UPDATES IN OVARIAN CANCER

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- I have no other financial disclosures

Objectives

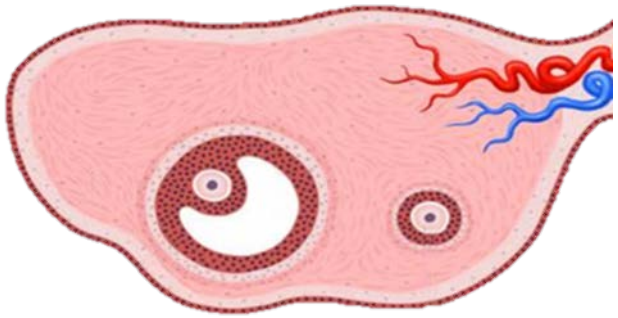
- Describe the treatments available for ovarian cancer and discuss how care can be personalized for patients
- Define new approved therapeutic approaches for the treatment of ovarian cancer patients
- Review histology specific indications for ovarian cancer therapies

Review & Update

2020
21,750 new cases of ovarian cancer
13,940 deaths due to ovarian cancer

• Epithelial ovarian cancer
  • Fallopian tube carcinoma
  • Primary peritoneal carcinoma
	95%

• Germ cell cancers of the ovary	3%
• Sex cord/stromal cancers of the ovary	1-3%

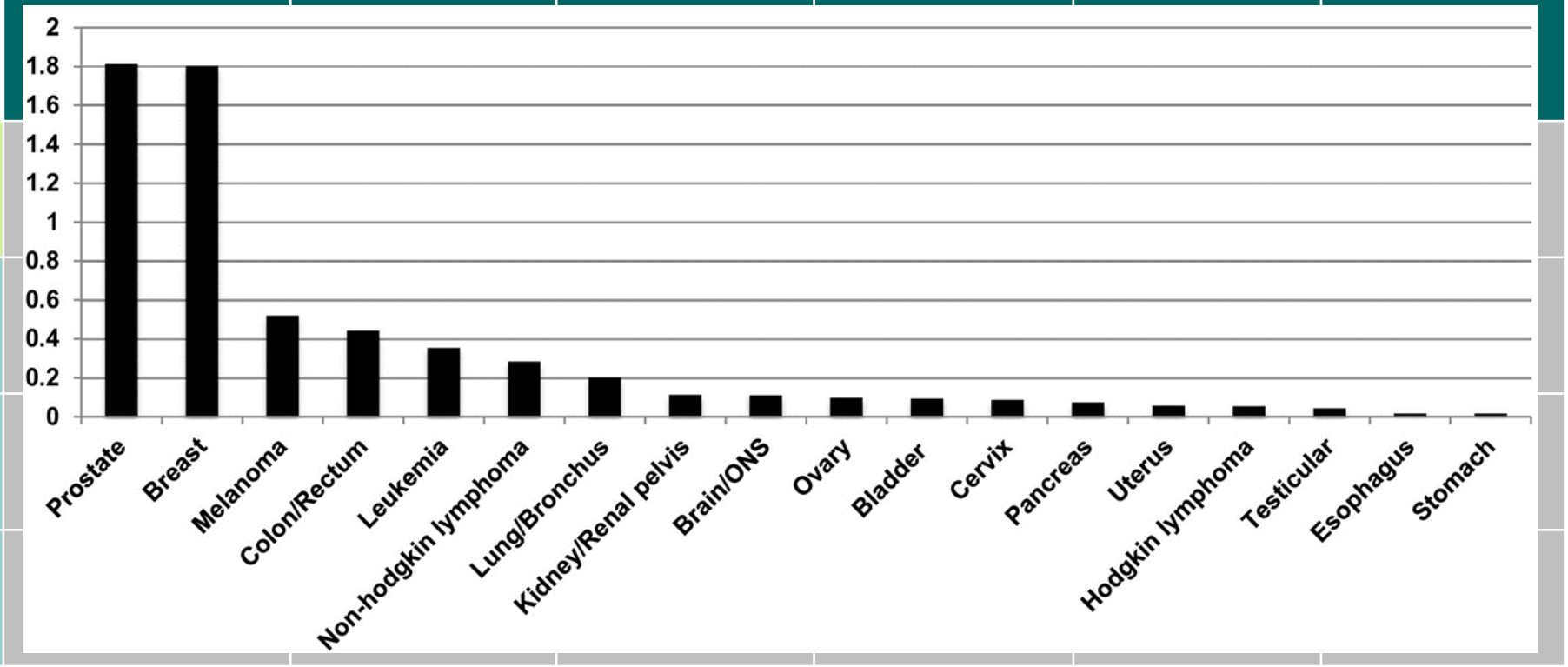


Cell Types within Ovary

Fallopian tube Endosalpingiosis	▶	Epithelial ovarian cancer
Germ cells (oocytes)	▶	Germ cell cancers
Sex hormone producing and stromal cells	▶	Sex cord stromal cancers

Ovarian Cancer Patterns of Care

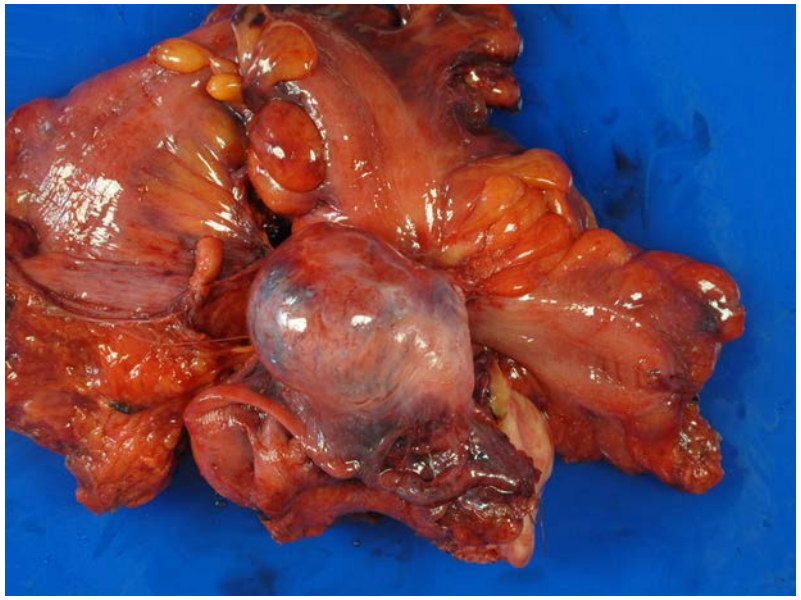
	Incidence/100,000	Age-Adjusted Cancer Death Rate
OVARY		
Breast		
Colorectal*		
Prostate		



Goff BA. *Gynecol Oncol* 2015.
Spencer RJ et al. *Gynecol Oncol* 2019.

Treatment

- **Surgery**
  - Diagnosis
  - Staging
  - Cytoreduction



- **Chemotherapy**
  - Recommended for nearly all patients

- Referral to a **gynecologic oncologist** has been associated with:
  - Increased surgical management
  - Improved survival

Mercado C et al. Gynecol Oncol 2010.
Chan JK et al. Obstet Gynecol 2003.

Surgical Staging

Staging of disease via surgery especially important

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

- 31% upstaged
- 77% actually were Stage III
- A more recent review showed 13% of "early" stage patients had positive lymph nodes

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

Postoperative Chemotherapy

Cycles of Chemo by Stage

	Platinum & Paclitaxel
Stages IA and IB *(grades 1 and 2 **only**)*	No further treatment
Stages IA & IB *(grade 3)*, and IC–II disease	3–6 cycles
Stages III–IV disease	6–8 cycles

Early Stage (Stage I-II)

A subset of women with early stage disease benefit from additional adjuvant treatment:

- **High-grade/serous tumors**
  - 6 cycles of adjuvant chemo associated with progression-free survival benefit
- **Clear cell histology**
- **Stage IC or greater disease**

Chan JK et al. Gynecol Oncol 2010.

Advanced Stage Disease

- Regimen should include a taxane and platinum
  - Carboplatin = cisplatin, but less toxicity
  - Docetaxel alternative, if neuropathy or hypersensitivity
- Response rate **70-80%**
- Encourage clinical trial participation

Modifications

Intraperitoneal chemotherapy

Dose-dense paclitaxel

Weekly carbo & taxol

Maintenance

Treatment Options

NCCN

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 Day 1
- 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[e] (ICON-7)
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 5–6 IV, and bevacizumab 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 bevacizumab[e] (GOG-218)
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 6 IV Day 1. Repeat every 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 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]

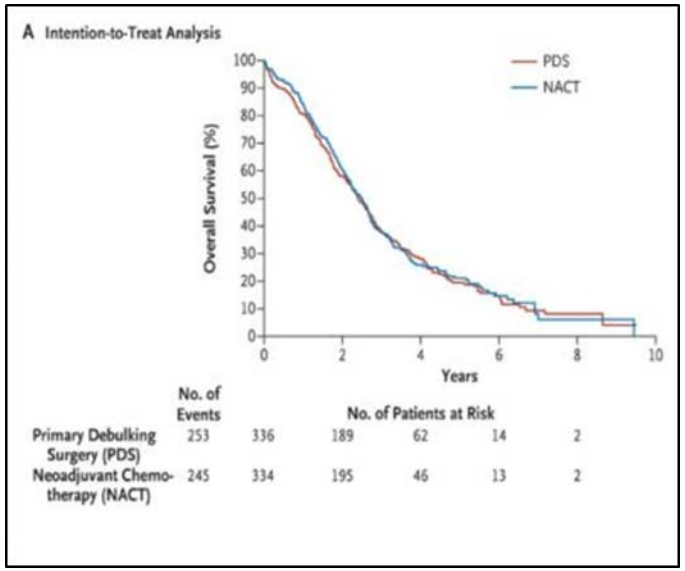
Paclitaxel weekly/carboplatin weekly
- Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)

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

Neoadjuvant Chemotherapy

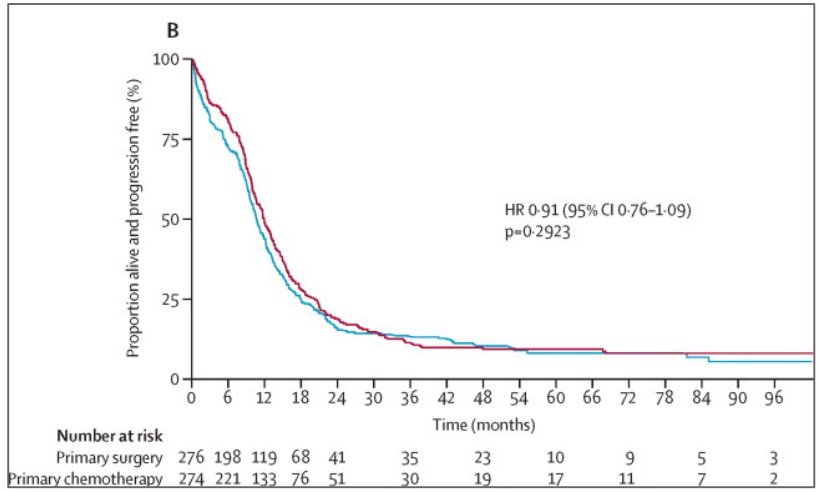
EORTC

- Neoadjuvant chemo followed by interval debulking surgery versus primary debulking & chemo
- Platinum-based chemotherapy
- Decreased surgical morbidity, increased rates of successful cytoreduction
- Similar PFS, OS



CHORUS

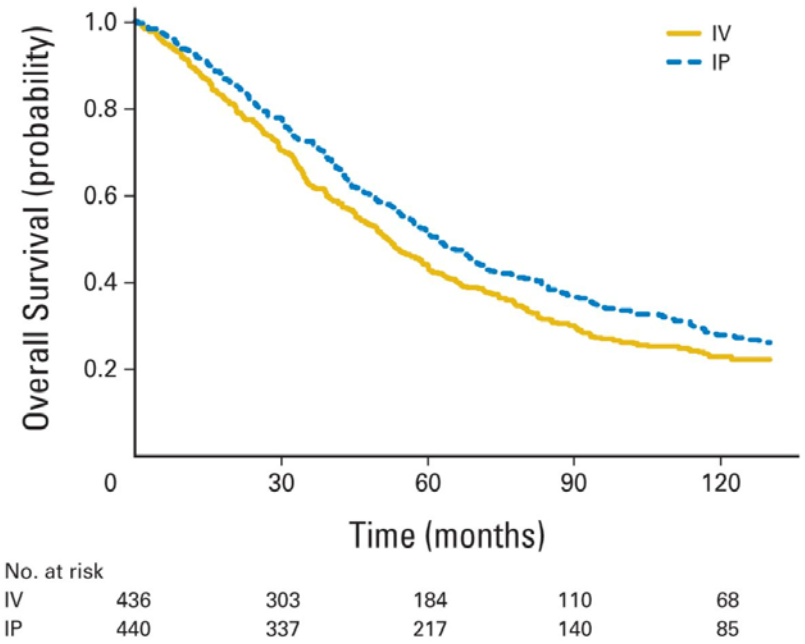
- Non-inferiority phase 3 trial
- Carbo/taxol either postoperatively or neoadjuvant (3:3)
- Decreased rates of surgical complication and postoperative deaths
- Similar PFS, OS



