – Is it dropping?
    - CT scan after cycle 3
      - Refer back to Gynecologic Oncology for review re: delayed debulking

Role of bevacizumab in newly diagnosed advanced stage disease

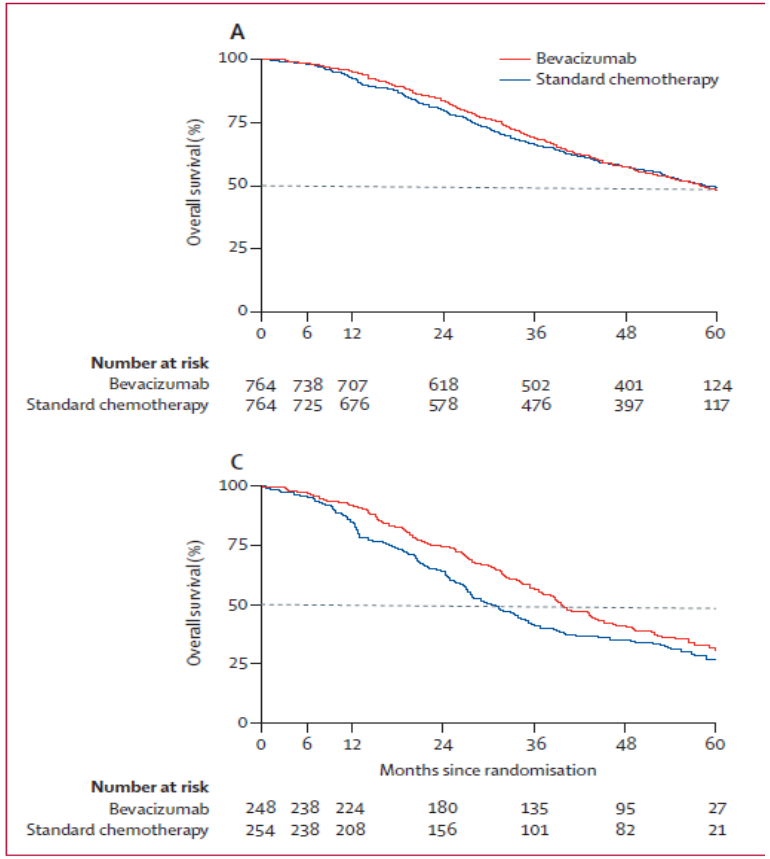

Figure 2: **Overall survival**

Intention to treat population

High risk for relapse population

- Stage IV
- Residual disease after primary surgery
- Inoperable disease

***Lancet Oncol* 2015; 16: 928–36**

Carboplatin and Paclitaxel – Toxicity

- **Infusion reactions** – anaphylactoid (not IgE mediated) – **can be premedicated**
- **Platinum allergy** - some patients have been pretreated with cisplatin – higher risk of IgE reaction to carboplatin (anaphylactic – **cannot be effectively premedicated**)
- **Nausea**
- **Vomiting**
- **Myalgias** (usually last 3-4 days, start on day 3 of the cycle)
- **Neuropathy** (paclitaxel causes **length-dependent axonal sensory neuropathy** ***correlating with the dose***, infusion time, ***underlying conditions***, and co-treatment with other drugs e.g. carboplatin)
  - Numbness and tingling and pain
    - (older patients this may add to gait instability, weakness and falls)
  - No way to prevent apart from **dose modifications or dose delays to reduce exposure**
- **Fatigue**
- **Gastritis** dexamethasone use ++

Carboplatin and Paclitaxel – Toxicity

- **Febrile Neutropenia - life-threatening oncologic emergency** defined by a fever (≥38.3C or equal to 38.0 C for more than 1 hour)) and neutrophils < 1.0).

  * *FN can occur at any timepoint in the treatment cycle*

  - low risk patients may be suitable for outpt management

  - high risk patients need admission and parenteral antibiotics

Treatment : very important to treat early and with broad spectrum antibiotics (including gram negs - pseudomonas).

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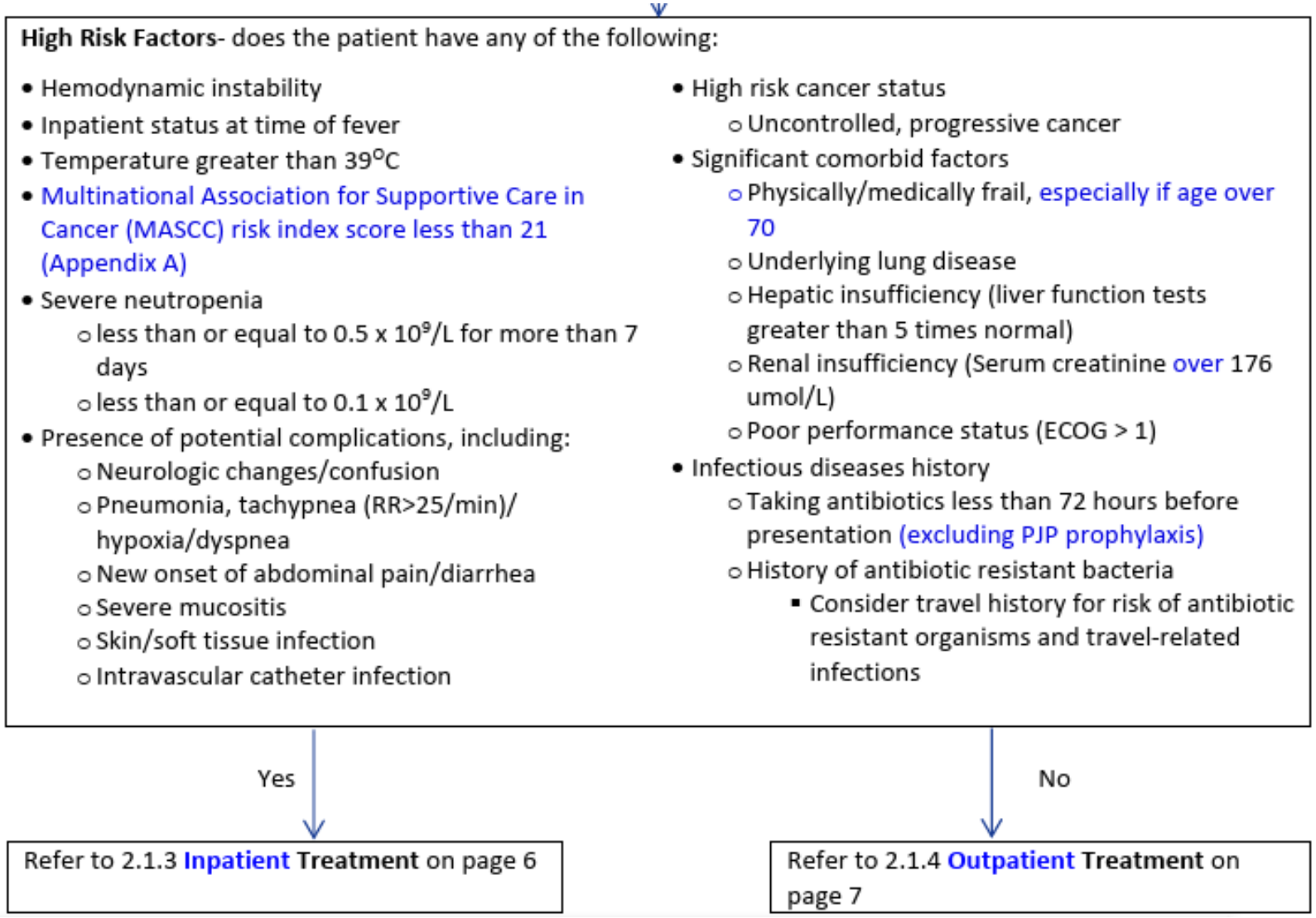
Febrile Neutropenia

https://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/supportive-care/febrile-neutropenia



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Bevacizumab – what to watch for

- Hypertension
- Proteinuria – can tolerate mild proteinuria (<2g/L)
- Fistulization and/or bowel perforation
  - Risk factors – prior RT to the pelvis/local disease progression
- Hoarseness of the voice (relatively common)
- Headaches, dizziness
- **Rare: PRES** - Posterior Reversible Encephalopathy Syndrome
  - seizures, confusion, visual disturbances, and a stiff neck
- **Rare: osteonecrosis of the jaw (ONJ)**
  - may need to avoid bev in those with poor dentition
  - Check oral health/ask dentist to review

PARP Inhibitors

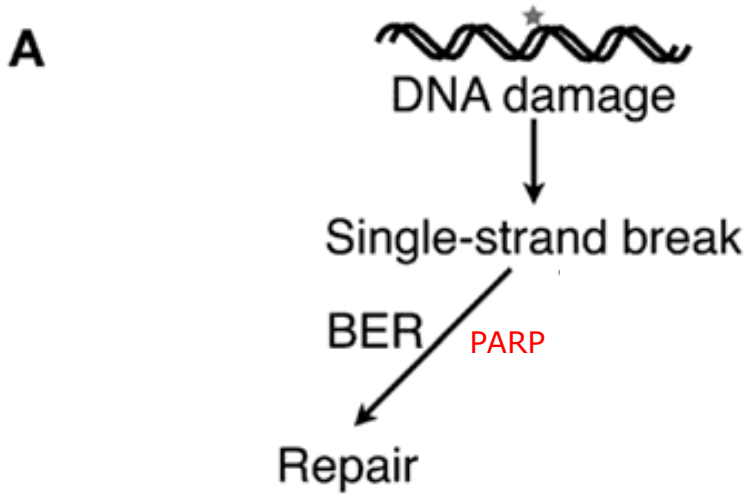
- **PARP enzyme** plays an important role in the repair of single-stranded DNA breaks
  - base excision repair pathway (BER) (high accuracy)

- Keep low-fidelity repair machinery in check
  - nonhomologous-end-joining DNA
  - Single strand annealing
  - Microhomology mediated end joining

- The other highly accurate DNA repair pathway is HR (double strand break repair)

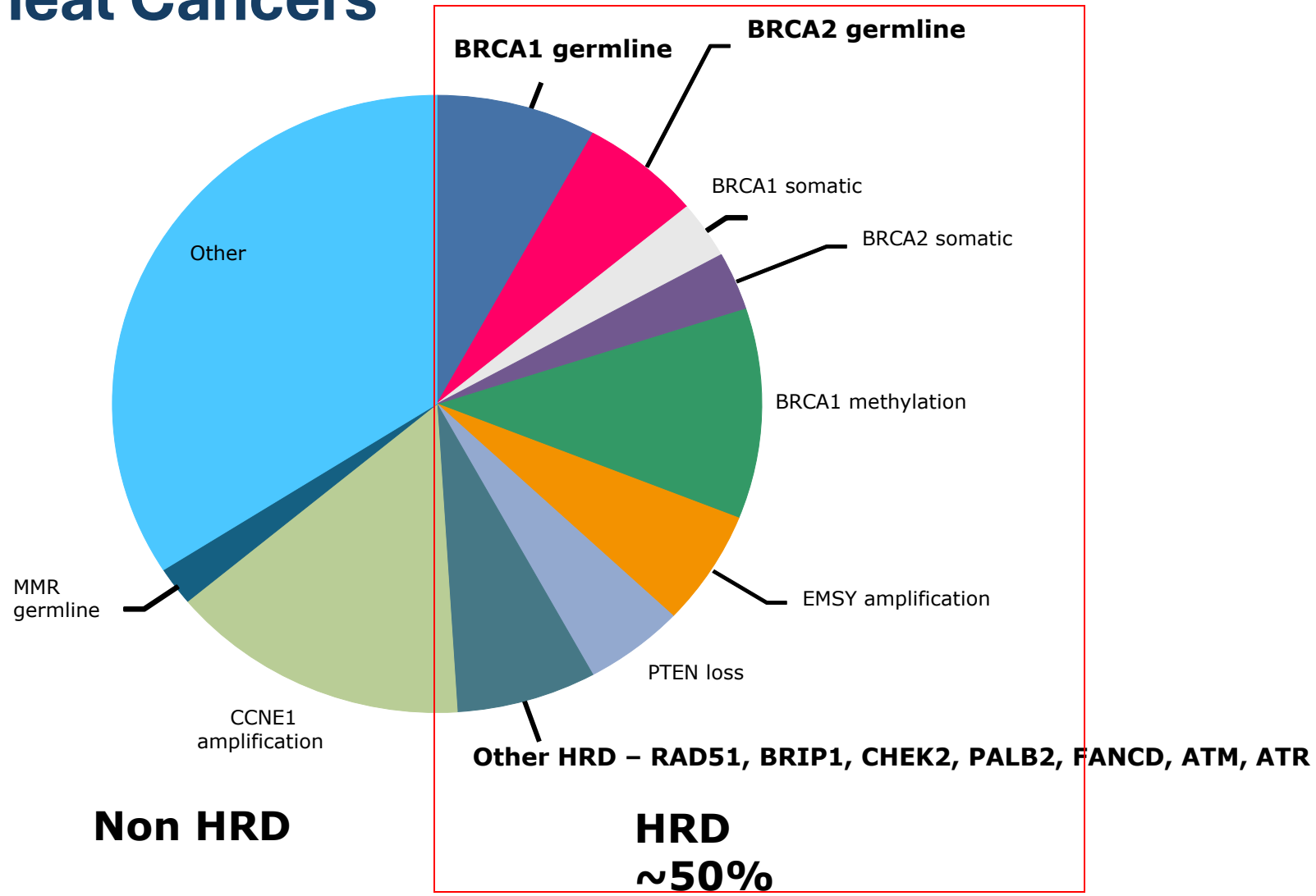
- Many HGSC of the ovary have defects in the HR pathway
  - BRCA mutation
    - Germline = 25%
    - Somatic = 25%