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

Intraperitoneal (IP) Chemotherapy

- Long-term survival analysis of GOG 114 and 172
- Among 876 patients, IP treatment associated with 17% ↓ risk of death
- Survival advantage evident in microscopic and gross residual disease



GOG 114

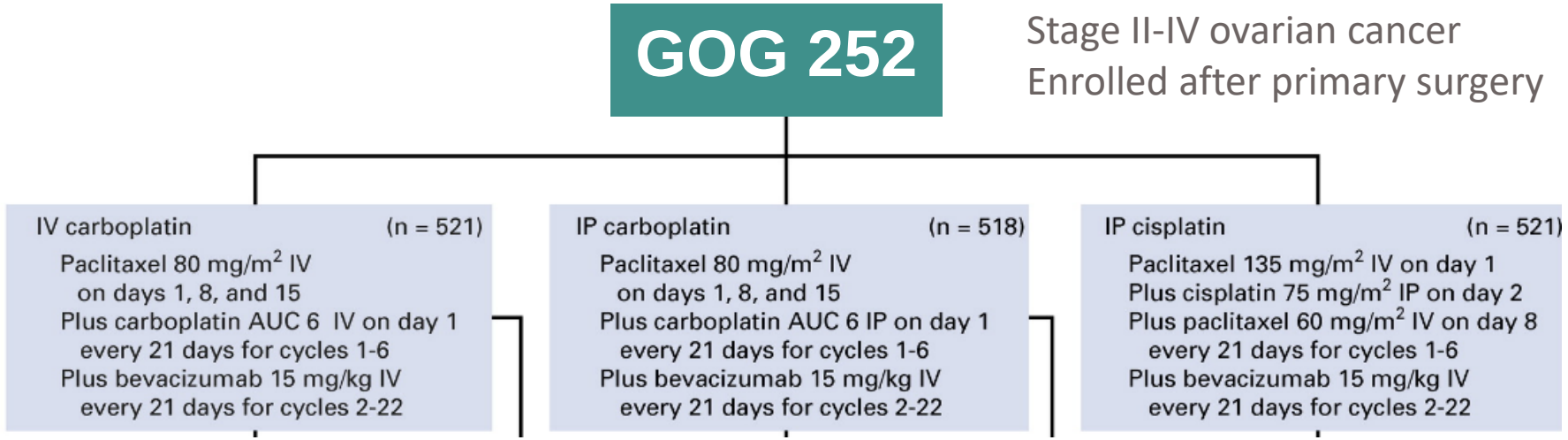
IV Cis / IV Taxol
vs.
IP Cis / IV Taxol / IV Carbo

GOG 172

IV Cis / IV Taxol
vs.
IP Cis / IV & **IP** Taxol

Tewari D et al. J Clin Oncol 2015.
Landrum L et al. Gynecol Oncol 2013.

Intraperitoneal (IP) Chemotherapy

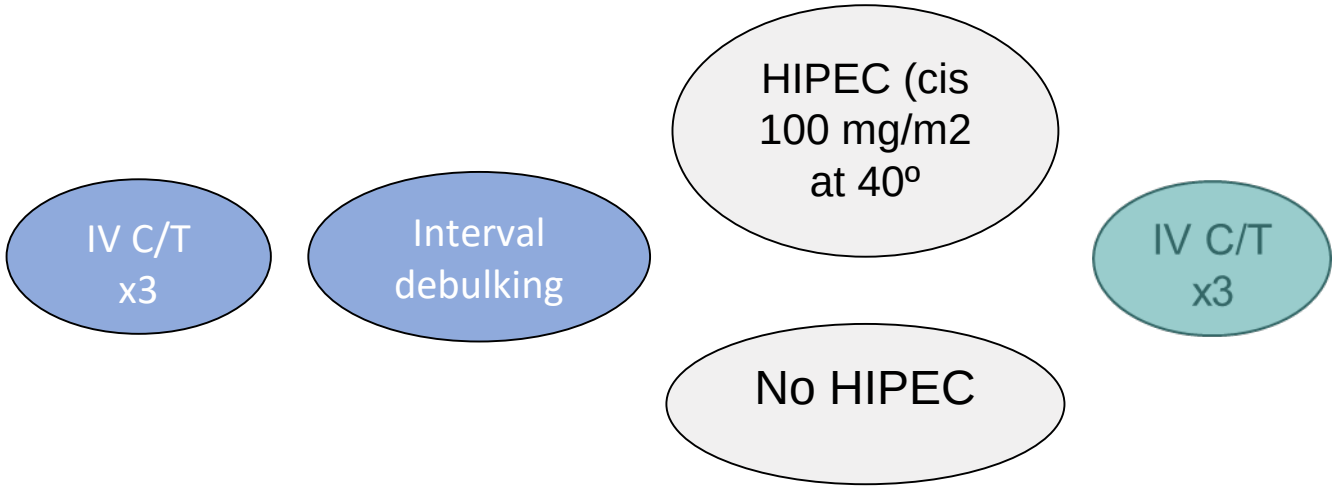


- Impact of bevacizumab
- Similar neurotoxicity scores for all arms
  - Worse FACT-TOI in IP cisplatin arm
- Similar PFS and OS
  - Median OS 75.5 mos (IV C), 78.9 (IP C), 72.9 (IP cis)

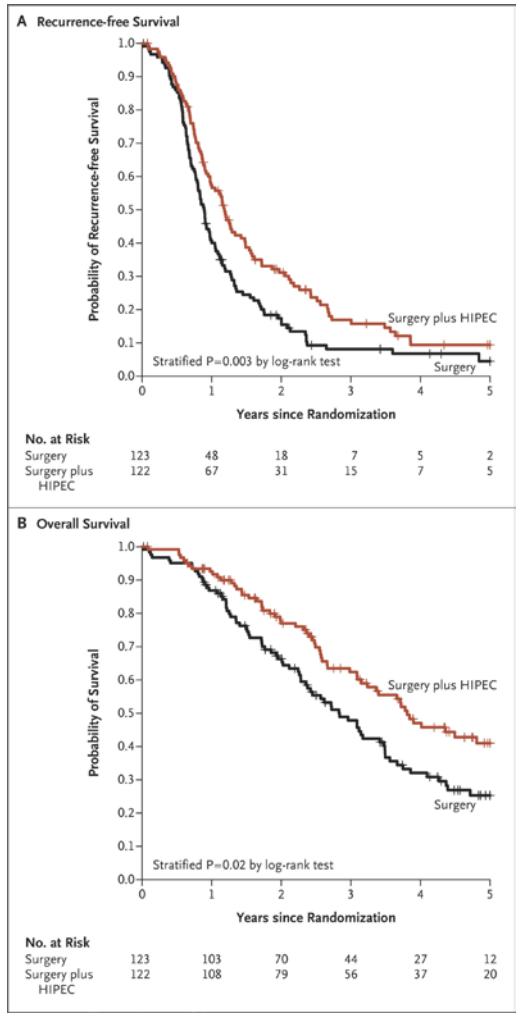
Walker JL et al. J Clin Oncol 2019.

Heated Intraperitoneal Chemotherapy (HIPEC)

- Randomized phase III trial



- No significant difference in adverse events
- Significant improvement in progression-free (14.2 vs 10.7 months) and overall survival 45.7 vs 33.9 months)
- ASCO 2020: randomized phase II trial of HIPEC after secondary cytoreductive surgery revealed no impact on survival



Van Driel WJ et al. N Engl J Med 2018
Zivanoic O et al. ASCO 2020

“Dose-Dense” Paclitaxel

JGOG 2016

- RCT: q3 wks carbo/Taxol vs carbo/weekly Taxol
- Improved 5-year OS (100.5 mos in weeklyT vs 62.6 mos on standard therapy)
- Controversy on generalizability of findings

GOG 262

- Bevacizumab optional, 84% providers/patients opted in
- No difference in PFS
- For cohort who did not receive bev (n=88), significant improvement in PFS (14.2 mos for weeklyT vs 10.2 mos, p=0.03)

ICON 8

- RCT: C/T q3w vs C/T q1w vs Cq3w/Tq1w
- Similar PFS in each arm
- Slight increase in heme toxicity in weekly arm

Katsumata N et al. Lancet 2009; Katsumata N et al. Lancet 2013
Chan JK et al. N Engl J Med 2016.; Clamp AR et al Lancet 2019.

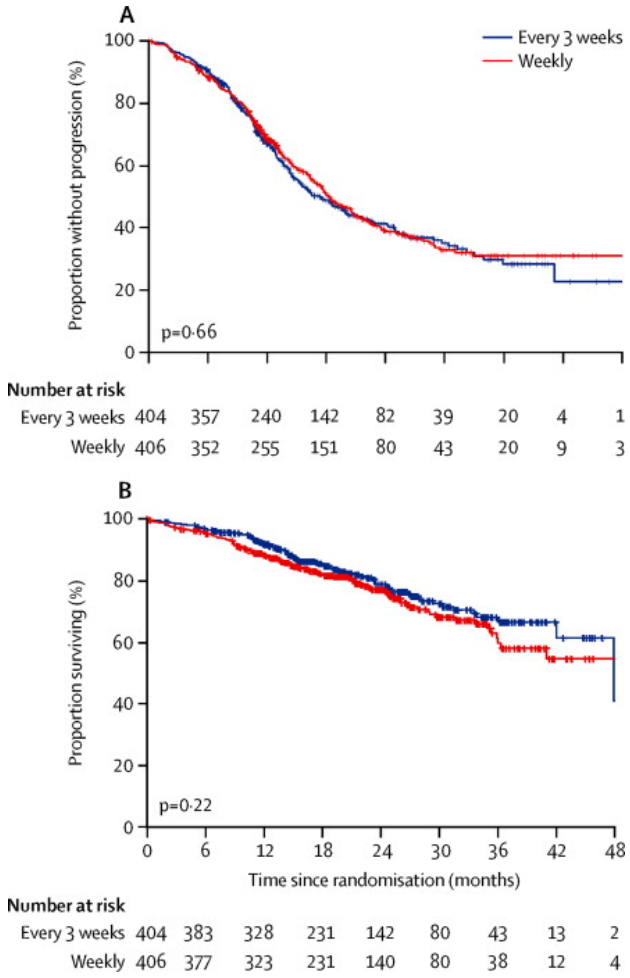
Tolerability of Chemotherapy

MITO-7

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

Eligibility: Stage IC-IV EOC
ECOG PS ≥ 2

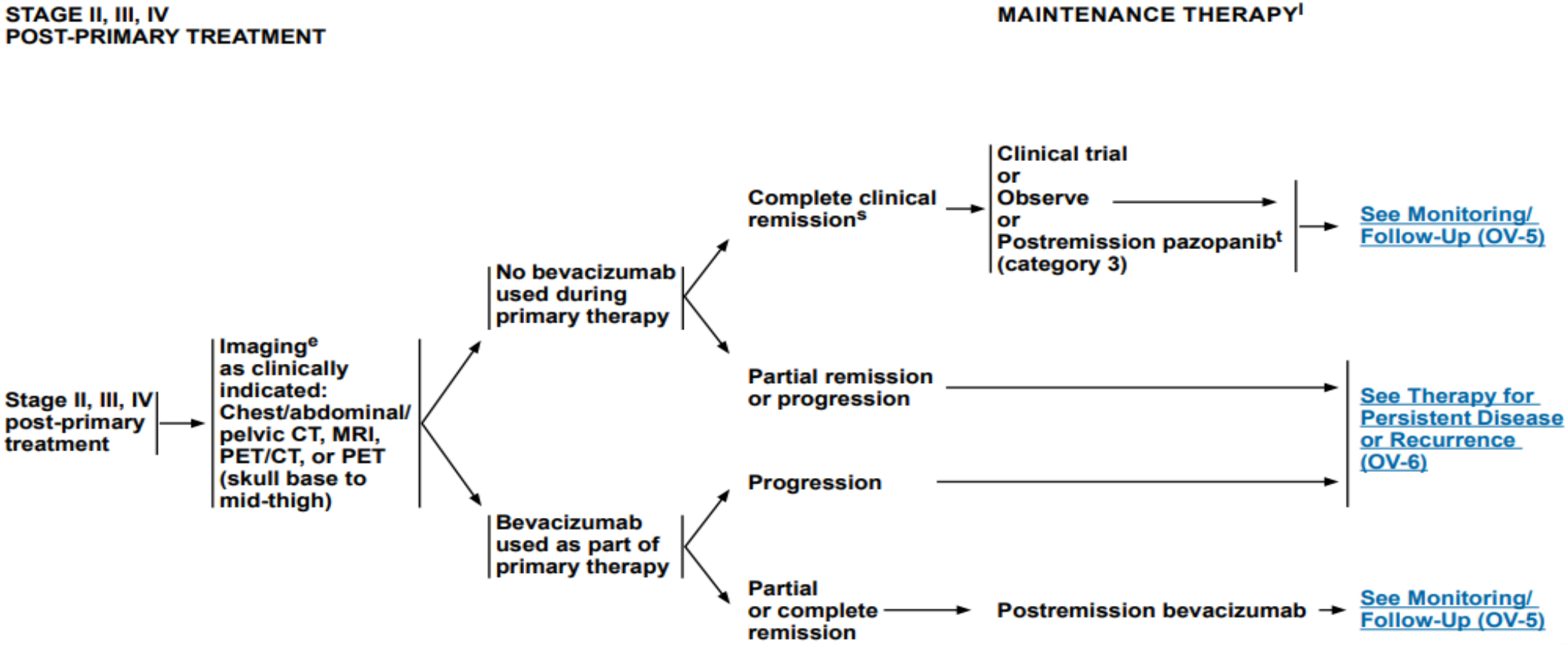
Outcomes: Similar PFS & OS in patients receiving weekly treatment



Pignata S et al. Lancet Oncol 2014.

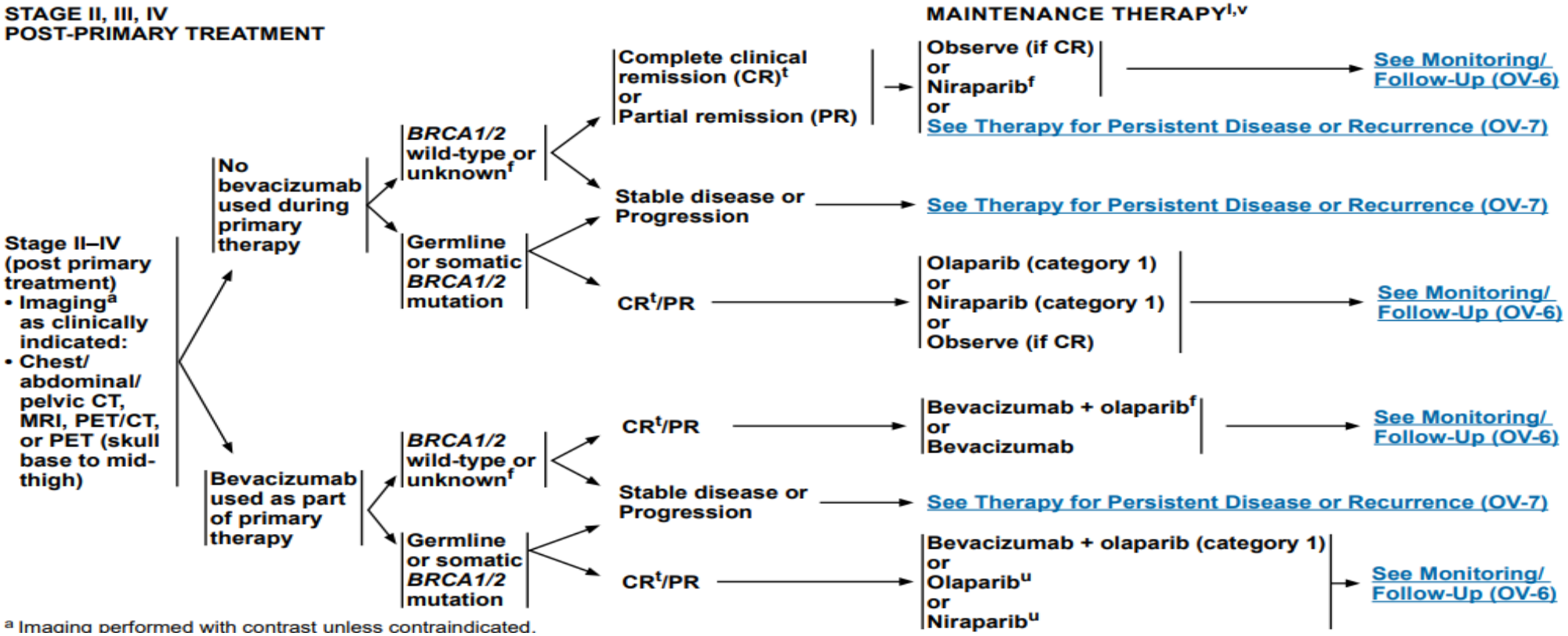
Maintenance Treatment

NCCN recommendations (2018)



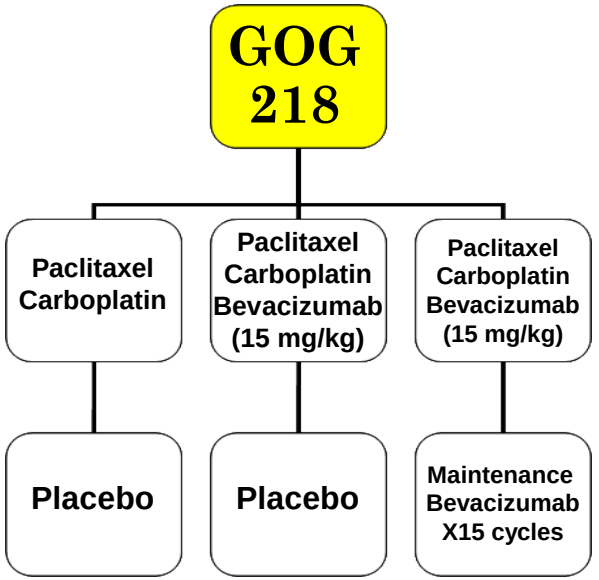
Maintenance Treatment

NCCN recommendations (2020)



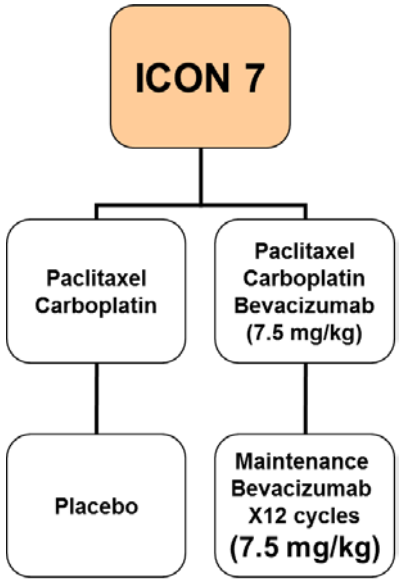
Maintenance Treatment

Role of Bevacizumab



Phase III RCT showed PFS of 6.2 months with C/T/B + B, no difference in OS

Burger RA et al. NEJM 2011.



European phase III RCT showing PFS of 1.7 months with C/T/B + B

Perren TJ et al. NEJM 2011.

June 13, 2018: FDA approved bevacizumab for treatment of Stage III-IV ovarian cancer in combination with carbo/taxol followed by maintenance bevacizumab

Candidates for Bevacizumab

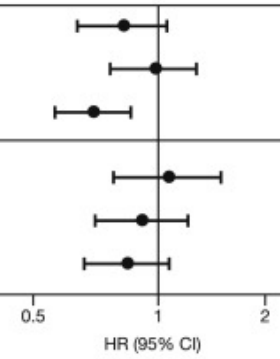
GOG 218

- PFS improvement, but no overall improvement in OS
- For stage IV patients, OS 42.8 mos (chemo/bev+bev) vs 32.6 mos (chemo alone) (HR 0.75, CI 0.59-0.95)

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)



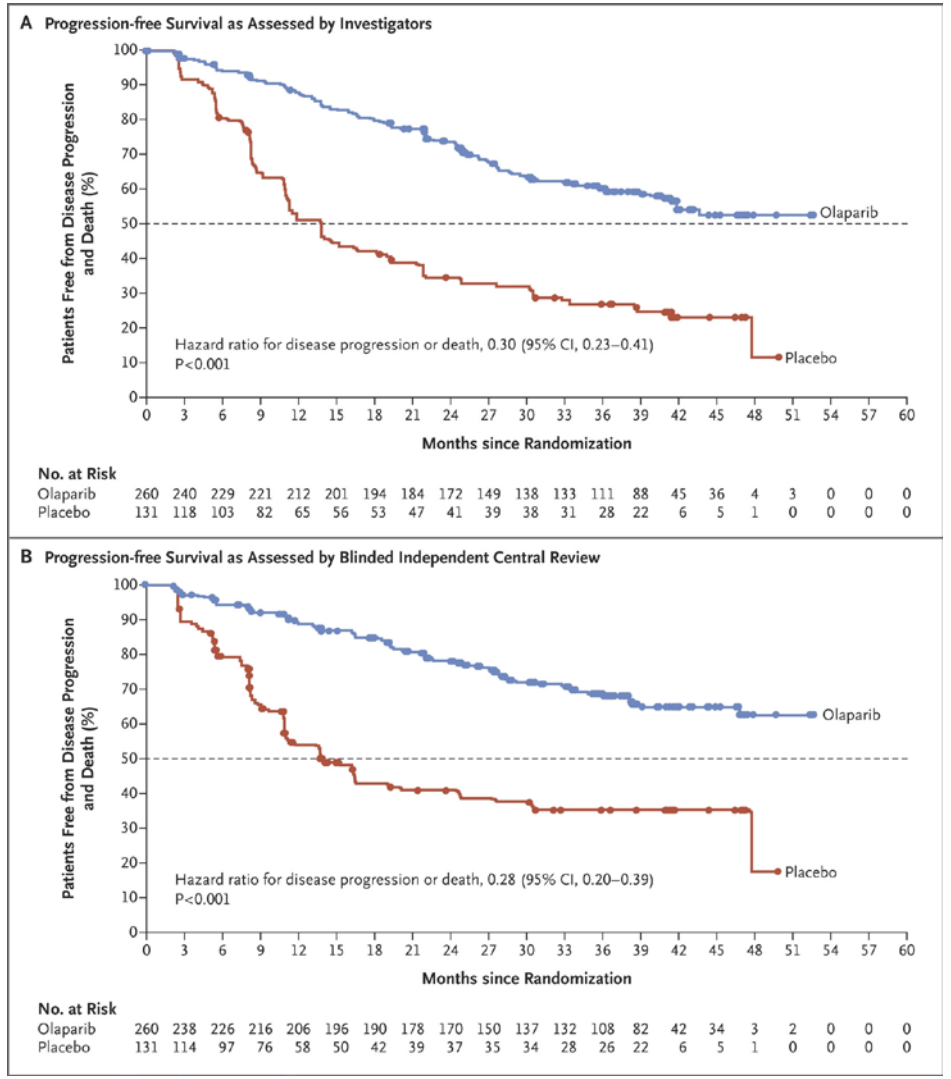
Tewari KS et al. J Clin Oncol 2019.
Gonzalez Martin A et al. Gynecol Oncol 2019.

Maintenance Treatment

PARP Inhibitors

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
- Median PFS 36 mos longer in olaparib group
- **70% risk in reduction of progression or death**
- 1% patients on olaparib developed AML



Moore K et al, N Engl J Med 2018

Maintenance Treatment

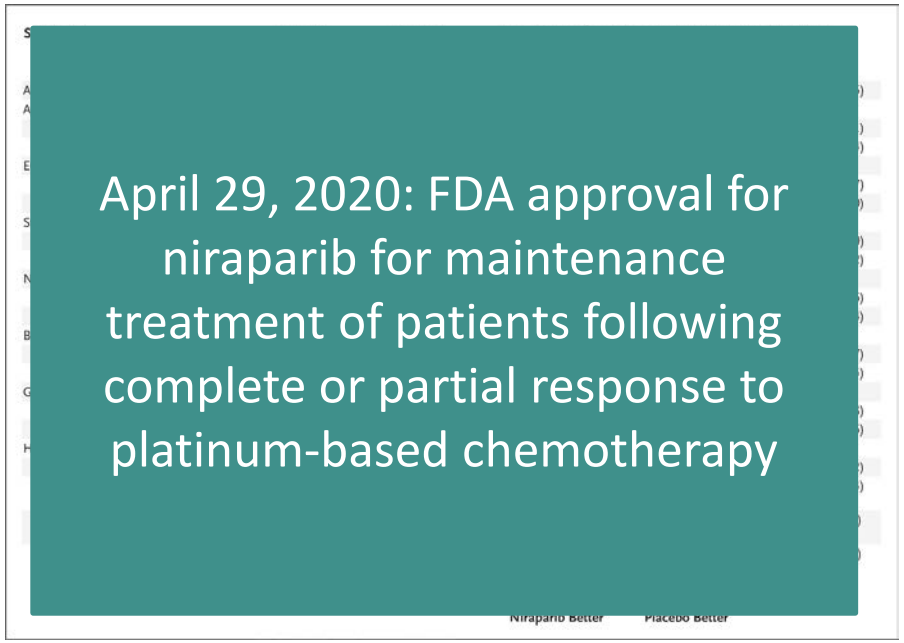
PARP Inhibitors

VELIA

- Randomized (1:1:1), placebo-controlled trial of chemo +- **veliparib** followed by placebo or veliparib maintenance
- Significant improvement in PFS seen in chemo/veliparib + veliparib cohort
- Bulk of benefit in patients with BRCA mutation (germline OR somatic) or tumors with homologous recombination deficiency (HRD)

PRIMA/ENGOT-OV26/GOG-3012

- Randomized (2:1), placebo-controlled trial of chemo +- **niraparib maintenance**
- Significant improvement in PFS seen in niraparib maintenance cohort
  - Pronounced benefit in patients with HRD tumors