Poly (ADP-ribose) polymerase 1 (PARP1)



NHEJ
MMEJ

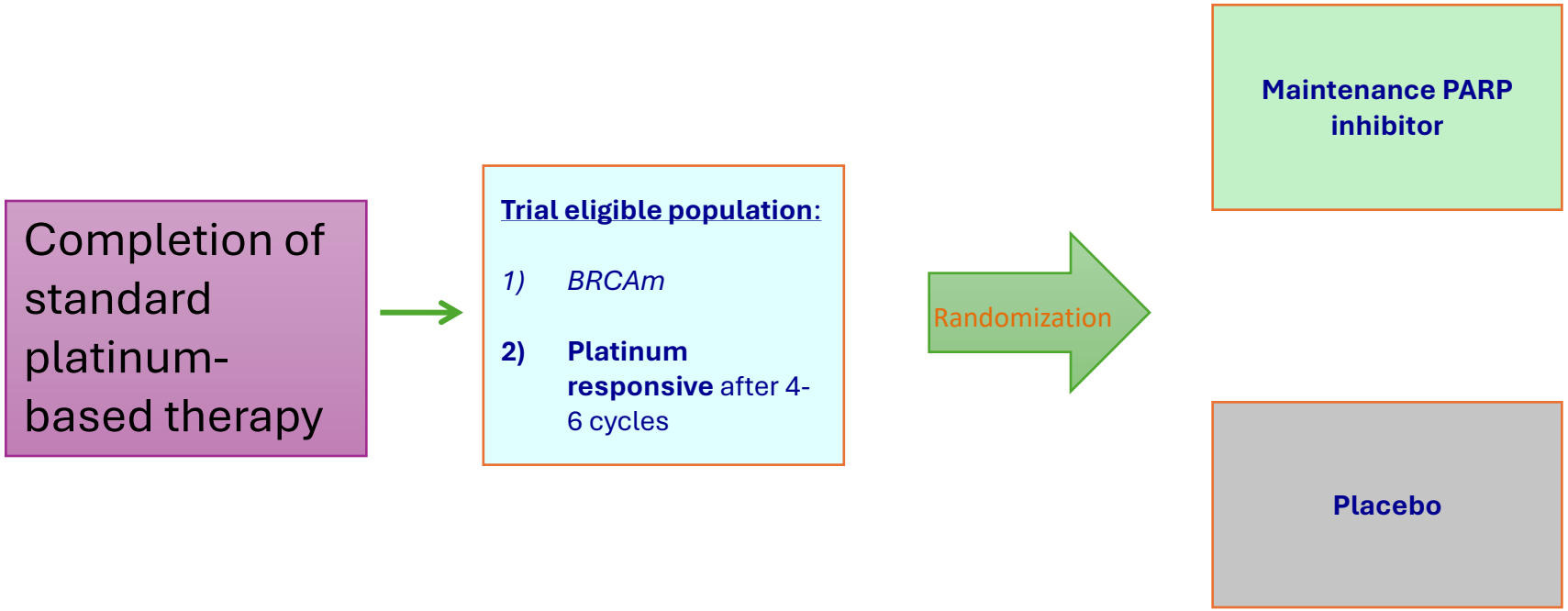
HRD: common in High Grade Serous Ovary/FT/Peritoneal Cancers



- *Levine D. The Cancer Genome Atlas, 2011*

PARP inhibitors

- PARP inhibitors major advance in ovarian cancer therapy
- Studied in multiple settings
  - Platinum-resistant…platinum-sensitive…**first-line therapy**



Maintenance Olaparib in BRCA Mutation Carriers

Olaparib is an oral therapy:

1) Starting dose 300 mg PO BID
2) Treatment should start within 8 weeks of last chemo cycle
3) **2 yrs of maintenance if no disease progression**

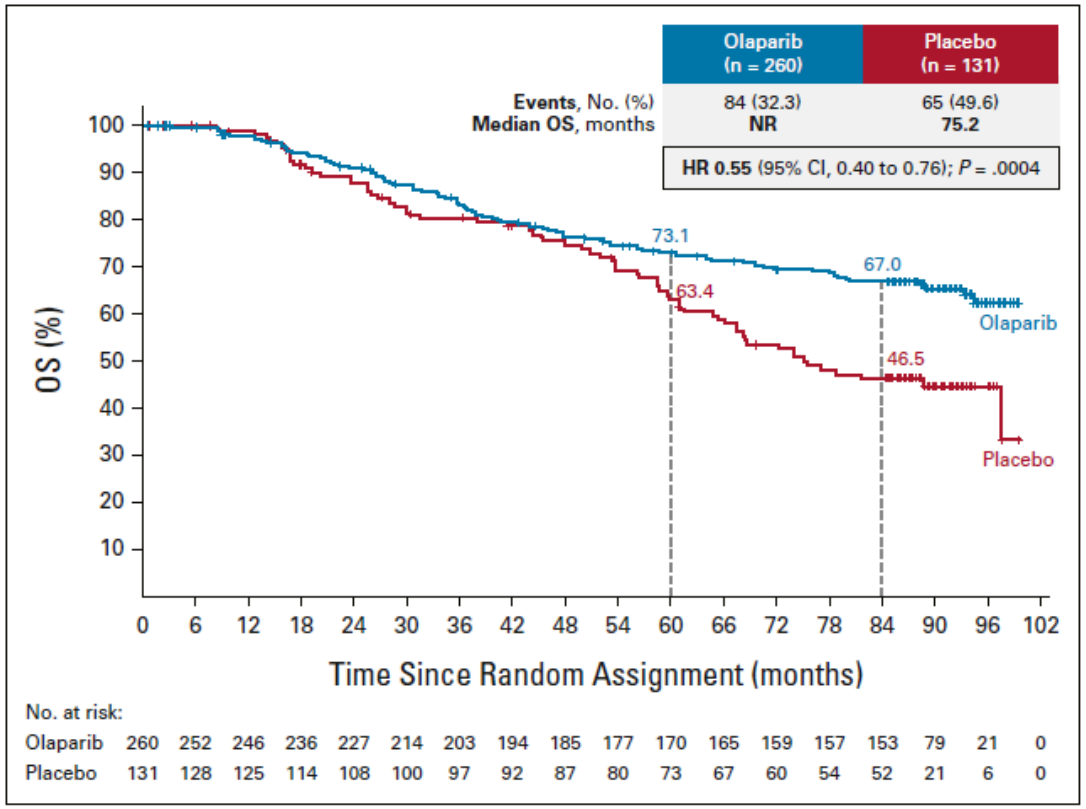


FIG 2. Kaplan-Meier estimates of OS. HR, hazard ratio; NR, not reached; OS, overall survival.

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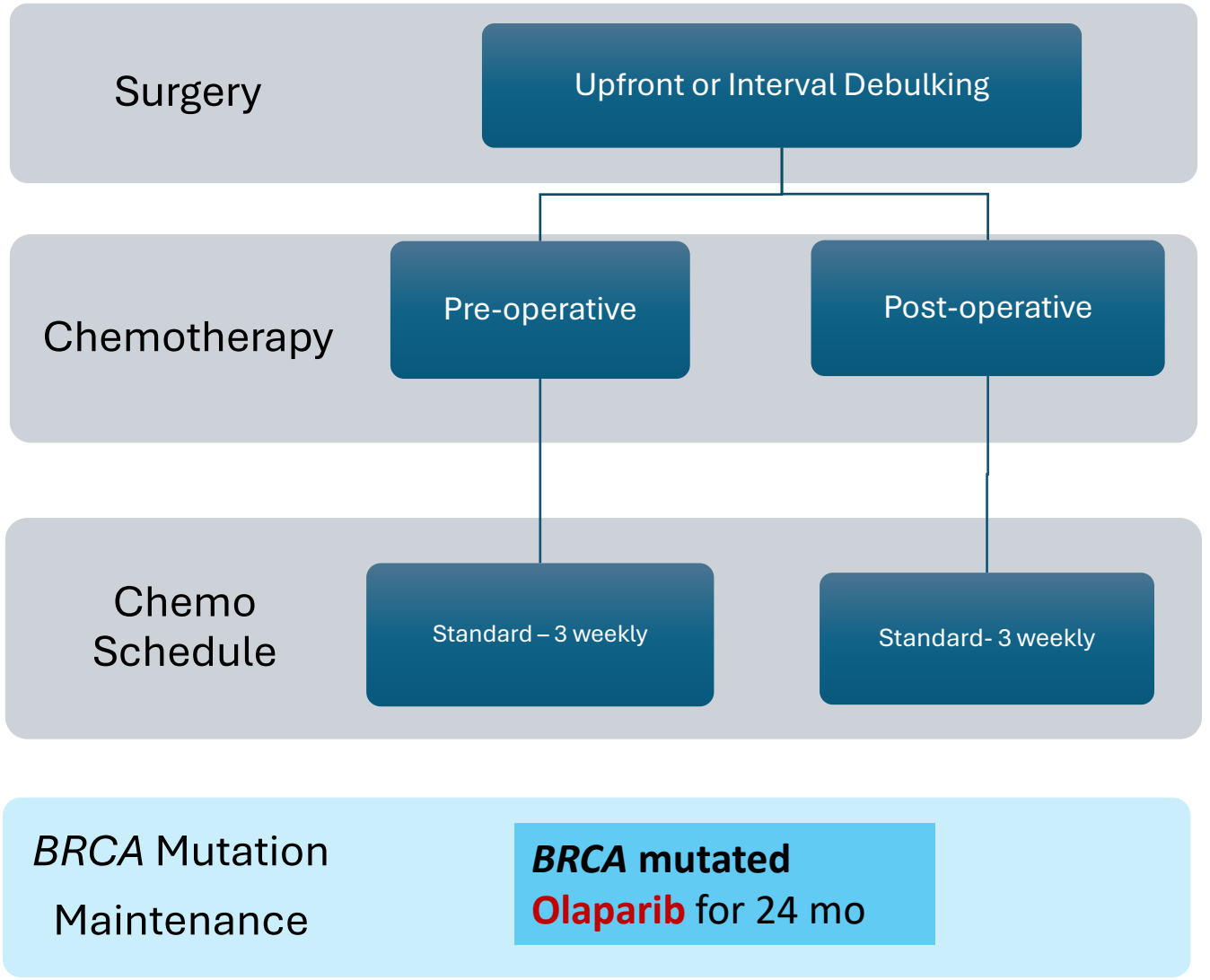
DiSilvestro P et al ; SOLO1 Investigators. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. J Clin Oncol. 2023 Jan 20;41(3):609-617. doi: 10.1200/JCO.22.01549. Epub 2022 Sep 9. PMID: 36082969; PMCID: PMC9870219.