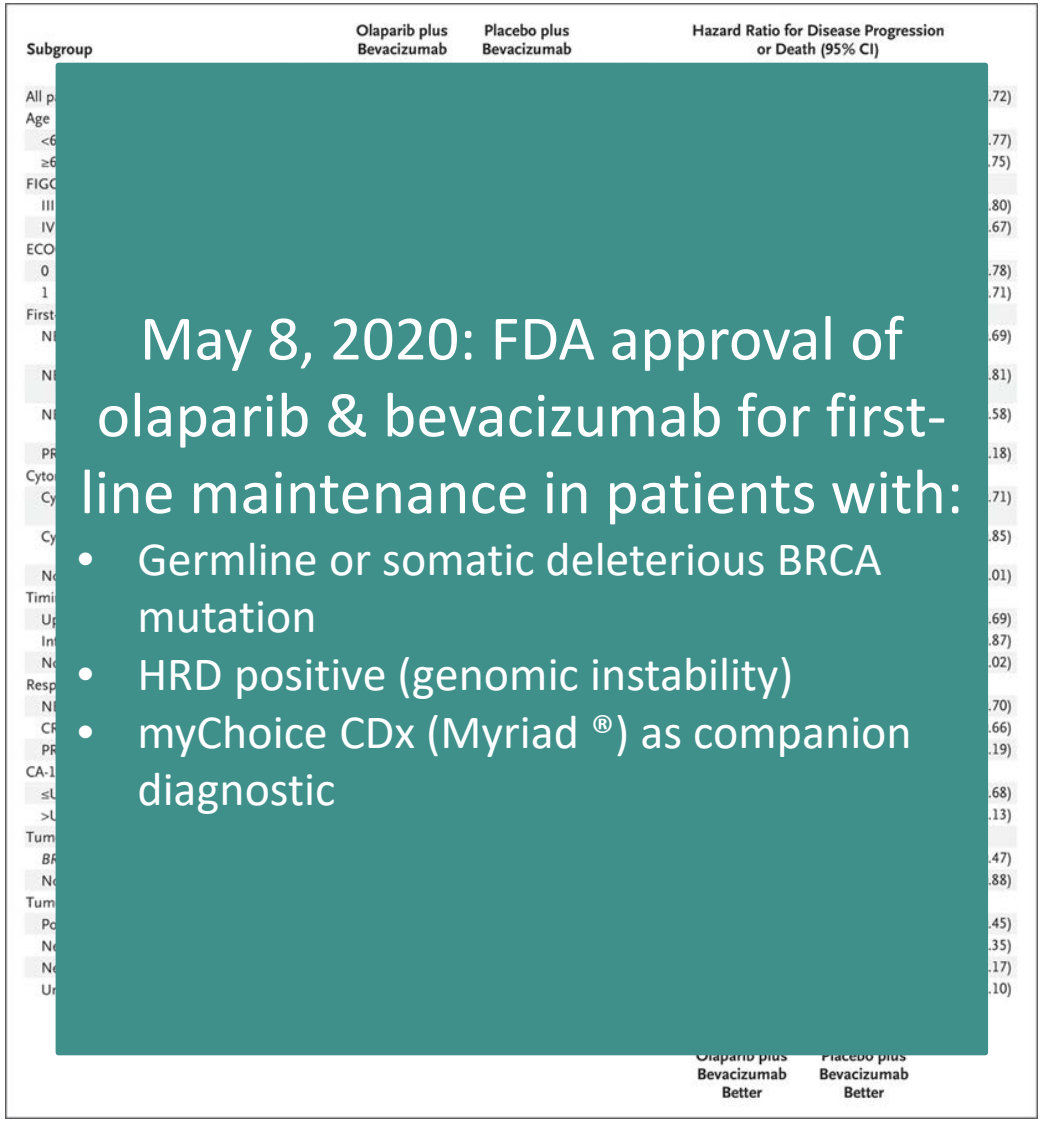
Coleman RL et al. N Engl J Med 2019.
Gonzalez-Martin A et al. N Engl J Med 2019.

Maintenance Treatment

PARP Inhibitors

PAOLA

- Randomized (2:1), placebo-controlled trial of carbo/taxol/bev +- **olaparib**
- Allowed to have primary surgery or interval following neoadjuvant chemo
- Significant improvement in PFS
  - HR 0.33 (HRD +BRCAm)
  - HR 0.43 (HRD, -BRCAm)
  - HR 0.92 (no/unknown HRD)



May 8, 2020: FDA approval of olaparib & bevacizumab for first-line maintenance in patients with:

- Germline or somatic deleterious BRCA mutation
- HRD positive (genomic instability)
- myChoice CDx (Myriad ®) as companion diagnostic

Ray-Coquard I et al. N Engl J Med 2019

Maintenance Treatment

PARP Inhibitors

Table 1. A Comparison of Three PARP Inhibitors in Patients with Ovarian Cancer.*

Trial Drug	Overall Population†			Mutated *BRCA*‡			HRD§			No HRD¶		
	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)
	median			*median*			*median*			*median*		
Niraparib												
Duration of progression-free survival	8.2 mo	13.8 mo	0.62 (0.50–0.75)	10.9 mo	22.1 mo	0.40 (0.26–0.62)	10.4 mo	21.9 mo	0.43 (0.31–0.59)	5.4 mo	8.1 mo	0.68 (0.49–0.94)
P value			<0.001						<0.001			
Veliparib												
Duration of progression-free survival	17.3 mo	23.5 mo	0.68 (0.56–0.83)	22.0 mo	34.7 mo	0.44 (0.28–0.68)‖	20.5 mo	31.9 mo	0.57 (0.43–0.76)	NR	NR	0.81 (0.60–1.09)
P value			<0.001			<0.001			<0.001			
Olaparib plus bevacizumab												
Duration of progression-free survival	16.6 mo	22.1 mo	0.59 (0.49–0.72)	21.7 mo	37.2 mo	0.31 (0.20–0.47)	17.7 mo	37.2 mo	0.33 (0.25–0.45)	16.2 mo	16.6 mo	1.00 (0.75–1.35)**
P value			<0.001									

* Evaluations were performed in 733 patients who received niraparib in the PRIMA trial,[4] in 1140 patients who received veliparib in the VELIA trial,[5] and in 806 patients who received olaparib in the PAOLA-1 trial.[6] HRD denotes homologous-recombination deficiency, PARP poly(adenosine diphosphate [ADP]–ribose) polymerase, and NR not reported.
† In all three trials, patients with *BRCA* mutations were overrepresented, as compared with the overall population of patients with ovarian cancer. The outcome for the overall population was favorable for each of the PARP inhibitors listed here.
‡ In all three trials, the PARP inhibitor substantially improved the duration of progression-free survival in patients with *BRCA* mutations.
§ In all three trials, the PARP inhibitor substantially improved the duration of progression-free survival in the HRD cohort.
¶ The effect of the PARP inhibitor among patients in the no-HRD cohort was more limited than in the other subgroups, and the size of the between-group difference was modest.
‖ The patients who were included in this comparison could have either tumor (somatic) or germline *BRCA* mutations.
** Patients who had unknown HRD status were excluded from this comparison.

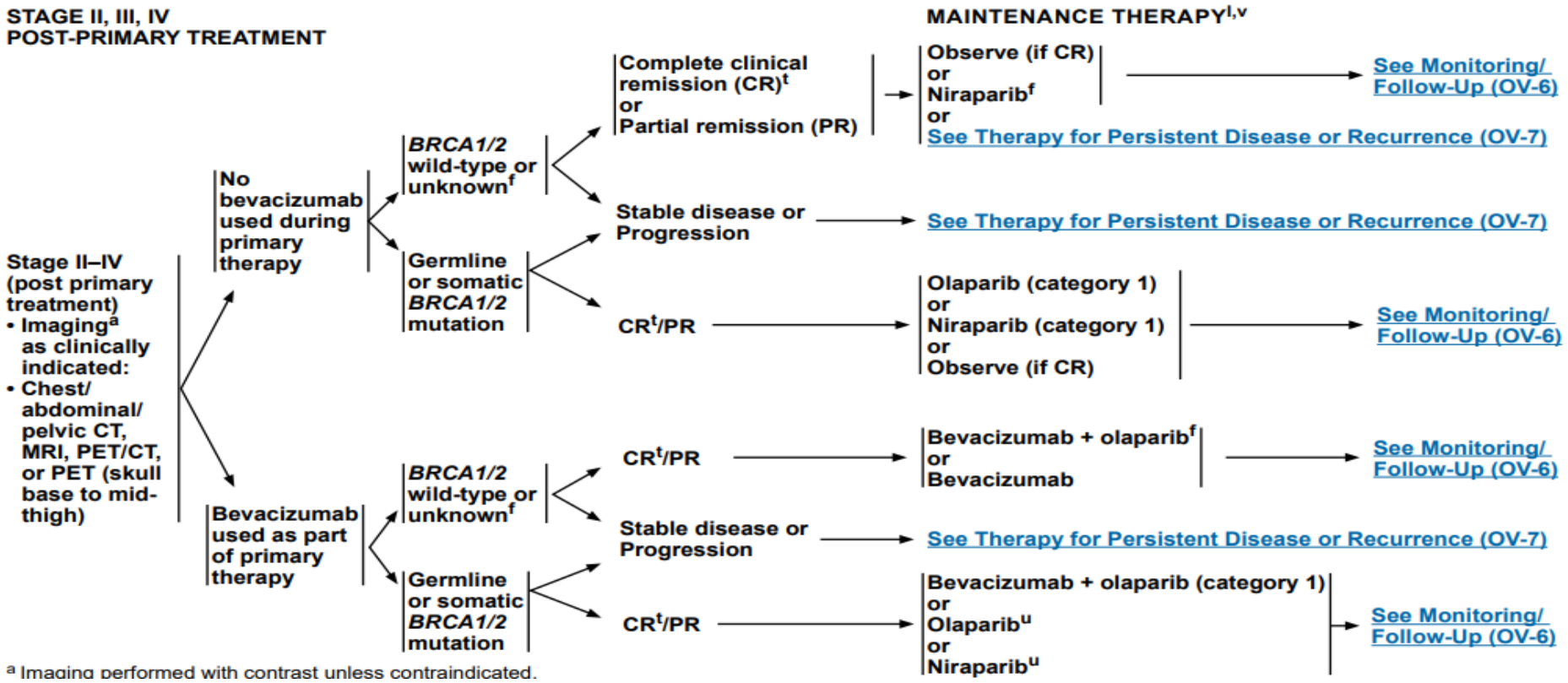
Longo DS. N Engl J Med 2019.

Candidates for PARP Inhibitors

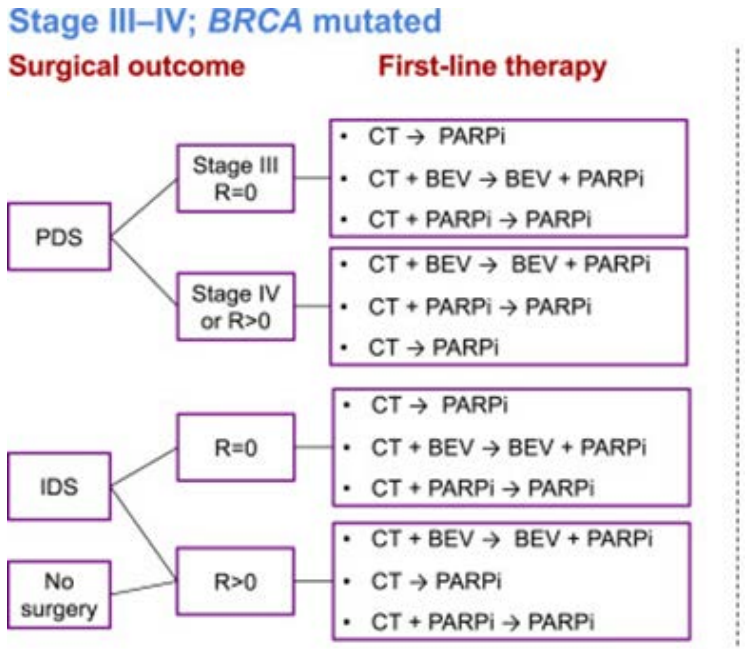
- Germline or somatic carriers of BRCA 1 or 2 mutation
  - ➡ Carriers of other gene mutations causing HRD (e.g. CHEK2, ATM, PALB2)
- Patients with tumors exhibiting HRD
  - ➡ How to best assess for HRD?
  - ➡ Recent trials utilized Myriad myRisk, cut-off varies between trials