First-Line Therapy in *BRCA1/2* Mutation Carriers



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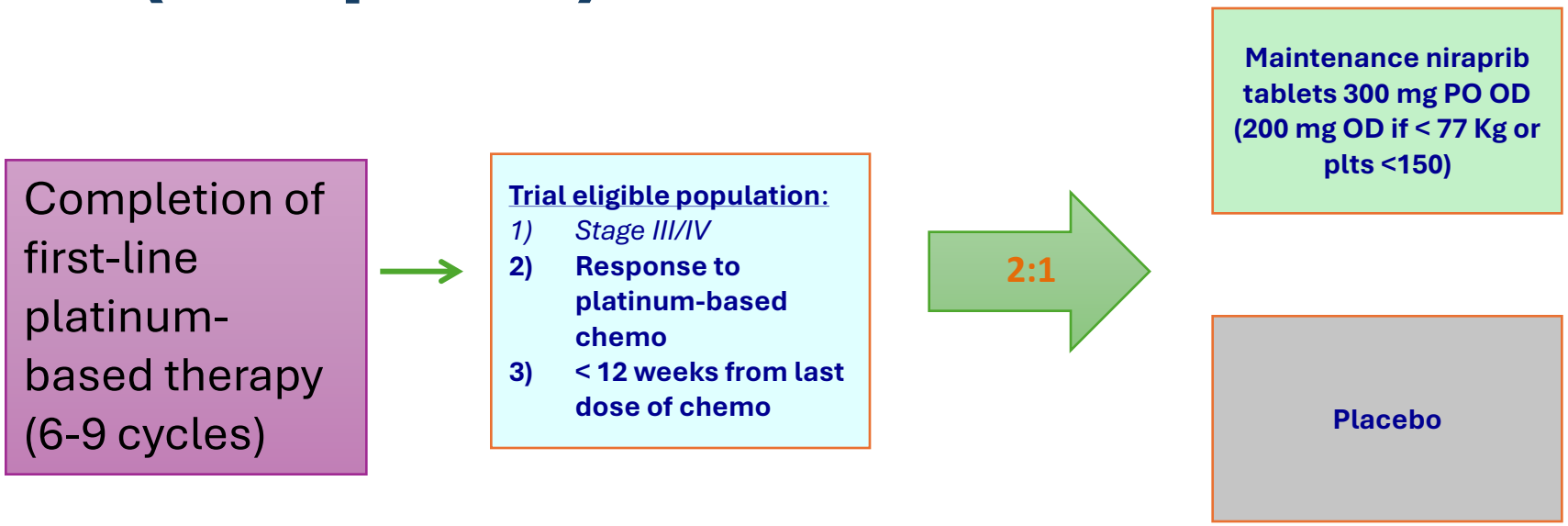
PRIMA (niraparib)



- Treatment Duration
  - Up to 36 months or until progression

- Primary endpoints :
  - **PFS in patients with HRD tumours** (MyChoice, Myriad Genetics)
    - *BRCA* mutated tumours
    - **HRD score ≥42**
  - **PFS in overall study population**

PRIMA results

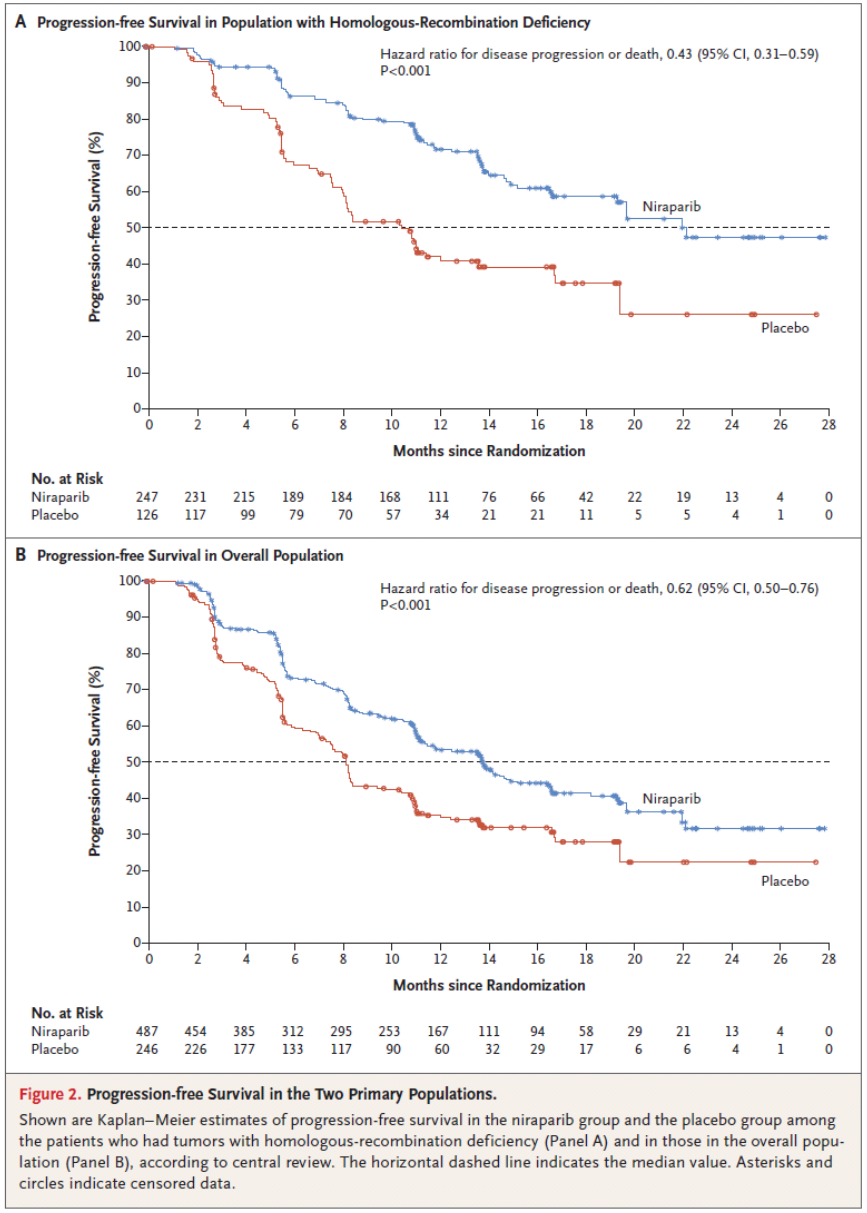


Figure 2. Progression-free Survival in the Two Primary Populations.
Shown are Kaplan–Meier estimates of progression-free survival in the niraparib group and the placebo group among the patients who had tumors with homologous-recombination deficiency (Panel A) and in those in the overall population (Panel B), according to central review. The horizontal dashed line indicates the median value. Asterisks and circles indicate censored data.

HRD Population (N=373):

mPFS 21.9 mo vs 10.4

- HR for disease progression or death, 0.43; 95% CI, 0.31 to 0.59; P<0.001

Overall Population (N=733):

mPFS 13.8 mo vs 8.2

- HR, 0.62; 95% CI, 0.50 to 0.76; P<0.001

N Engl J Med 2019; 381:2391-2402

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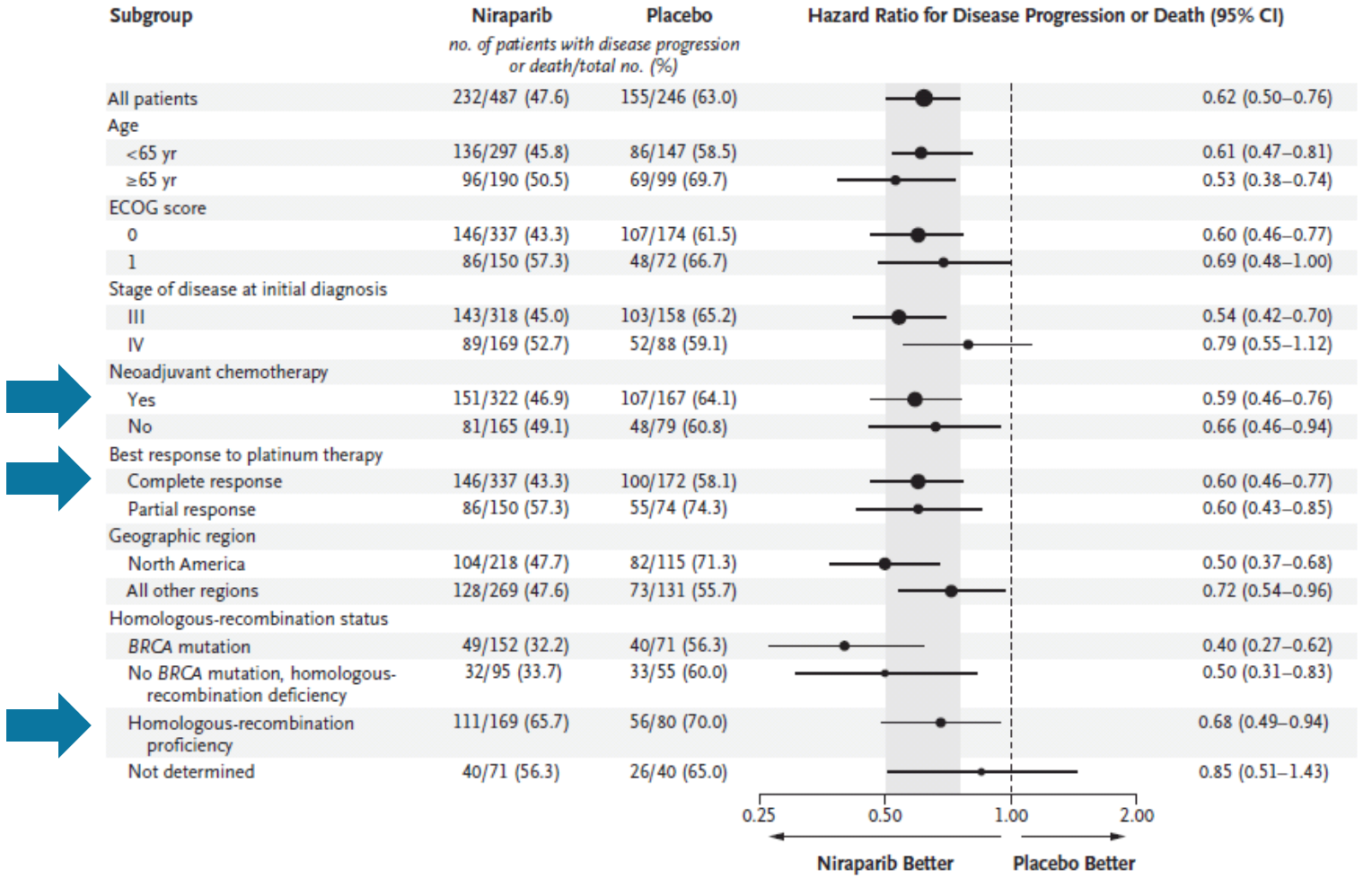
PRIMA – Pre-specified subgroup analysis



Subgroup	Niraparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	232/487 (47.6)	155/246 (63.0)	0.62 (0.50–0.76)
Age			
<65 yr	136/297 (45.8)	86/147 (58.5)	0.61 (0.47–0.81)
≥65 yr	96/190 (50.5)	69/99 (69.7)	0.53 (0.38–0.74)
ECOG score			
0	146/337 (43.3)	107/174 (61.5)	0.60 (0.46–0.77)
1	86/150 (57.3)	48/72 (66.7)	0.69 (0.48–1.00)
Stage of disease at initial diagnosis			
III	143/318 (45.0)	103/158 (65.2)	0.54 (0.42–0.70)
IV	89/169 (52.7)	52/88 (59.1)	0.79 (0.55–1.12)
Neoadjuvant chemotherapy			
Yes	151/322 (46.9)	107/167 (64.1)	0.59 (0.46–0.76)
No	81/165 (49.1)	48/79 (60.8)	0.66 (0.46–0.94)
Best response to platinum therapy			
Complete response	146/337 (43.3)	100/172 (58.1)	0.60 (0.46–0.77)
Partial response	86/150 (57.3)	55/74 (74.3)	0.60 (0.43–0.85)
Geographic region			
North America	104/218 (47.7)	82/115 (71.3)	0.50 (0.37–0.68)
All other regions	128/269 (47.6)	73/131 (55.7)	0.72 (0.54–0.96)
Homologous-recombination status			
BRCA mutation	49/152 (32.2)	40/71 (56.3)	0.40 (0.27–0.62)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)	0.50 (0.31–0.83)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)	0.68 (0.49–0.94)
Not determined	40/71 (56.3)	26/40 (65.0)	0.85 (0.51–1.43)

8.1 mo vs 5.4 mo PFS

Figure 3. Disease Progression or Death, According to Prespecified Subgroups.

Shown is the incidence of disease progression or death, according to the listed subgroups, in the two trial groups. On the Eastern Cooperative Oncology Group (ECOG) performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

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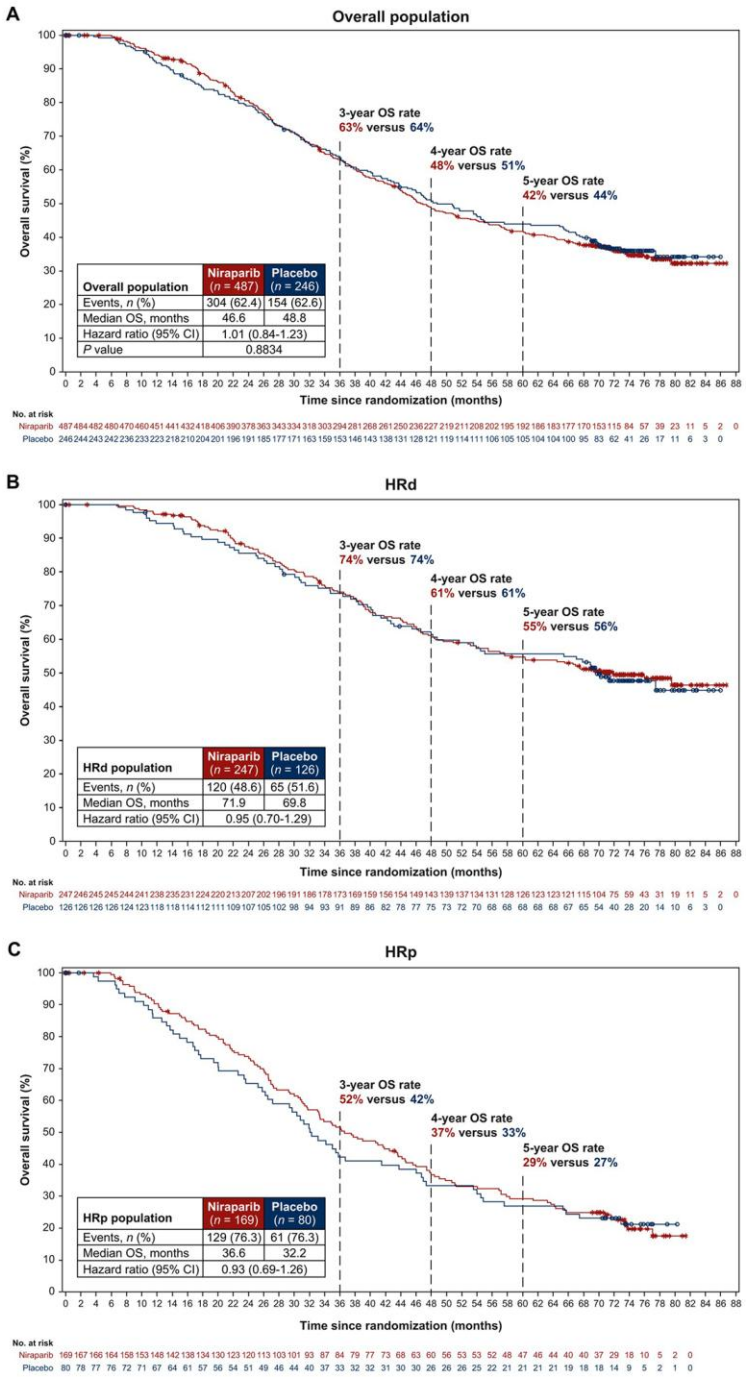
N Engl J Med 2019; 381:2391-2402

Updates Overall Survival from the PRIMA study

- update to **the 5-yr OS data** (a secondary endpoint in the trial), published in 2024
- **no survival benefit from maintenance niraparib was demonstrated for any molecular subgroup**



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Niraparib

- **Niraparib is an oral therapy:**

1) Starting dose 300 mg PO OD
2) Starting dose 200 mg PO OD if:

Baseline weight: <170 lb (77 kg)

OR

Baseline Platelets: <150,000/µL

- If pt had a lot of myelosuppression with chemo, has existing HTN, poor/slow recovery post chemo, I start many on 200 mg PO OD or even 100 mg PO OD

3) Treatment should start within 12 weeks of last chemo cycle
4) **3 yrs of maintenance if no disease progression**

Tell patients from the start that **dose interruption and modifications** are VERY common on maintenance niraparib, they should expect it. **Efficacy data suggests no meaningful impact on outcomes.**

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Dose levels for PARP inhibitors

Olaparib

- 300 mg PO BID
- 250 mg PO BID
- 200 mg PO BID
- (150 or 100 mg PO BID?)

- Can take with or without food
- Cannot have grapefruit

Niraparib

- 300 mg PO OD
- 200 mg PO OD
- 100 mg PO OD
- Discontinue

- With or without food

Side Effects of PARP Inhibitors*

	Olaparib (%)	Niraparib (%)
Side Effects (any G)		
Nausea	77	57
Fatigue	63	35
Vomiting	40	22
Headache	23	26
Hypertension		G3/4 – 8%, any G – 20%
Palpitations		10
Insomnia		23
Hematologic toxicity/Biochemistry		
Anemia	39	63
Neutropenia	23	26
Thrombocytopenia	11	46
Elevated Creatinine	Seen in practice	

* From multiple sources

~1-2% risk of myelodysplastic syndrome and acute myelogenous leukemia

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Monitoring for PARP Inhibitors

First 1-2 months of treatment:

- Q 2 wks X4 olaparib
- Q1 week X 8 for niraparib
- Lab tests: CBC, electrolytes, Cr, LFTs, including tumour markers
- In person review every 4 weeks

Monthly thereafter and as needed:

- Monitor for adverse events
- Lab tests and tumour markers
- Imaging (as needed – if CA125 stable and no new symptoms, not essential)

Post 12 months Or once on a stable dose and counts remain normal

- Assessments can be done every 2 months

Baseline imaging before starting PARP is reasonable, and then can consider 6-12 mo scan, and scan again at end of therapy

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Dose Interruptions and Reductions

- **VERY common**:
  - Olaparib trials: **dose reductions occurred in 28%** and **interruptions in 50%** of olaparib-treated patients
  - Niraparib: **dose reductions occurred in 40-60%** and **interruptions in 60-70%**

- **Usually occur early in the treatment course** – stable dosing by cycle 3 is likely

- Dose reductions and interruptions **do not appear to compromise efficacy**.
  - no significant difference in PFS or OS across relative dose intensity categories from analyses of trials and real-word data (olaparib)

- Individualized starting doses have no impact on efficacy for niraparib (but improve toxicity!)

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Francis KE et al. . The impact of olaparib dose reduction and treatment interruption on treatment outcome in the SOLO2/ENGOT-ov21 platinum-sensitive recurrent ovarian cancer. Ann Oncol. 2022 Jun;33(6):593-601. doi: 10.1016/j.annonc.2022.02.222. Epub 2022 Feb 24. PMID: 35219776.

Managing Side Efffects

- Nausea – improves with time, use antiemetics
- Fatigue – rule out contributors (anemia, depression, insomnia, etc.)
  - Rest and exercise!
  - Can interrupt drug for short time and start again
  - **Dose reduction**
    - Usually effective
  - **Niraparib** BP Monitoring – weekly on niraparib
    - May need to start anti-HTN meds, or intensify current regimen

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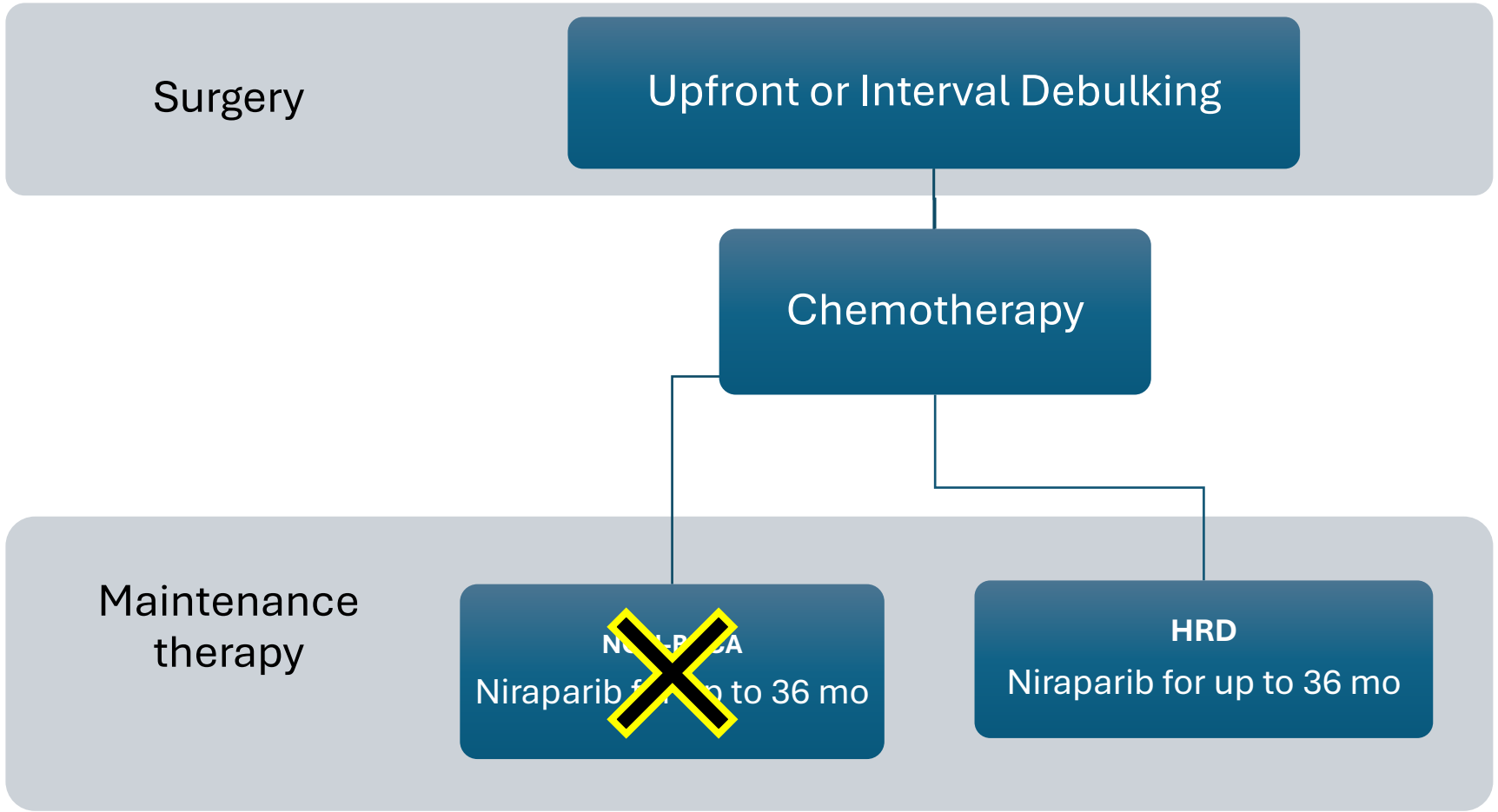
First-Line Therapy in NON-BRCA Mutated Cases



HRD testing to be available late in 2026

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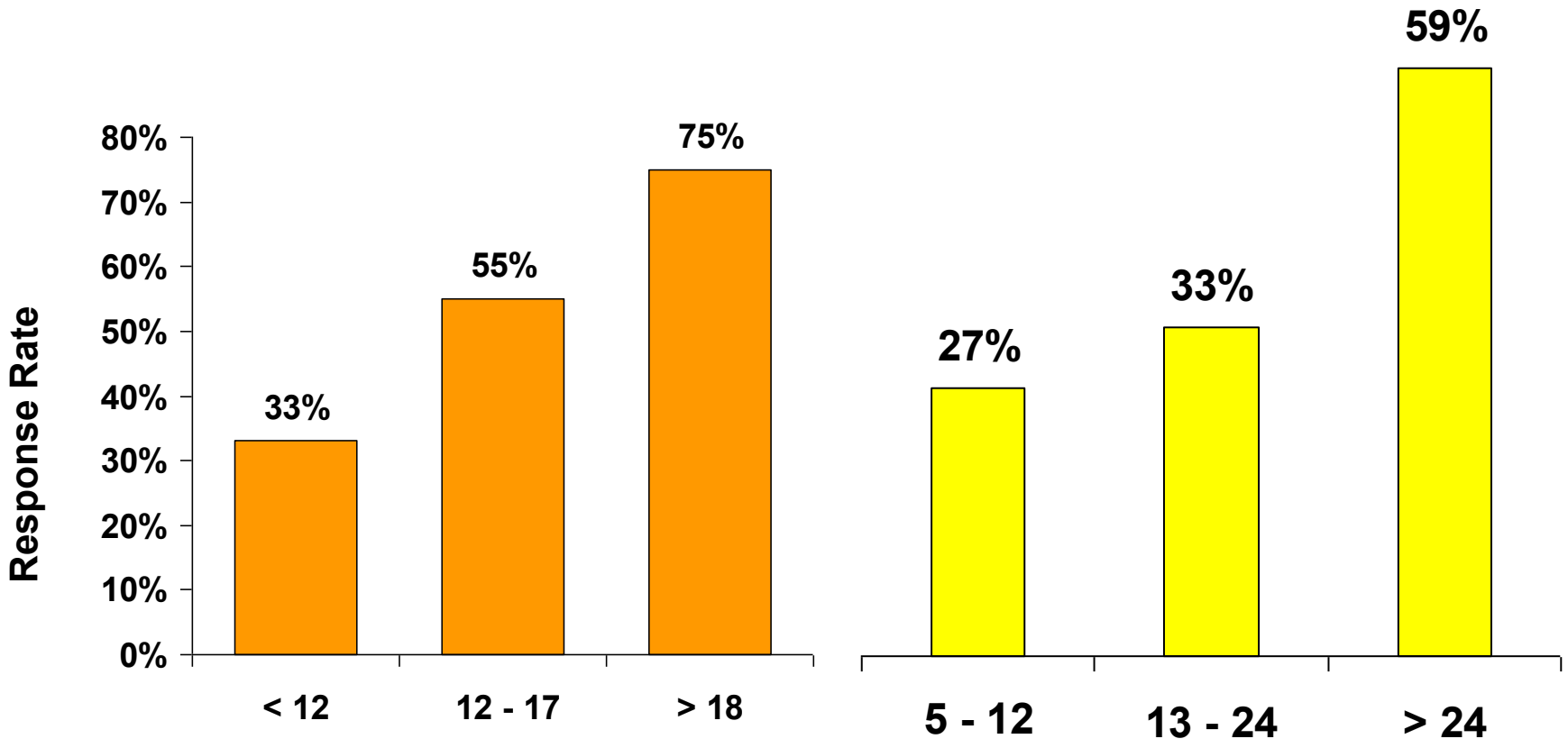
Recurrent Ovarian Cancer



Effect of Platinum-Free Interval on Platinum Rechallenge

Markman et al. *J Clin Oncol*. 2004;22:3120-3125.