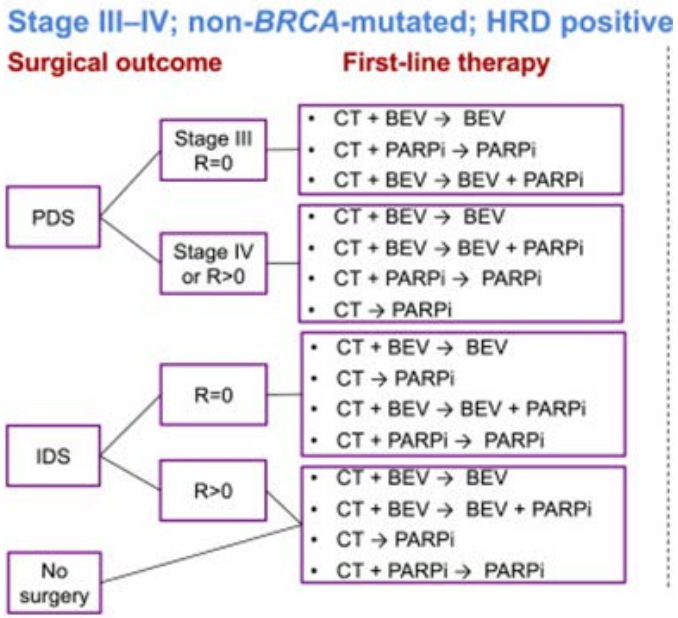
Maintenance Treatment

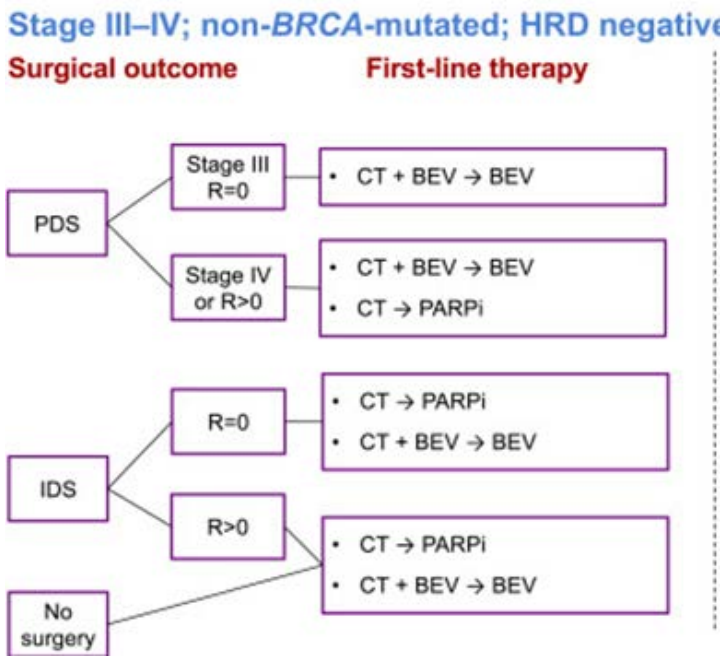
- **NCCN recommendations (2020)**



Maintenance Treatment







Mirza MR et al. Ann Oncol 2020

Current & Future Issues

- Further work on benefit of IP versus IV

JGOG 3016

IV carbo & IV dose-dense paclitaxel

IP carbo & IV dose-dense paclitaxel

- Combining PARP inhibitors with immunotherapy

FIRST Primary OC

Platinum-based chemo + placebo

Platinum-based chemo + niraparib

Platinum-based chemo + niraparib + anti-PD1

- Modifying neoadjuvant treatment

NRG GY007

Carbo/taxol + placebo

Carbo/taxol + ruxolitinib

Tumor reductive surgery

Genetic Testing

- Patients with EOC MUST be offered genetic counselling & testing
- ***15-20% Rate of HRD mutations (BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2, BARD1 and MMR genes)***
- Unfortunately, referral rates for genetic counseling are low – 10-30% in recent review
  - In retrospective review from Brown, of those referred, 70.8% consulted with genetics

Referral based on family hx alone may miss 1/3 cases of mutation carriers

NCCN *recommends*

Genetic risk evaluation and germline & somatic testing for all patients with a new diagnosis of ovarian, fallopian tube or primary peritoneal cancer

Febbraro T et al. Gynecol Oncol 2015.
Hospins PJ and Gotlieb WH. CA Cancer J Clin 2017.

Pat T et al. Cancer 2005. Pennington & Swisher. Gynecol Oncol 2012.
NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2020.

Recurrence

Likelihood of recurrence:

- >80% with advanced disease will recur

Timing of relapse:	*Treatment-free Interval*
Platinum-sensitive	≥6 mos
Platinum-resistant	<6 mos

Prognosis - cure unlikely following recurrence

Numerous trials open through SCCA for recurrent epithelial ovarian cancer

Platinum Sensitive Recurrent EOC

Re-treat with:

- Carboplatin/paclitaxel
- Carboplatin/Gemcitabine
- Carboplatin/Doxil
- Superior platinum regimen?

Gemcitabine thought to reverse platinum resistance

Rose PG et al. Gynecol Oncol 2003.

CALYPSO:
Phase III comparison C/D vs C/T: equivalent outcomes, but less toxicity in C/D arm

Pujade-Lauraine E et al. J Clin Oncol 2010.

ENGOT-ov 18:
C/G/B +B vs C/D/B + B

Significant improvement PFS, OS with C/D/B + B arm

Global QOL slightly superior in C/D/B+B

Pfisterer J et al. Lancet Oncol 2020.

Maintenance Treatment Recurrent Disease

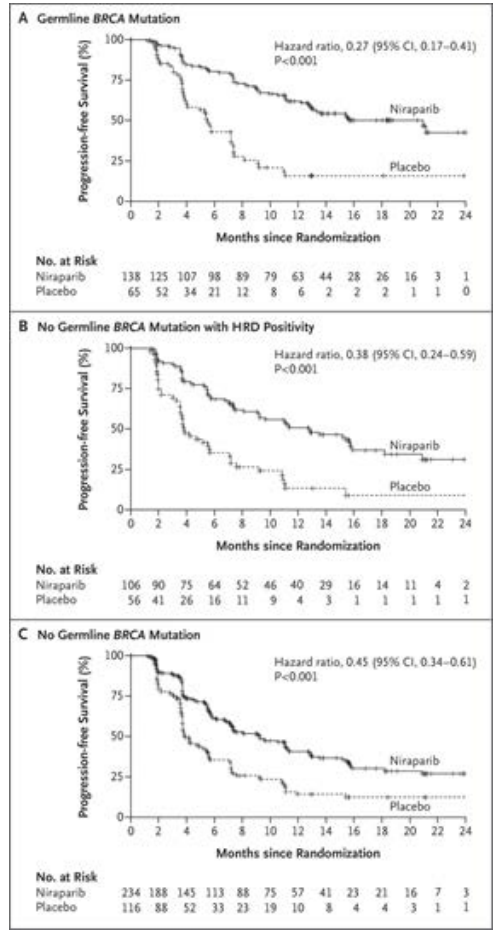
PARP inhibitors

ENGOT-OV16/NOVA

RCT phase 3 of maintenance niraparib

Most improvement seen in patients with BRCA mutations and evidence of HRD

Improved PFS compared to placebo in all groups



Niraparib FDA-approved for maintenance following complete or partial response to platinum-based chemo for recurrent disease (olaparib, rucaparib also approved)

Mirza MR et al. N Engl J Med 2016.

SOLO-3

RCT phase 3 of olaparib vs non-platinum-chemo for BRCA 1 or 2 mutation carriers

Significant improvement in ORR and PFS

Penson RT et al. J Clin Oncol 2020.

Maintenance Treatment Recurrent Disease

Bevacizumab

OCEANS:

C/G vs C/G/B + maintenance B showed significant improvement in PFS

Aghajanian C et al. J Clin Oncol 2012.

GOG 213

C/T or C/G vs C/T/B or C/G/B showed PFS survival benefit with addition of bevacizumab, trend towards OS benefit (42.2 vs 37.3 mo)

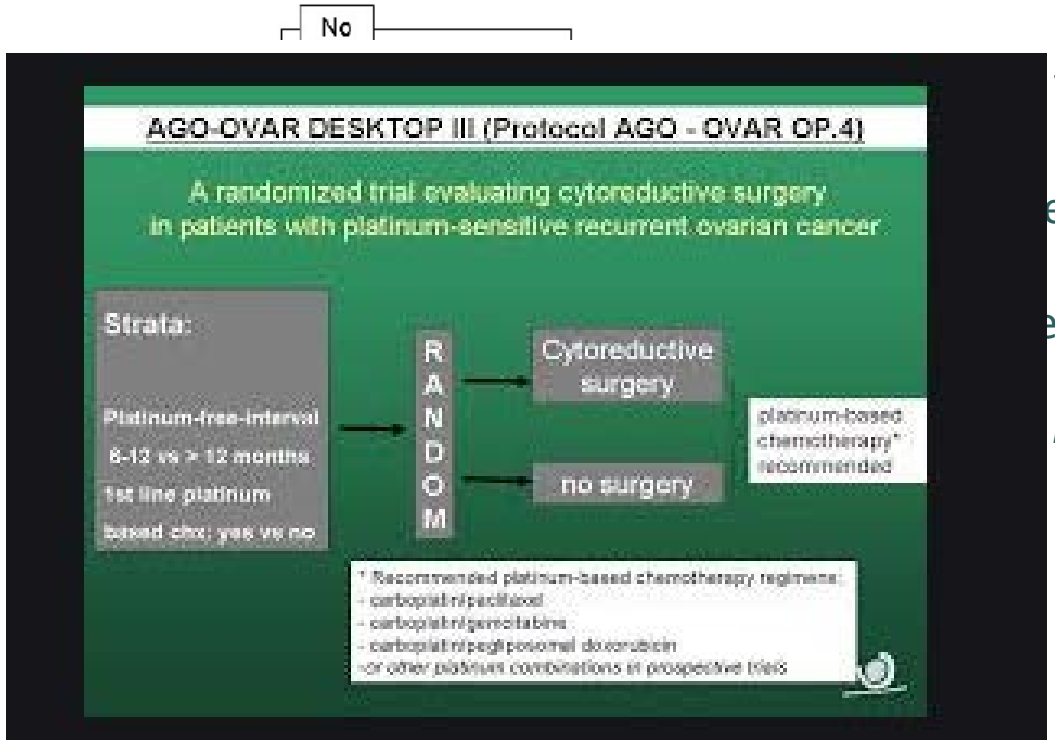
Coleman RL et al. Lancet Oncol 2017.

Platinum Sensitive Disease Secondary Cytoreduction?

- Historically considered for patients with recurrent disease
  - Long disease-free interval
  - Limited sites of disease
- Retrospective studies suggest survival benefit

GOG 213

DESKTOP III



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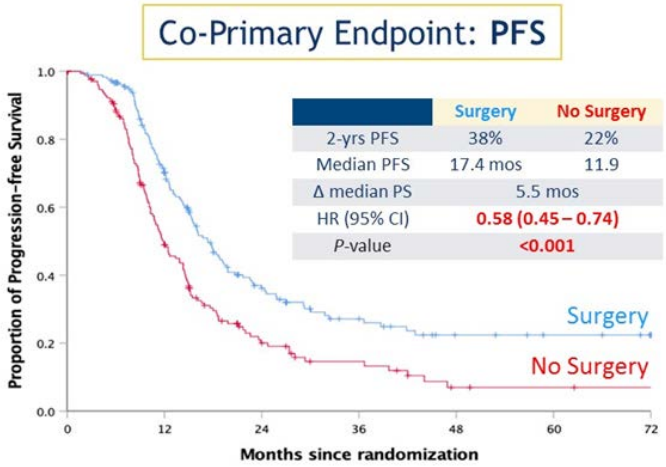
Med 2019.

Platinum Sensitive Disease Secondary Cytoreduction?

SOC-1



Secondary cytoreduction associated with improved PFS & OS

- Standardized means of patient selection (iMODEL)
- No maintenance therapy used

Zang R et al. ASCO 2020

GOG-213, DESKTOP III and SOC-1 Comparison: PFS

	GOG-213	AGO Desktop III	SGOG SOC-1
PFS - Surgery (median)	18.2 mos	18.4 mos	17.4 mos
PFS - No Surgery (median)	**16.5 mos**	14.0 mos	11.9 mos
HR, 95% CI	0.88 (0.70-1.11)	0.66 (0.54-0.82)	0.58 (0.45-0.74) P < 0.001

- Secondary cytoreduction may be appropriate, but careful patient selection using validated models is crucial

Platinum Resistant Options

Multiple treatment options:

- Topotecan
- Doxil
- Oral VP16
- Tamoxifen
- Abraxane
- Pemetrexed
- Gemcitabine
- Bevacizumab
- Cyclophosphamide
- Paclitaxel, docetaxel
- Hexamethamelamine

Encourage clinical trial participation!

- Phase III AURELIA trial showed PFS benefit of adding bevacizumab to chemotherapy (topo, taxol, Doxil), as well as improvement in QOL

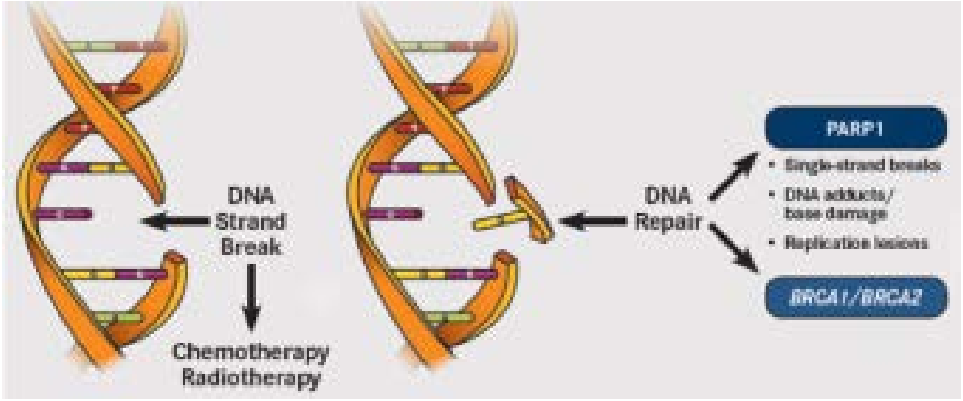
Pujade-Lauraine et al. J Clin Oncol 2014
Stockler MR et al. J Clin Oncol 2014.