Markman et al. *J Clin Oncol*. 1991;9:389-93.

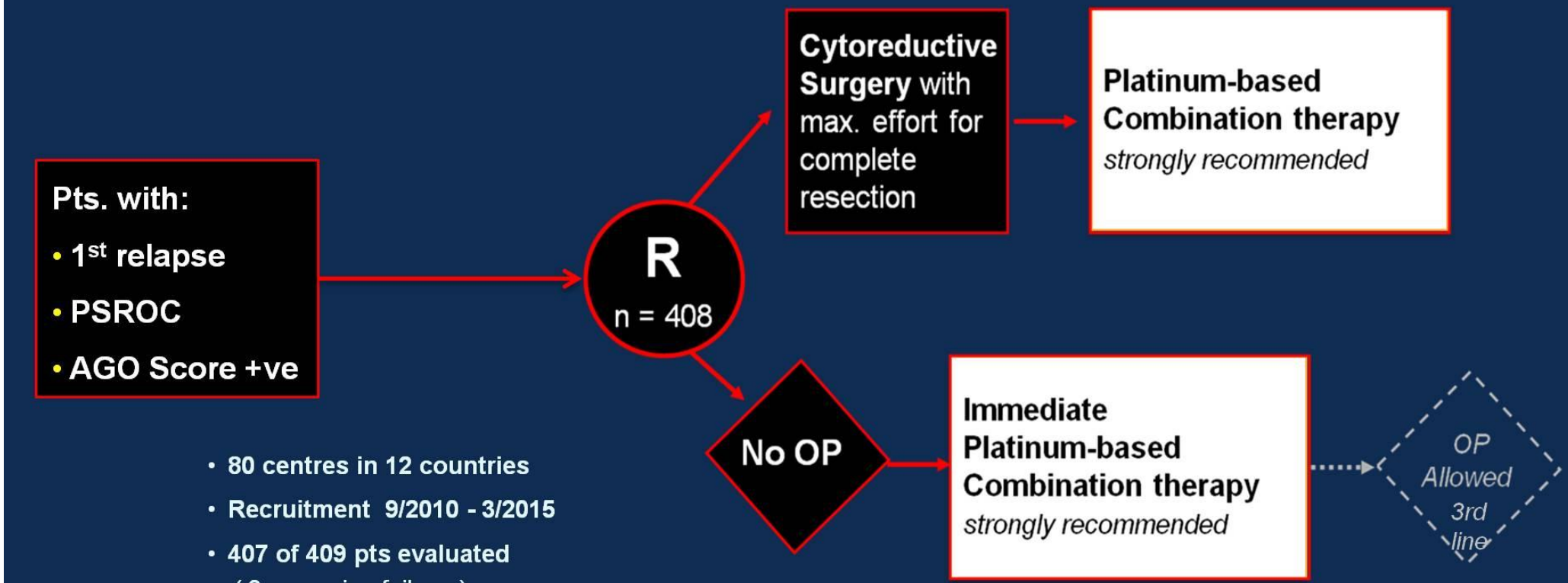
Recurrence After First-Line Chemotherapy

Platinum Refractory/Resistant	Platinum Sensitive
< 6 Mos	> 6 Mos
Non-Platinum Single Agent	Chemotherapy Doublet

Design: AGO DESKTOP III

(ENGOT-ov20; NCT01166737)

Sponsor: AGO
ENGOT Model A



- 80 centres in 12 countries
- Recruitment 9/2010 - 3/2015
- 407 of 409 pts evaluated
  (2 screening failures)

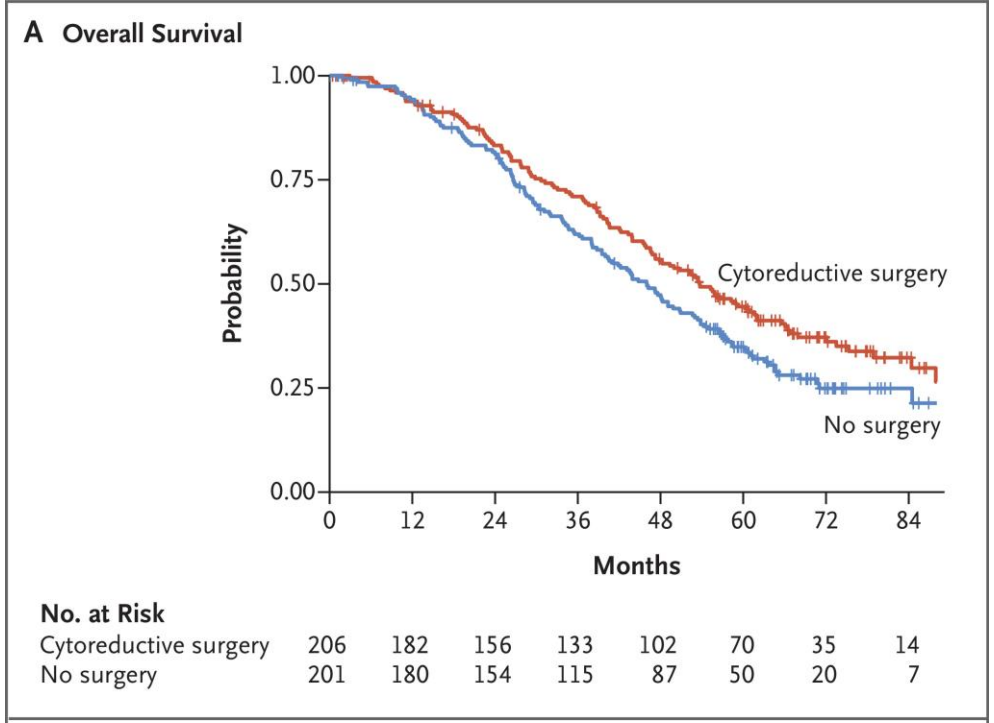
Presented by: Andreas du Bois
AGO & KEM
Essen, Germany

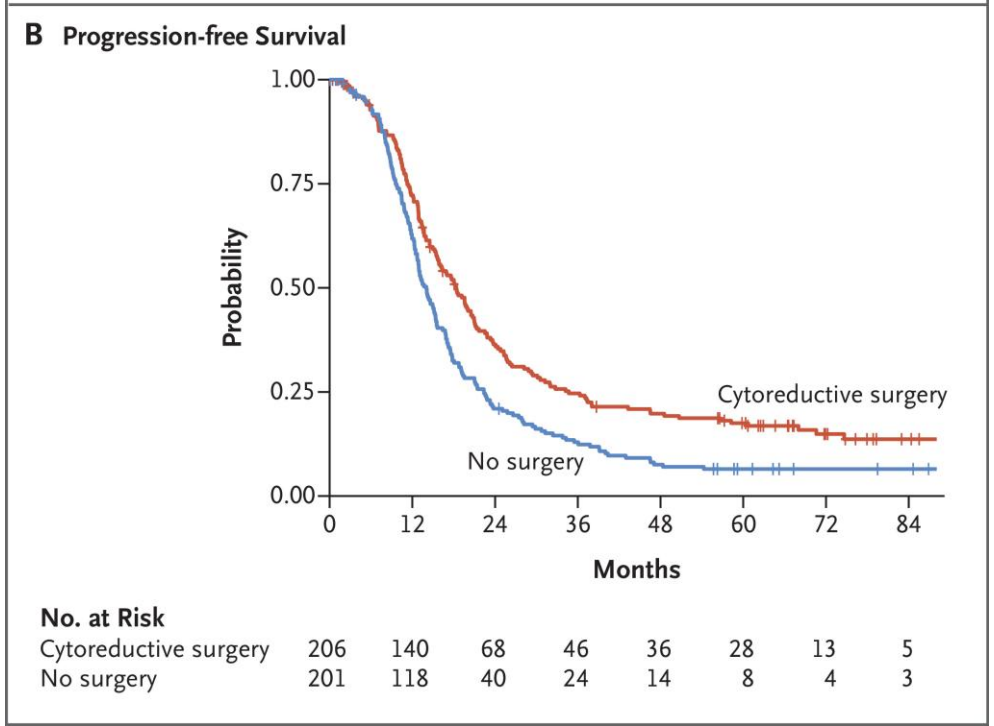
DESKTOP III

Final analysis **demonstrated PFS and OS improvements from having surgery**

Carefully selected cases.

- Median overall survival:
  - **53.7 months** (95% confidence interval [CI], 46.8 to 61.6) in the surgery group
  - **46.0 months** (95% CI, 39.5 to 52.6) in the no-surgery group (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.96)
  - P=0.02





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Recurrent Ovarian Cancer

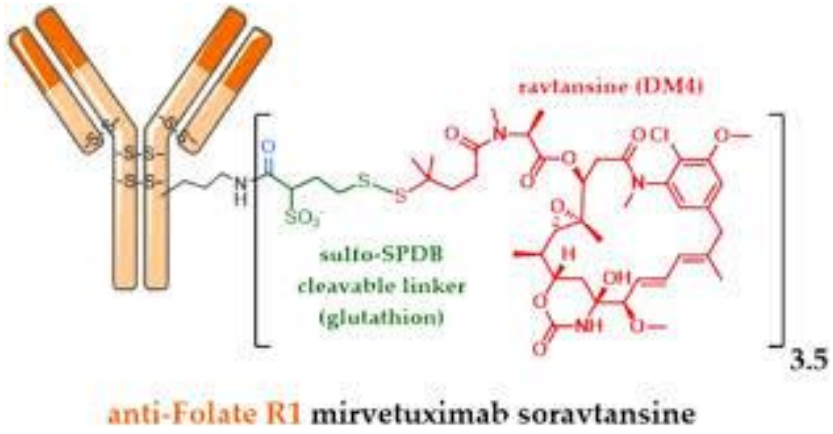
- **Platinum sensitive**:
  - Return to platinum
    - as single agent
    - as a doublet
      - Carboplatin-paclitaxel
      - Carboplatin-liposomal doxorubicin (better QoL)
      - Carboplatin-gemcitabine
        - Choice is made by considering residual toxicity (neuropathy), comorbidities, convenience (travel)
        - Choice may be influenced by future treatment options as well
      - (Maintenance PARP inhibitor (BRCA+))

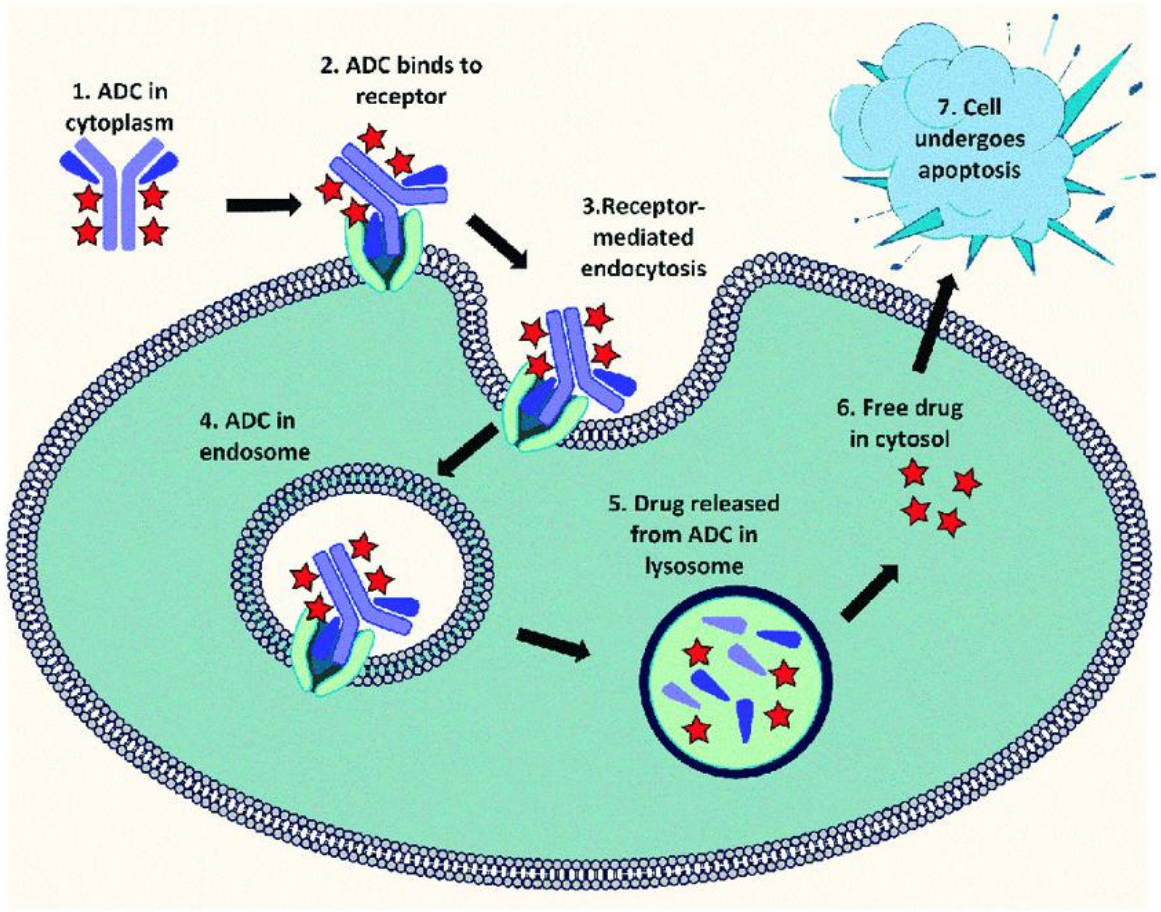
Recurrent Ovarian Cancer

- **Platinum resistant:**
  - New evidence-based therapies with **survival benefit:**
    - mirvetuximab soravtansine
    - Weekly paclitaxel with pembrolizumab
  - Consider sequential single agents (+/- bevacizumab)
    - Paclitaxel
    - Gemcitabine
    - Liposomal doxorubicin
    - Vinorelbine
    - Etoposide