- Recent Australian data suggest that our definition of "platinum resistance" may need revision
  - In patients with platinum-free interval of 3-6 months, improved outcomes were seen with platinum-based chemo compared with no platinum

Lindemann K et al. Gynecol Oncol 2018

PARP Inhibitors

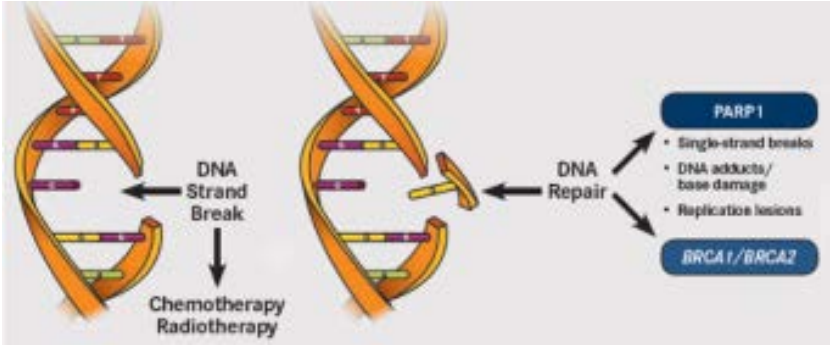
- Current FDA-approved PARP inhibitors
  - Olaparib (Lynparza)
  - Rucaparib (Rubraca)
  - Niraparib (Zejula)



- Approved indications
  - Maintenance following platinum-based primary treatment in BRCA-mutated ovarian cancer
  - Maintenance following platinum-based treatment of platinum sensitive recurrence
  - Monotherapy in patients with platinum-sensitive recurrent disease (>2 lines of treatment) and germline or somatic BRCA 1 or 2 mutation and/or HRD+ tumor

Moore K et al. N Engl J Med 2018.
Mirza MR et al. N Engl J Med 2016.
Kaufman B et al. J Clin Oncol 2015.
Swisher EM et al. Lancet Oncol 2017.
Coleman RL et al. Lancet 2017.

PARP Inhibitors



- Consider PARPi in patients with germline BRCA 1 or 2 mutation with platinum resistant disease

Domchek SM et al. Gynecol Oncol 2016.

- Management of toxicities
  - Upfront dose modification of niraparib in patients with baseline weight of <77 kg or baseline platelets <150K
  - Aggressive use of antiemetics when starting PARP inhibitor

Moore KN et al. Gynecol Oncol 2018.
Mirza MR et al. N Engl J Med 2016.

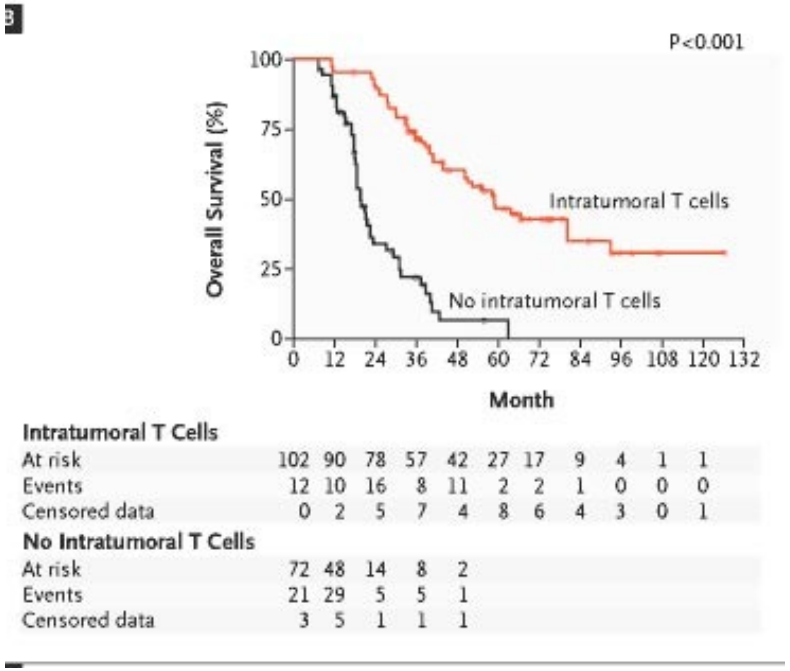
- Future directions
  - Combination with antiangiogenic agents (olaparib & cediranib)
  - Combination with immunotherapy
    - TOPACIO/KEYNOTE-16: niraparib & pembrolizumab, ORR 18%, DCR 65%
    - MOONSTONE: niraparib + anti-PD-1 antibody

Washington C et al. Curr Op Obst Gyn 2019.
Konstantinopoulos PA et al. JAMA Oncol 2019

Immunotherapy in EOC/FTC/PPC

Rationale for approach:

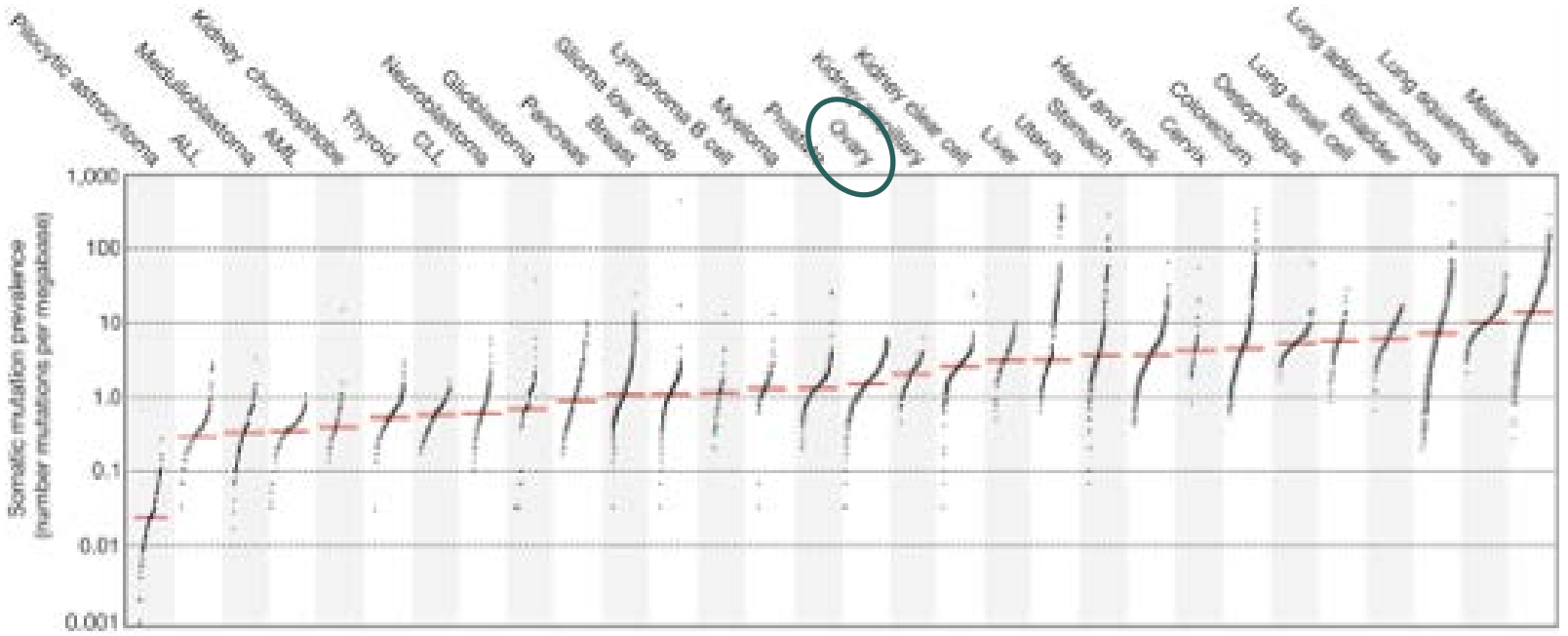
- Overall survival in ovarian cancer found to correlate to presence/absence of tumor-infiltrating lymphocytes
- Analysis of the TCGA has shown “immunoreactive-like" subtype of ovarian cancer to have improved survival
  - 20% of samples fit profile



Zhang L et al. NEJM 2003.
Konecny GE et al. J Natl Cancer Inst 2014.

To date, modest response in clinical trials → **currently no approved immune therapies for ovarian cancer**

Prevalence of Somatic Mutations



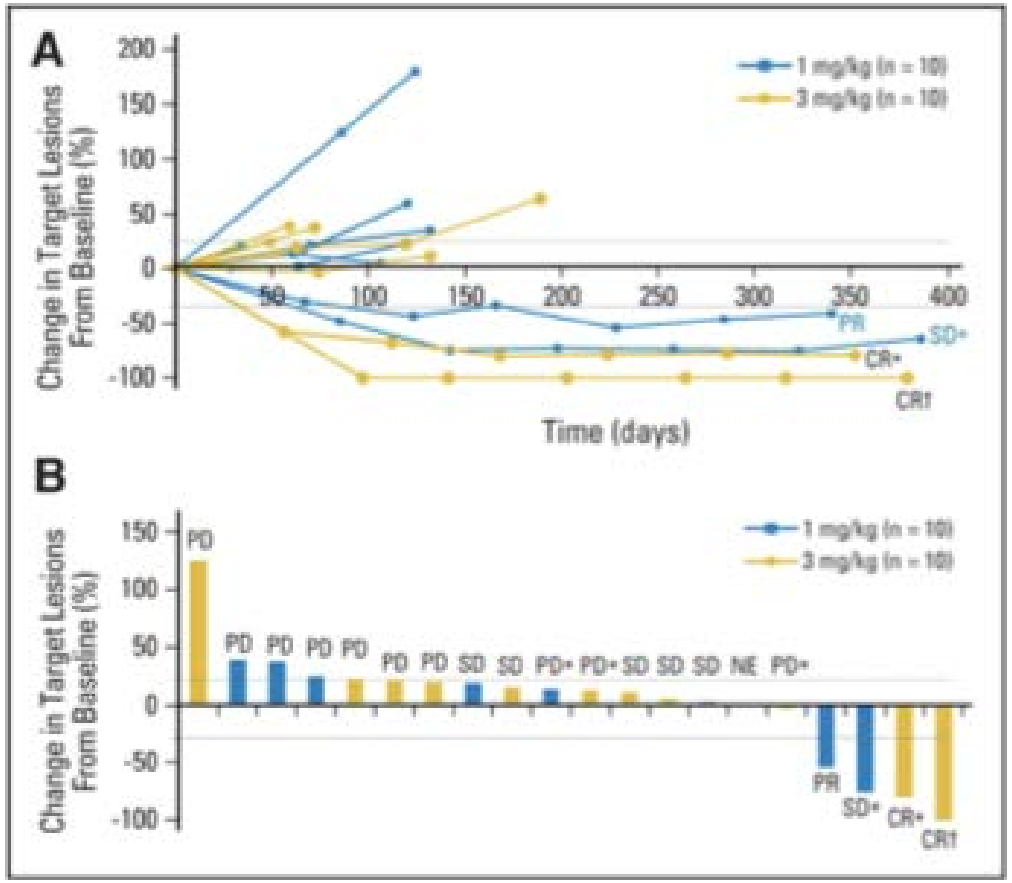
Why limited benefit to immunotherapy in ovarian cancer?

1. Low mutational burden
2. Expression of multiple co-inhibitory receptors on infiltrating T-cells
3. Upregulation of immune checkpoints if another is blocked
4. Redundant immune suppressive mechanisms

Alexandrov LB et al. Nature 2013.
Odunsi K. Ann Oncol 2017.

Immune Checkpoint Inhibition

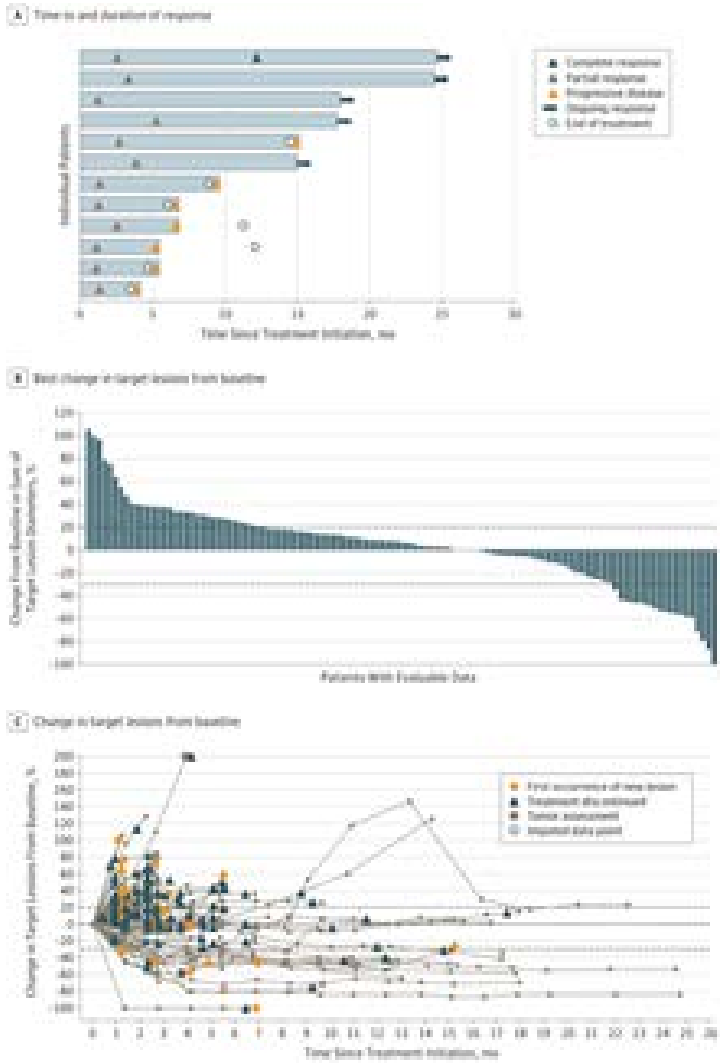
- Phase 2 study of nivolumab in platinum resistant ovarian cancer with ORR of 15%
- Two durable complete responses, one partial response, one stable disease
- Response to therapy did not correlate with tumor PD-L1 IHC



Hamanishi J et al. J Clin Oncol 2015.