Antibody Drug Conjugate for Ovarian Cancer

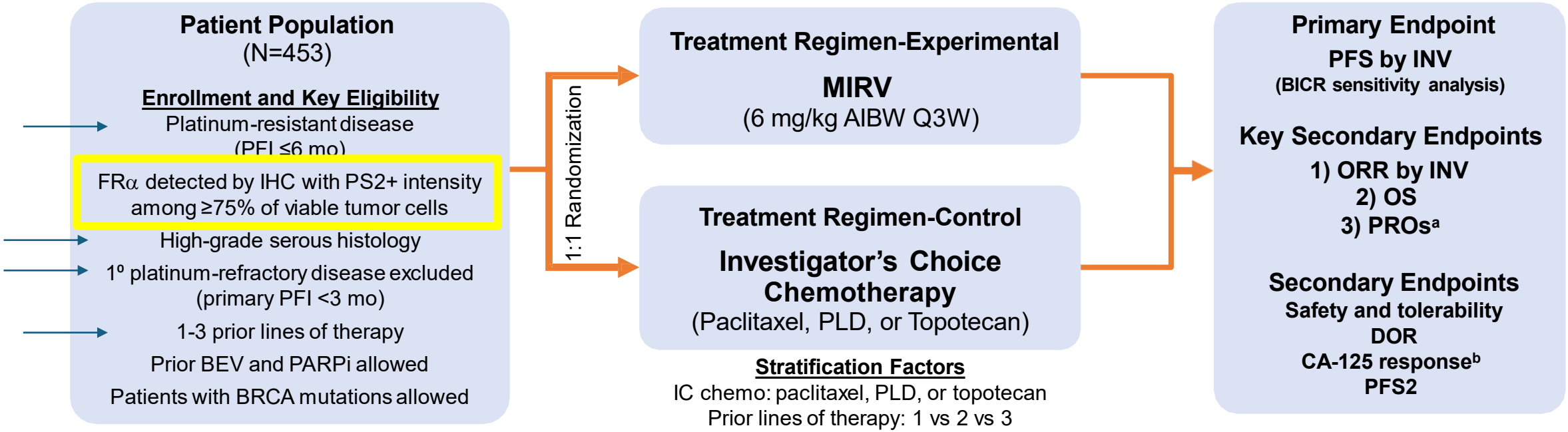
- **Mirvetuximab soravtansine**
  - Targets Folate Receptor
  - Cleavable linker
  - Maytansinoid (DM4) payload
  - Drug anti-body ratio (DAR) is 4.





MIRASOL trial and a New Standard of Care

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer



AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.

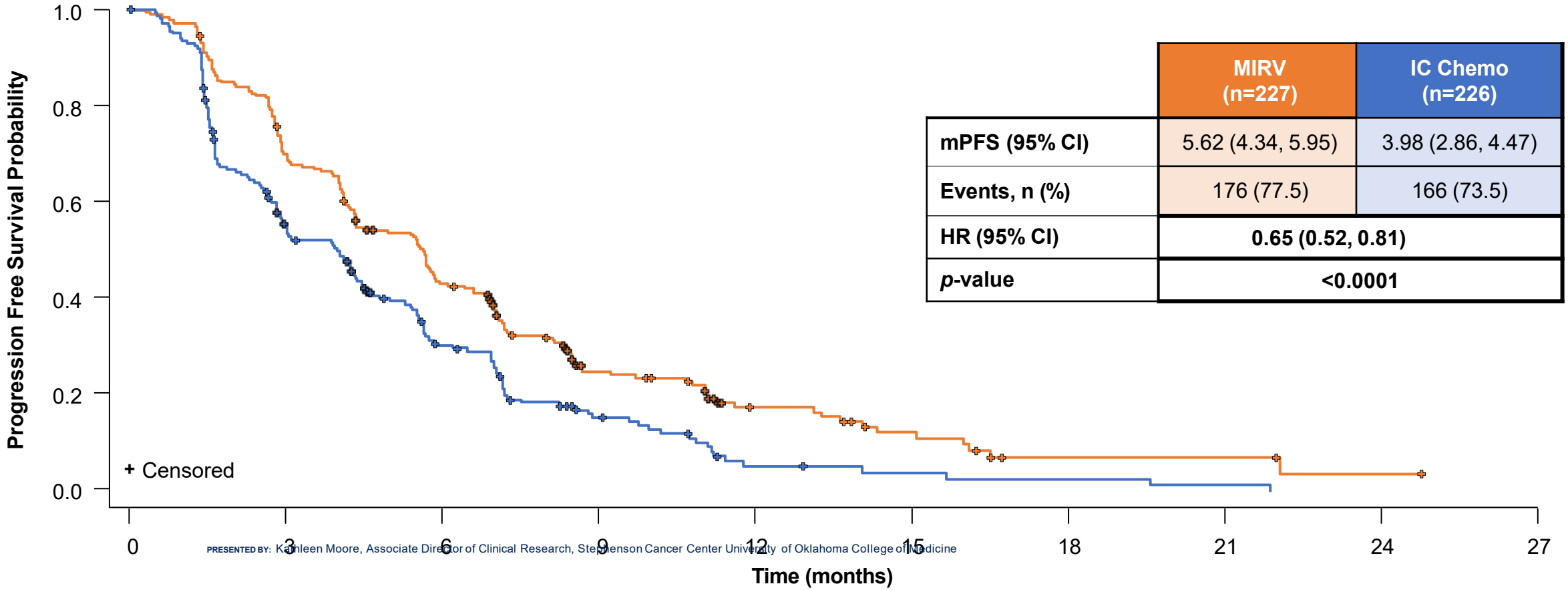
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.

[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
***p*-value**	**<0.0001**	

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

No. Participants at Risk

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

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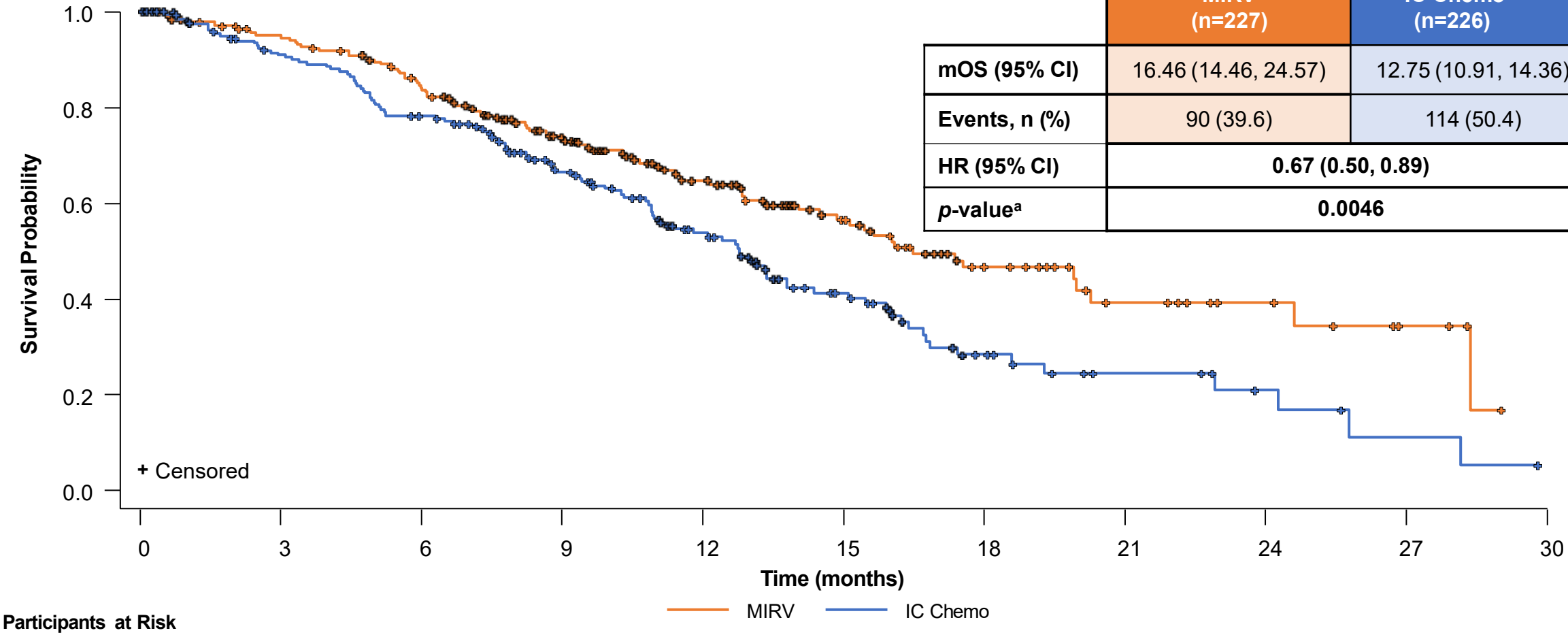
Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
***p*-value[a]**	**0.0046**	



No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

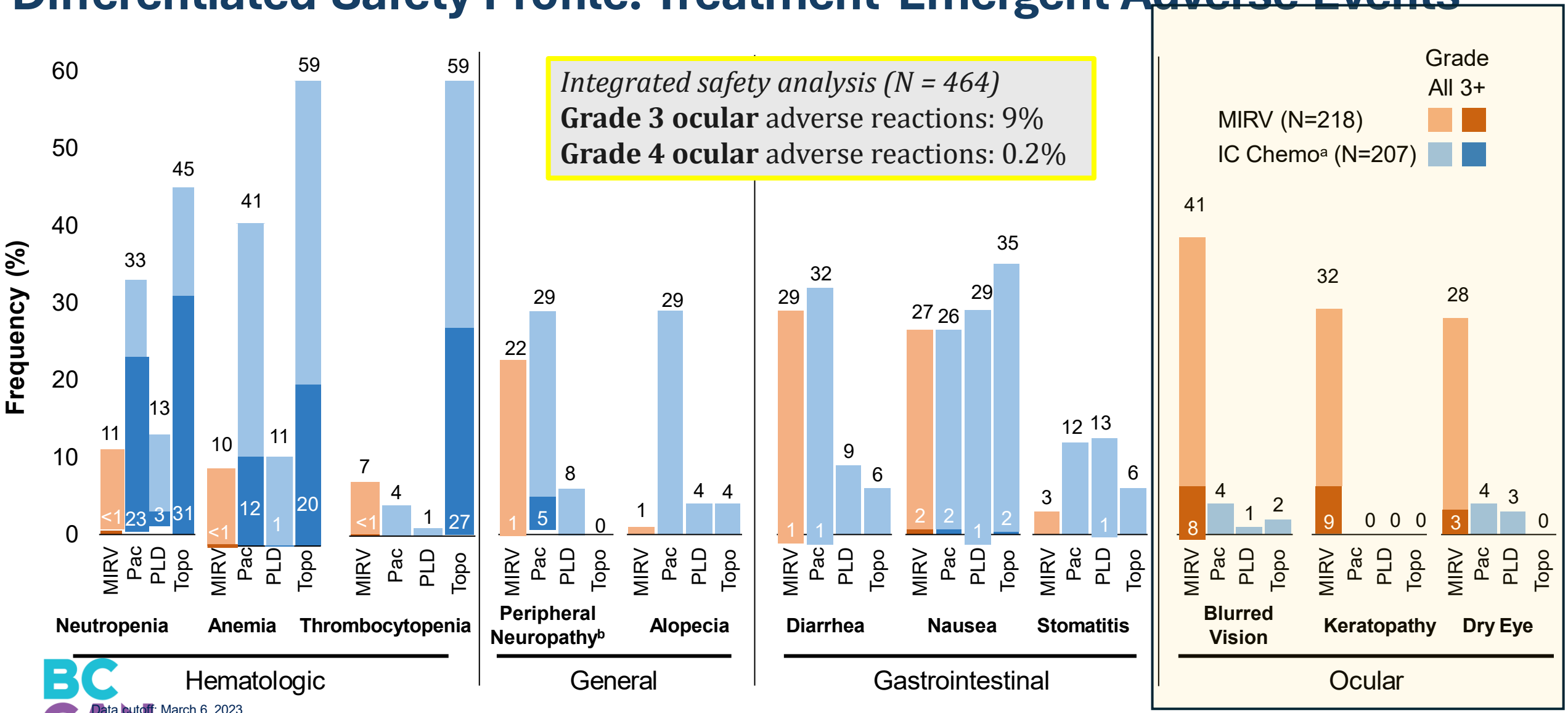
Data cutoff: March 6, 2023; median follow-up time: 13.11 months
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Mirvetuximab Soravtansine - Toxicity

- The drug payload is an **anti-microtubule agent**
  - Neurotoxicity
  - Myelosuppression
- **10% risk of pneumonitis**!
- **Eye toxicity**
  - DM4 payload had direct toxicity to the cornea!
    - Baseline eye exam
    - Preservative free eye drops 4X per day
    - No contacts
    - Dose modifications as needed

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

Mirvetuximab and Eye Toxicity

- Median time to onset of drug toxicity: **5 weeks**
- **No cases of corneal ulcers or perforation** have occurred with MIRV monotherapy to date
- MIRV-associated ocular AEs have been generally confined to the corneal epithelium
- 1% of study participants discontinued MIRV due to ocular side effects

Hendershot A, Slabaugh M, Riaz KM, Moore KN, O'Malley DM, Matulonis U, Konecny GE. Strategies for prevention and management of ocular events occurring with mirvetuximab soravtansine. Gynecol Oncol Rep. 2023 Feb 28;47:101155. doi: 10.1016/j.gore.2023.101155. PMID: 37102083; PMCID: PMC10123335.