Immune Checkpoint Inhibition

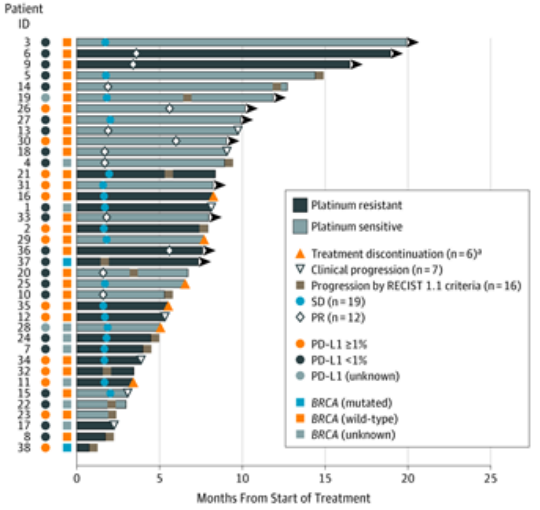
- Phase 1B KEYNOTE-100 – RR of 7.4-9.9% with pembrolizumab in recurrent ovarian cancer
  - ASCO 2020: Final analysis showed trend towards increased ORR with higher PD-L1 expression
- Phase 1b KEYNOTE-028 – pembrolizumab for PD-L1+ recurrent ovarian cancer reported ORR of 11.5%
- Phase 1b JAVELIN – ORR 9.6% with avelumab in recurrent ovarian cancer, DCR 54%

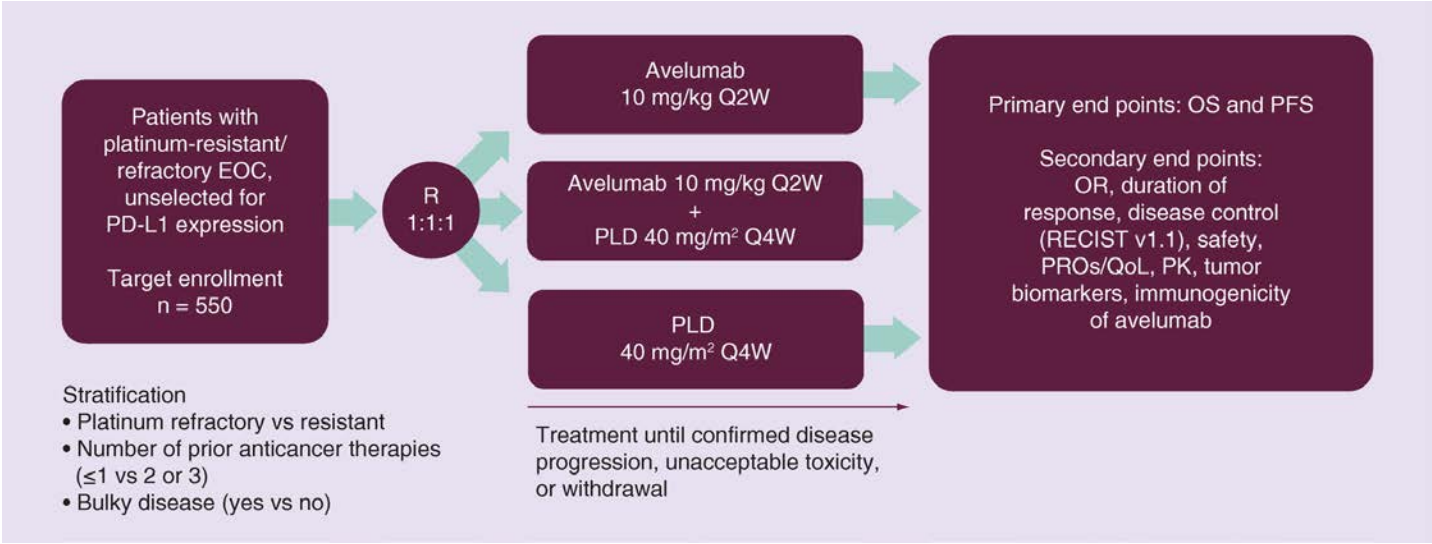


Matulonis UA et al. Ann Oncol 2019.
Matulonis U et al. ASCO 2020.
Varga A et al. Gynecol Oncol 2019
Disis ML et al. JAMA Oncol 2019.

Immune Checkpoint Inhibition

- Phase 2 combination therapy with nivolumab and bevacizumab
  - 38 patients with recurrent ovarian cancer (relapse within 12 months of last platinum)
  - ORR 28.9% (40.0% pt-sensitive, 16.7% pt-resistant)
  - Response not correlated with PD-L1 staining
- JAVELIN OVARIAN 200





Liu JF et al. JAMA Oncol 2019.
Pujade-Lauraine E et al. Future Oncol 2018.

Immunotherapy

- Vaccination studies: CA 125, NY-ESO-1
- Recent pilot clinical trial of “personalized vaccine” generated by autologous DCs

Berek J et al. J Clin Oncol 2009,
Sabbatini P et al. J Clin Oncol 2010.
Tanyi JL et al. Sci Transl Med 2018.

- Future studies testing agents in combination with chemo, antiangiogenic agents and PARP inhibitors

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Ovarian Cancer

NCCN Ovarian Cancer Panel Members
Summary of the Guidelines Updates

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer:
Clinical Presentation, Workup, Clinical Stage, Primary Treatment (OV-1)
Poor Surgical Candidate or Low Likelihood of Optimal Cytoreduction (OV-2)
Diagnosis by Previous Surgery: Findings and Primary Treatment (OV-3)
Pathologic Staging, Primary Chemotherapy/Primary Adjuvant Therapy (OV-4)
Post-Primary Treatment: Maintenance Therapy (OV-5)
Monitoring/Follow-Up, Recurrent Disease (OV-6)
Disease Status, Therapy for Persistent Disease or Recurrence (OV-7)

Less Common Ovarian Histopathologies:
Diagnosis (LCOH-1)
Carcinosarcoma (Malignant Mixed Müllerian Tumors) (LCOH-2)
Clear Cell Carcinoma of the Ovary (LCOH-3)
Mucinous Carcinoma of the Ovary (LCOH-4)
Grade 1 Endometrioid Carcinoma (LCOH-5)
Low-Grade Serous Carcinoma (LCOH-6)
Ovarian Borderline Epithelial Tumors (Low Malignant Potential) (LCOH-7)
Malignant Sex Cord-Stromal Tumors (LCOH-10)
Malignant Germ Cell Tumors (LCOH-11)

Principles of Surgery (OV-A)
Principles of Pathology (OV-B)
Principles of Systemic Therapy (OV-C)
- Primary Systemic Therapy Regimens (OV-C, 3 of 9)
- Acceptable Recurrence Therapies (OV-C, 6 of 9)

Management of Drug Reactions (OV-D)
WHO Histologic Classification (OV-E)
Staging (ST-1)

“One Size No Longer Fits All”

Low-grade Serous (LGS)
LG Endometrioid
Clear Cell
Mucinous

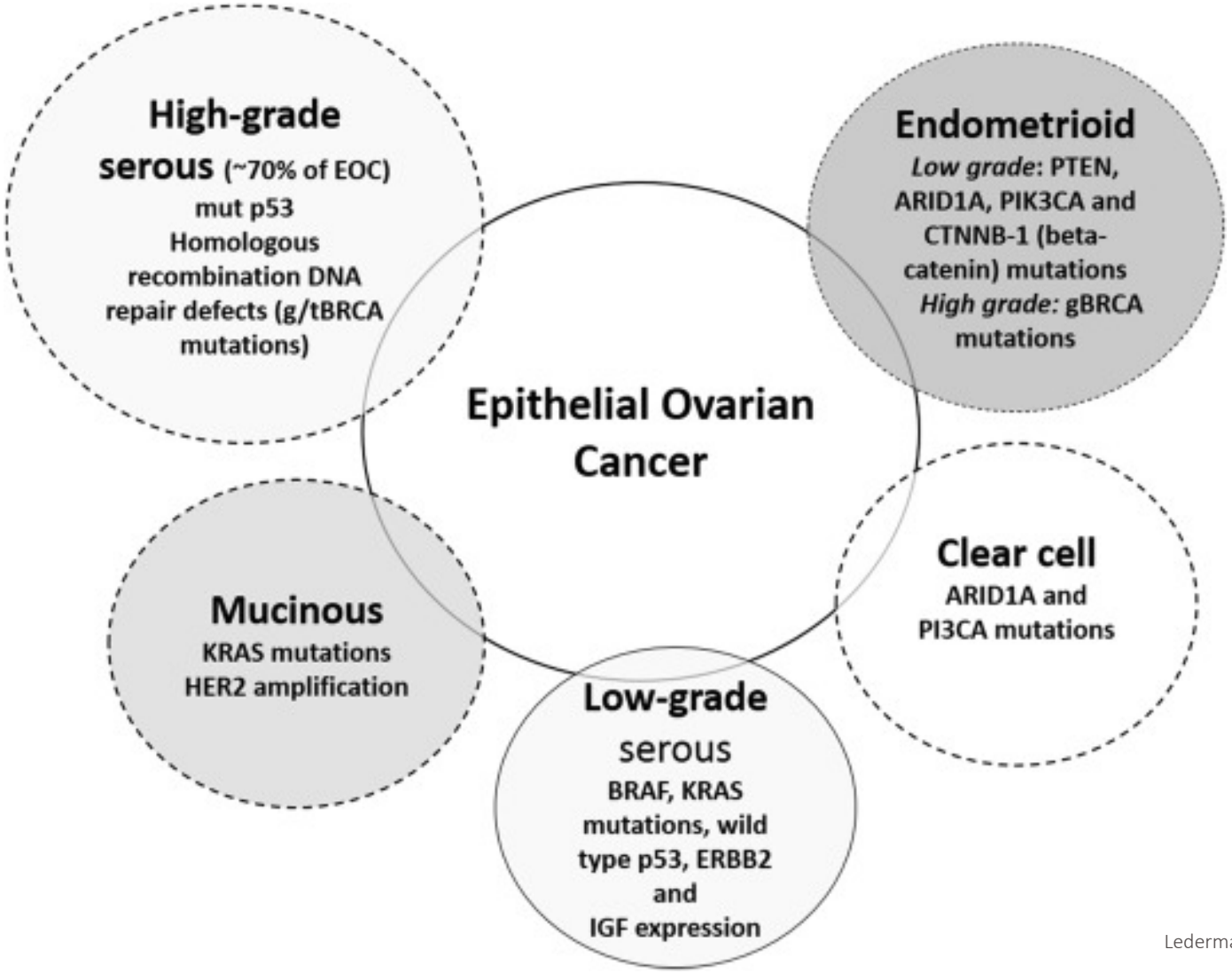
- Develop in stepwise fashion
- Activating mutations in:
  - PTEN
  - KRAS
  - BRAF
  - P13KCA

High-grade Serous (HGS)
HG Endometrioid
Carcinosarcoma
Undifferentiated

- Present with **ADVANCED** disease
- May have mutations in BRCA 1 & 2, nearly universal p53 mutations

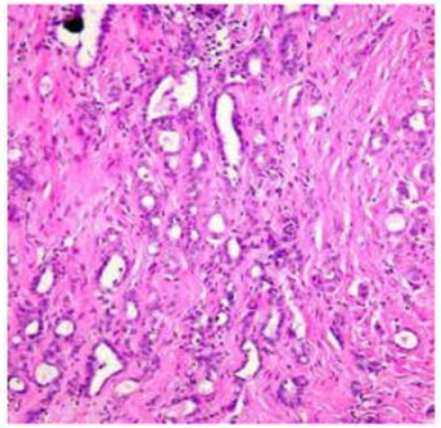
Groen RS et al. Gynecol Oncol 2015.
Kurman & Shih. Am J Surg Pathol 2010.

Molecular Subtypes

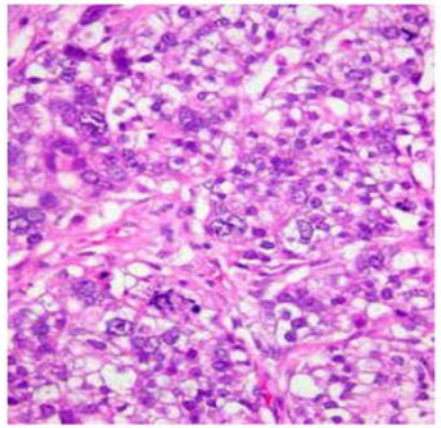


Ledermann JA et al. Eur J Cancer 2016.