Mirvetuximab Ocular Toxicity – RESOLVABLE

Of those with ocular events, **49% had complete resolution**, and 39% had partial resolution

Grade 4 ocular adverse reaction (1/464) resolved to grade 0 **within 15 days**

The lack of permanent sequelae is likely due to the corneal surface's **regenerative ability.**
Corneal epithelium typically **regenerates within 7 to 14 days** after an injury.

Hendershot A, Slabaugh M, Riaz KM, Moore KN, O'Malley DM, Matulonis U, Konecny GE. Strategies for prevention and management of ocular events occurring with mirvetuximab soravtansine. Gynecol Oncol Rep. 2023 Feb 28;47:101155. doi: 10.1016/j.gore.2023.101155. PMID: 37102083; PMCID: PMC10123335.

Maqsood S., Elsawah K., Dhillon N., Soliman S., Laginaf M., Lodhia V., et al. Management of persistent corneal epithelial defects with human amniotic membrane-derived dry matrix. Clin. Ophthalmol. 2021;15:2231–2238. doi: 10.2147/OPTH.S299141

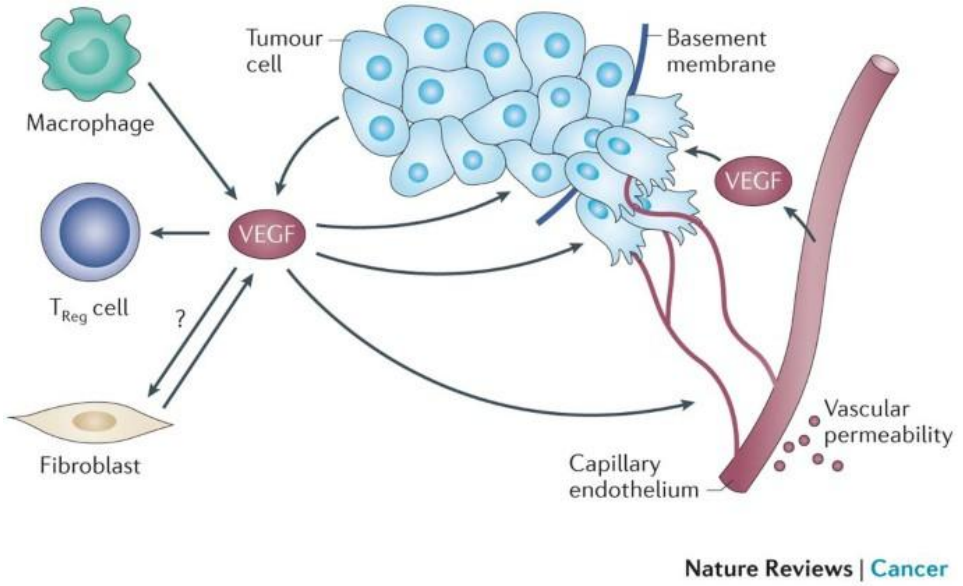
Role of Bevacizumab – Plt Resistant Disease

- Bevacizumab is an anti-body inhibitor of VEGF

- VEGF is commonly over expressed in the ascites of ovarian cancer patients
  - Involved in the mechanism of ascites formation and in angio-neogenesis for cancer

- Phase III trials have shown that Bevacizumab has activity in several treatment settings for ovarian cancer
  - First line therapy – improved PFS and OS in a subset
  - Second line, platinum sensitive – improved PFS
  - Platinum resistant – improved PFS and QoL

- **<u>In BC, funding is provided for those getting chemo for platinum-resistant recurrence</u>**
  - Bev improved Qol (and reduced the need for malignant fluid removal)
  - Bev prolonged PFS ~ 3 mo



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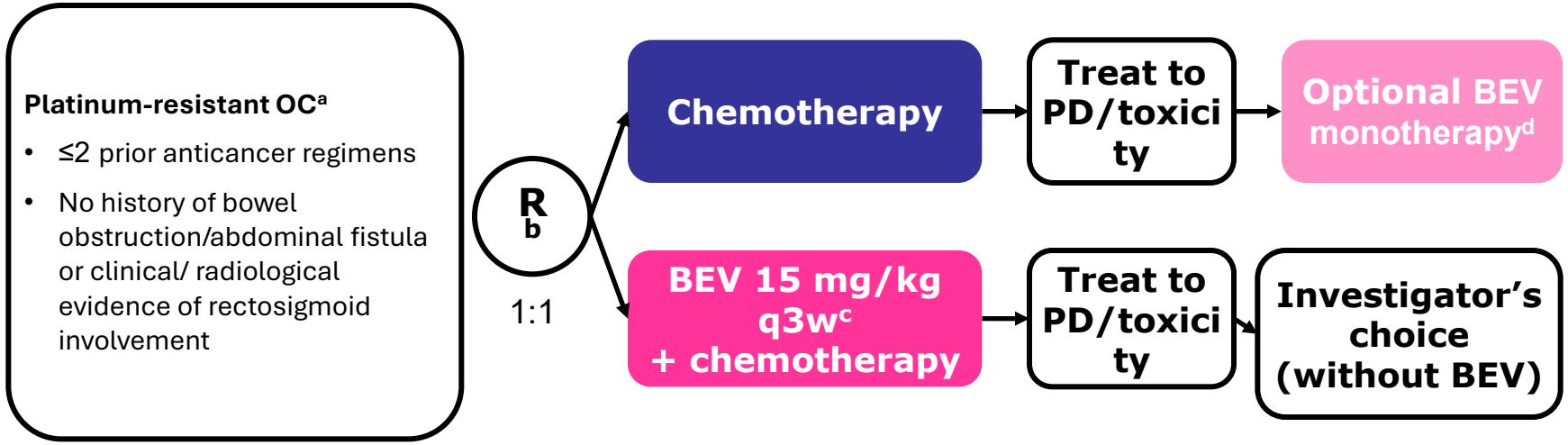
AURELIA trial design



Primary endpoint: PFS (RECIST v1.0)

Secondary endpoints:

- ORR
- OS (after OS events in 70%)
- Quality of life
- Safety and tolerability

Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

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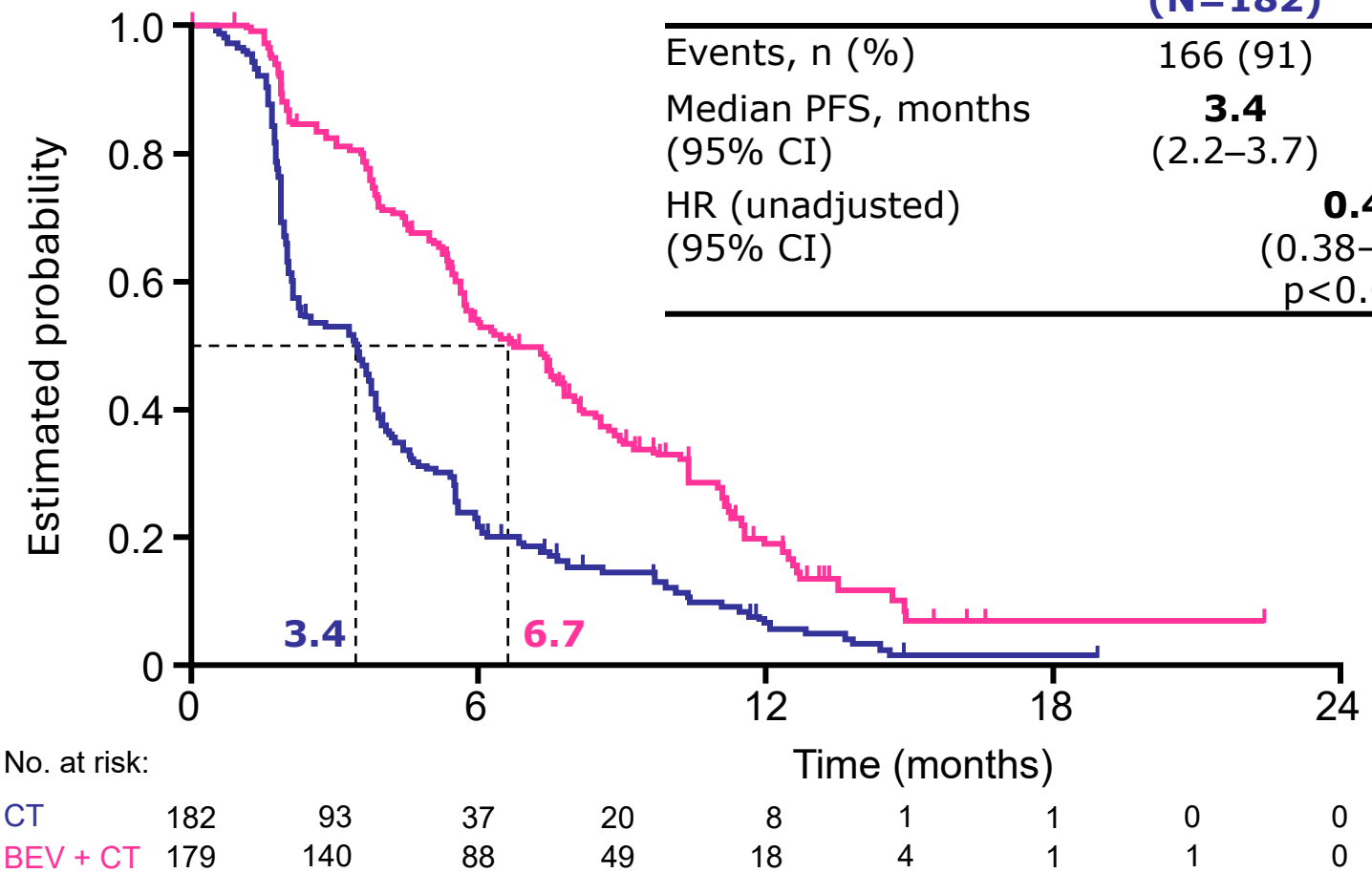
LBA presented by Witteveen at the ECCO 17 Meeting, Amsterdam, Netherlands, Sep 27 – Oct 1, 2013

Primary PFS analysis



	CT (N=182)	BEV + CT (N=179)
Events, n (%)	166 (91)	135 (75)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60) p<0.001[a]	

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LBA presented by Witteveen at the ECCO 17 Meeting, Amsterdam, Netherlands, Sep 27 – Oct 1, 2013

Immunotherapy in Platinum-Resistant OvCa

ENGOT-ov65/KEYNOTE-B96 Study Design (NCT05116189)

Key Eligibility Criteria

- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- 1 or 2 prior lines of therapy; at least 1 platinum-based chemotherapy
  - Prior anti-PD-1 or anti-PD-L1, PARPi and bevacizumab permitted
- Radiographic progression within 6 months after the last dose of platinum-based chemotherapy
- ECOG PS 0 or 1

Stratification Factors

- Planned bevacizumab use (yes vs no)
- Region (US vs EU vs ROW)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)[b]

R 1:1
N = 643

Pembrolizumab 400 mg (Q6W, 18 cycles) + Paclitaxel[a] 80 mg/m^2 Days 1, 8, 15 of each Q3W cycle *(± bevacizumab 10 mg/kg Q2W)*

Placebo (Q6W, 18 cycles) + Paclitaxel[a] 80 mg/m^2 Days 1, 8, 15 of each Q3W cycle *(± bevacizumab 10 mg/kg Q2W)*

Primary Endpoint: PFS per RECIST v1.1 by investigator

Key Secondary: OS

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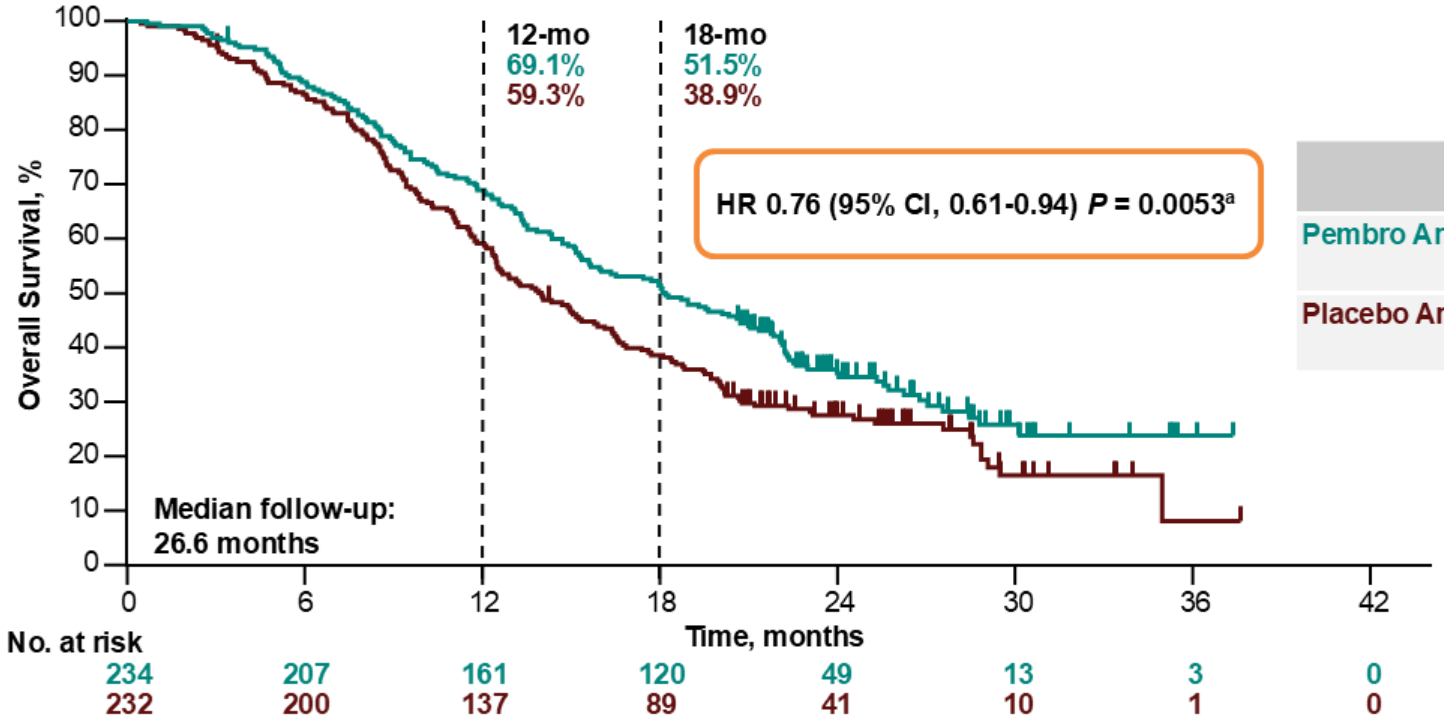
KNB96 OS analysis

N Colombo KNB96 FA ESGO 2026

Statistically Significant OS in CPS ≥1 Population at IA2



	Events	Median, mo (95% CI)
Pembro Arm	67.1%	18.2 (15.3-21.0)
Placebo Arm	75.4%	14.0 (12.5-16.1)

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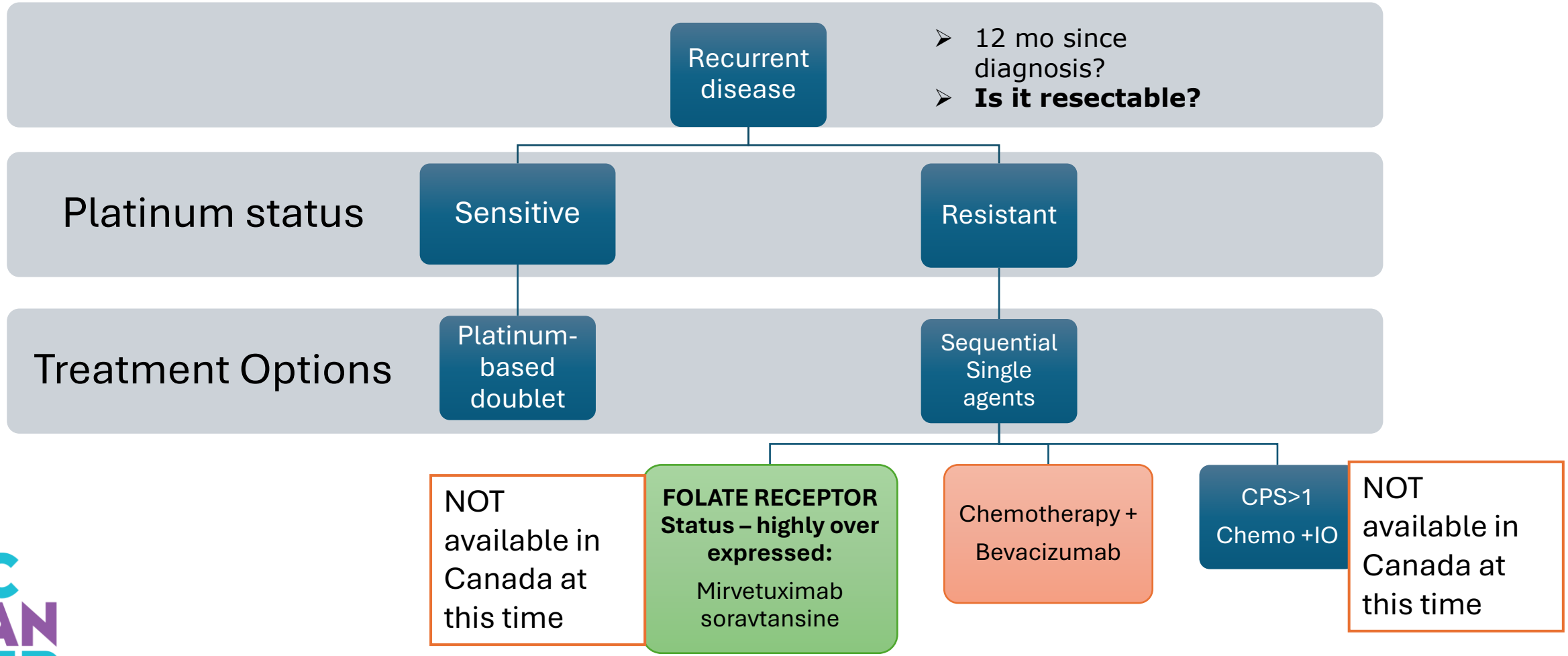
Recurrent Ovarian Cancer: Approach to Therapy



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Case 1. First-line Therapy and Neutropenia

- 65 yo female, stage IIIC HGSC ovary, receiving chemotherapy pre-operatively (had surgery after cycle 3)
- PHM: HTN, overweight, hypercholesterolemia
- Molecular: BRCA wt, HRD not done

- Current status: pre-cycle 5 evaluation**, treatment booked in 2 days**
  - Mild nausea, but managed
  - Fatigue, especially first 11 days, but now better (seems worse with each cycle)
  - Grade 1 neuropathy, some numbness in fingers and toes, no pain
  - Labs this AM:
    - Hgb 109
    - Plts 138
    - WBC: 2.7
      - **Neutrophils 0.9**

Case 1. First-line therapy and Neutropenia

- **What to do about low neutrophils**?
- 1) check again on the day of treatment, if recovered to >/= 1.0 treat with no dose modification
- 2) check again on the day of treatment, if recovered to >/= 1.0 treat with a dose reduction
- 3) delay 1 week, check CBC and treat if recovered to >/= 1.0 treat with no dose modification, but increase treatment interval (from 3 to 4 weeks)
- 4) 2 or 3

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Case 1. First-line therapy and Neutropenia

- Message is:
  - You have to do something to either change the dose or the frequency of therapy
  - Without modification
    - Risk of prolonged neutropenia – increases risk of febrile neutropenia
    - Will almost certainly be neutropenia at the next cycle

Case 1. First-line therapy and Neutropenia

DOSE MODIFICATIONS:

1. **Hematology:**

a) on treatment day:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 100	Proceed with same dose unless nadir labs completed. If nadir labs completed, treat according to nadir values.
Less than 1.0*	or	Less than 100	Delay until recovery. If using 21-day interval, switch to 28-day interval. If 2nd delay, use filgrastim (G-CSF) or dose reduction.

* If ANC greater than 0.8 and monocytes greater than or equal to 20%, neutrophil count recovery is likely imminent. Continuation without delay may occur at physician's discretion.

Case 2. First-line therapy and neuropathy

- 65 yo female, stage IIIC HGSC ovary, receiving chemotherapy pre-operatively
- PHM: HTN, overweight, hypercholesterolemia, DM2
- Molecular: BRCA wt, HRD not done

- Current status: pre-cycle 3 evaluation, treatment booked in 2 days
  - Mild nausea, but managed
  - Fatigue, especially first 11 days, but now better (seems worse with each cycle)
  - Grade 2 neuropathy, affecting fingers and toes, with mild burning and numbness

Case 2. First-line therapy and neuropathy

- What do you want to do:

1) No change, carry on with same dose
2) Dose reduce the carboplatin from AUC 5 to AUC 4
3) Dose reduce the paclitaxel from 175 mg/m2 to 135 mg/m2
4) Delay treatment one week

PERIPHERAL NEUROPATHY GRADING SCALE(S)

Adapted NCI CTCAE (Version 4.03)

NORMAL	GRADE 1 (Mild)	GRADE 2 (Moderate)	GRADE 3 (Severe)	GRADE 4 (Life - threatening)
Motor Grade				
Normal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental activities of daily living (IADLs) (e.g. preparing meals, shopping, managing money)	Severe symptoms; limiting self-care ADLs (e.g. bathing, dressing, feeding self, using the toilet, taking medications) ; assistive device indicated	Life – threatening, consequences; urgent intervention indicated
Sensory Grade				
Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting IADLs (e.g. preparing meals, shopping, managing money)	Severe symptoms; limiting self-care ADLs (e.g. bathing, dressing, feeding self, using the toilet, taking medications)	Life – threatening, consequences; urgent intervention indicated
PAIN GRADING SCALE				
No pain	Mild pain	Moderate pain; limiting (IADLs) (e.g. preparing meals, shopping, managing money)	Severe pain, limiting self-care, ADLs -(e.g. bathing, dressing, feeding self, using the toilet, taking medications)	—

Case 2. First-line therapy and neuropathy

- Both carboplatin and paclitaxel can cause neuropathy, but **paclitaxel is more neurotoxic**
- Neuropathy risk is related to underlying predisposing factors (DM2) and to **total drug exposure**
- As starting cycle 3 (e.g. still have 4 cycles to go!) would suggest a dose reduction now to prevent significant worsening
- Delay without dose modification will not help overall

Case 3. Maintenance Parp Inhibitor

- 65 yo female, stage IIIC HGSC ovary, completed 6 cycle of chemotherapy and had delayed surgery
- PHM: HTN, overweight (pt weight is 82 kg), hypercholesterolemia, DM2
- Molecular: BRCA wt, HRD not done

- Returns 6 weeks post last chemotherapy to start niraparib
- Feels tired, neuropathy persisting, CBC shows hgb – 110, plts 160, neutrophils 1.8

Case 3. Maintenance Parp Inhibitor

- Do you:

1. Start niraparib 300 mg PO OD
2. Start niraparib 200 mg PO OD
3. Delay start, ask to return in 1 month

Case 3. Maintenance Parp Inhibitor

- Patient returns in 1 month. Feeling better, labs are fine, Baseline BP is 144/86.
- Niraparib 300 mg PO OD is started
- Labs ordered weekly
- Pt monitoring BP at home

- On week 2 of therapy the patient calls the nurse line:
  - Nausea daily, fatigue, headaches and BP now persistently 160/90 or even higher.

Case 3. Maintenance Parp Inhibitor

- What do to now?

- 1) given anti-emetics, increase BP meds, carry on with same dose, reassess in 4 week
- 2) stop therapy, reassess in 1-2 weeks, restart at same dose if improved
- 3) stop therapy, reassess in 1-2 weeks and start with a dose reduction
- 4) stop therapy all together

Summary

- The treatment of ovarian cancer is changing rapidly
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- Most patients have advanced disease, and cure is seldom achieved (which means that treatment is for disease control and optimization of longevity and QoL)
- Surgery timing can be up front or delayed, and can be used for highly selected cases with disease recurrence
- Several chemotherapy options at diagnosis, followed by maintenance therapy
  - PARP inhibitor or bevacizumab
- **Platinum Sensitive disease**
  - Use platinum until no longer tolerated or responsive
- **Platinum resistant disease**
  - Poor prognosis
  - No SOC for Folate receptor expressing cancers – Mirvetuximab.
  - use single agents +/- bevacizumab
  - Immunotherapy may be coming…