Histology-Specific Therapy
Low Grade Serous (LGS)



1A Low Grade Serous Carcinoma

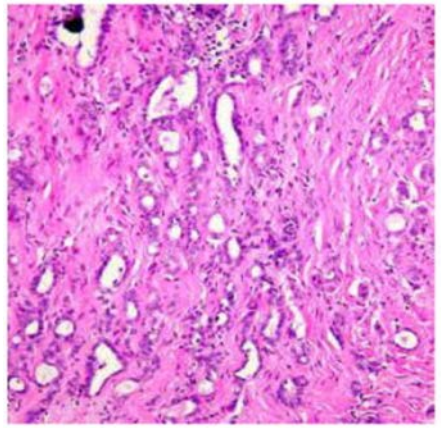


1B High Grade Serous Carcinoma

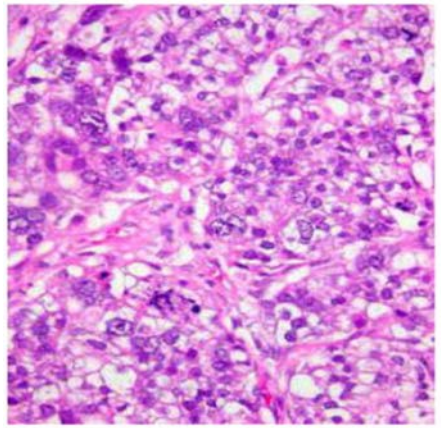
- Represents 5% of all ovarian cancers, and a minority of all serous cancers
- Such patients are often younger & survive longer
- Review of patients with LGS on phase III clinical trial showed that only residual disease after surgery was associated with improvement in survival

Fader AN et al. Obstet Gynecol 2013.
Gershenson DM et al. Obstet Gynecol 2006.

Histology-Specific Therapy
Low Grade Serous (LGS)



1A Low Grade Serous Carcinoma



1B High Grade Serous Carcinoma

Lack response to chemotherapy compared to high-grade serous tumors

- Often have activating mutations in PTEN, KRAS, BRAF, PI3KCA
- Higher expression of ER, PR receptors

MEK inhibitors

- 15% ORR, 65% SD with selumetinib
- GOG 281: ORR 26.2% trametinib vs 6.2% with IC chemo

Hormonal therapy

- Recent MDACC review of hormonal maintenance therapy showed significant improvement in PFS

Farley J et al. Lancet Oncol 2013.
Gershenson DM et al. J Clin Oncol 2017.
Gersenson DM et al. SGO 2020.

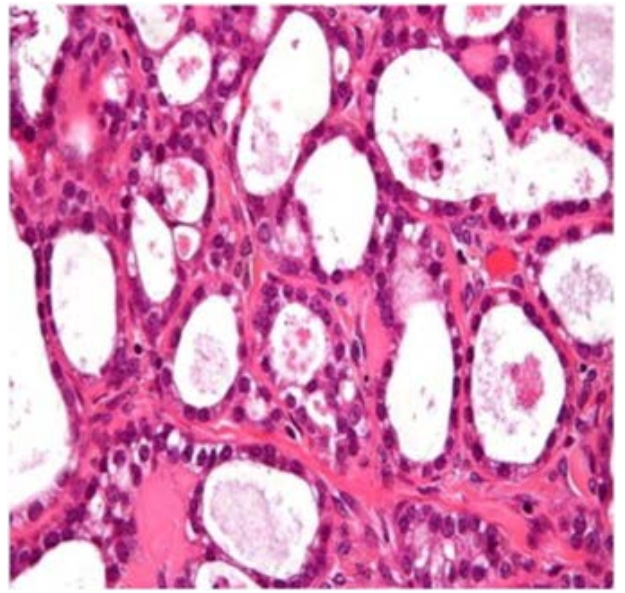
NRG GY 019

Debulking surgery

Carbo/taxol + letrozole

Letrozole

Histology-Specific Therapy
Clear Cell



- 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
- Consider checking for mismatch repair protein expression (11.5%)
- Use of radiation?
  - Improved DFS in patients with high-risk early stage disease
  - Improved outcomes in patients with recurrent ovarian clear cell cancer

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

Histology-Specific Therapy Endometrioid Ovarian Cancer

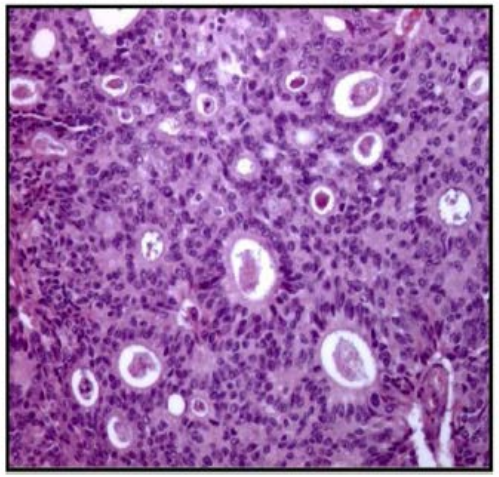


Fig. 3. Grade 2 endometrioid carcinoma demonstrating atypical crowded, back-to-back glands, little intervening stroma and few mitotic figures.

- 11% of epithelial ovarian cancers
- Often found in association with endometriosis
  - High rate of estrogen, progesterone expression
- Check for microsatellite instability (19.2%)
  - In patients with Lynch syndrome, have a strong association with synchronous endometrial cancer
  - Consider checking for microsatellite instability
- No benefit of chemotherapy in *low grade* early stage disease
  - High grade endometrioid ovarian cancers behave similarly to high-grade serous

Trimbos JB et al. J Natl Cancer Inst 2003.

Histology-Specific Therapy Mucinous Ovarian Cancer

- 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 (e.g. CAPOX), given similar molecular profiles
  - Studies to date suggest survival benefit
  - Interpretation difficult given use of bevacizumab

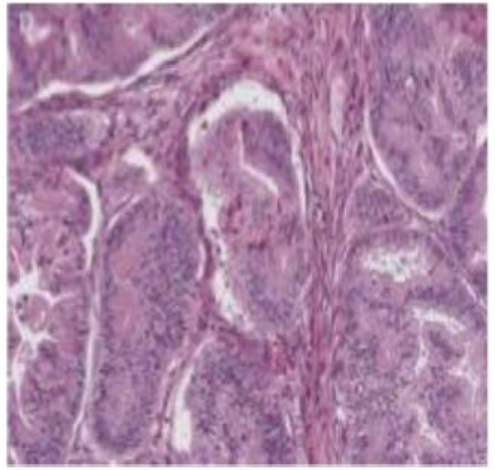


Fig. 4. Mucinous carcinoma exhibiting an expansive pattern with few mitotic figures. All figures were borrowed with permission from David M. Gershenson and Anais Malpica, MD Anderson Cancer Center.

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.

Conclusions

- Ovarian cancer is a heterogenous disease & histology is key in management
- Maintenance treatment following primary therapy for all?
  - Upfront molecular profiling is essential to determine potential benefit of maintenance
- Consult with gynecologic oncologists at diagnosis and throughout the disease continuum

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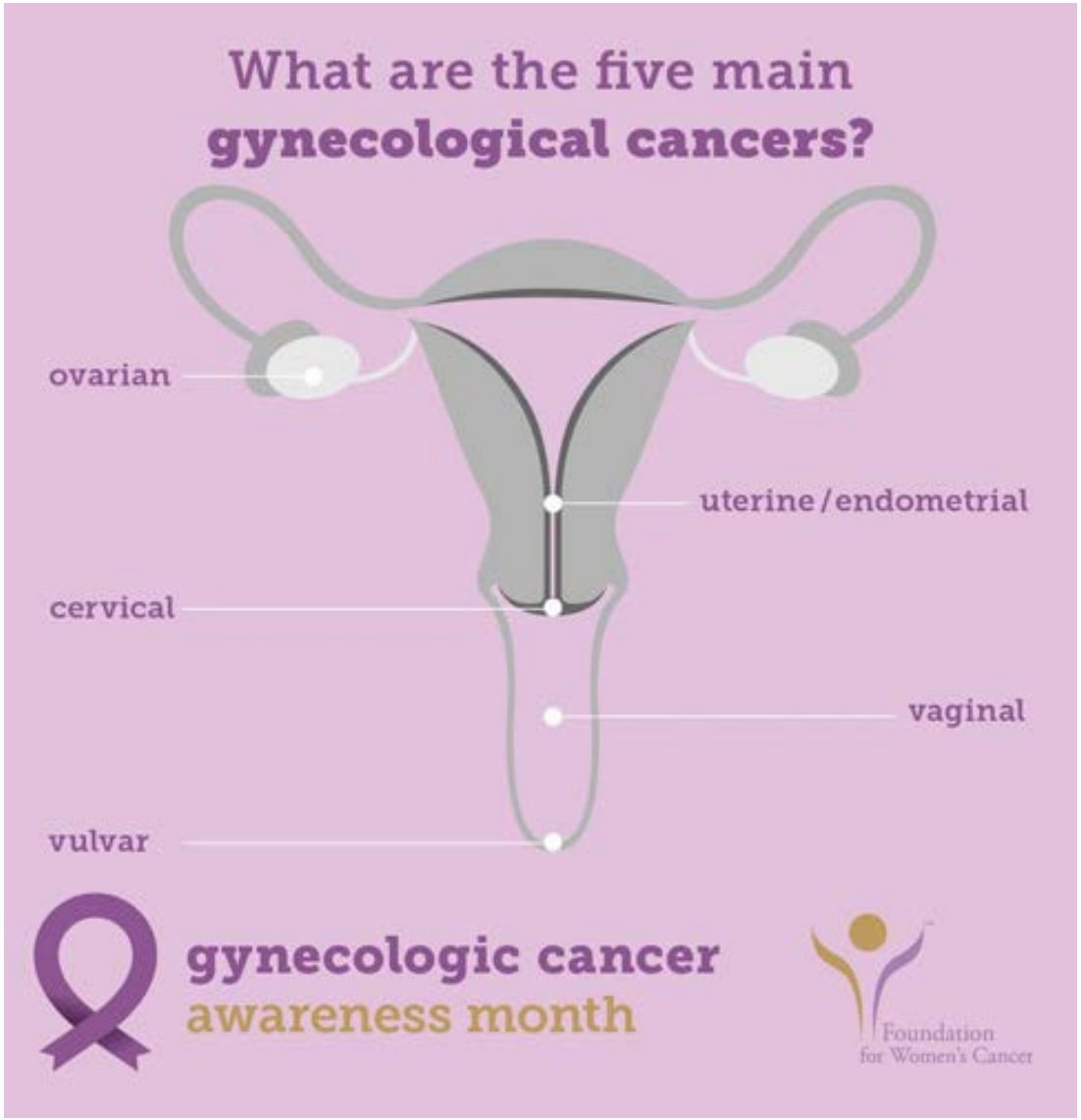
Email: urbanr@uw.edu



Genetic Testing

Expanded panel testing – 30 genes panel

- BROCA(UW panel), Foundation One, Myriad, Ambry
- Insurance will only pay for one $$$

Color genomics

$249, need Dr. to approve

19 gene panel (including BRCA1 & 2)

Sample Case

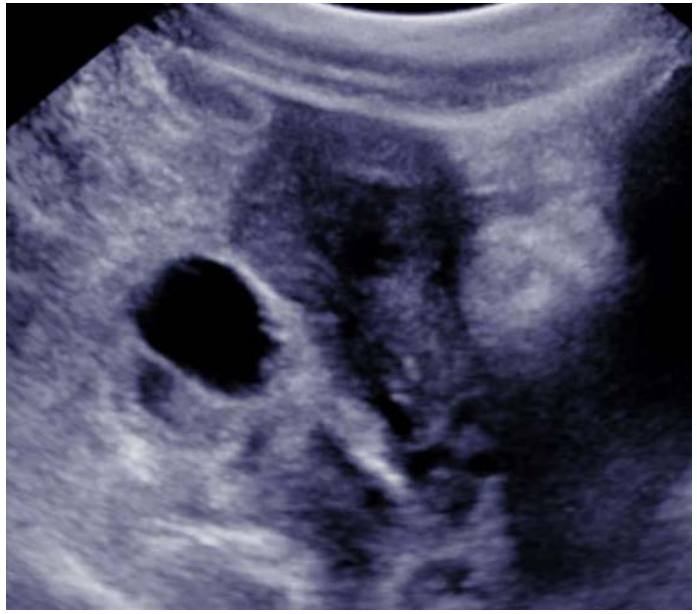
ZA, 65 yo, referred to your office by her PCP:

- 3 months of abdominal bloating
- CT showed a pelvic mass and ascites
- CA 125 = 1,031; CEA = 0.9

How to proceed with a presumed advanced ovarian cancer?

Diagnostic Approaches - Imaging

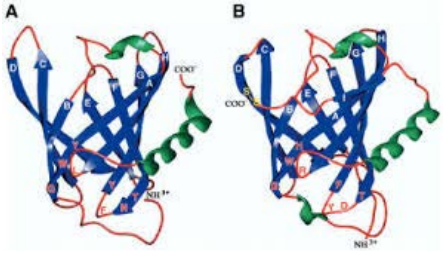
- Pelvic (transvaginal) ultrasound
  - Useful for gynecologic tract
  - Cheapest
- CT abdomen/pelvis ± chest
  - If concerned about abdominal disease or exam findings
- MRI
  - Good for distinguishing solid ovarian tumors
- Role of PET?
  - Not cost-effective for primary disease
  - May be useful in recurrent disease



Tumor Markers

CA-125 (normal <35 U/mL)

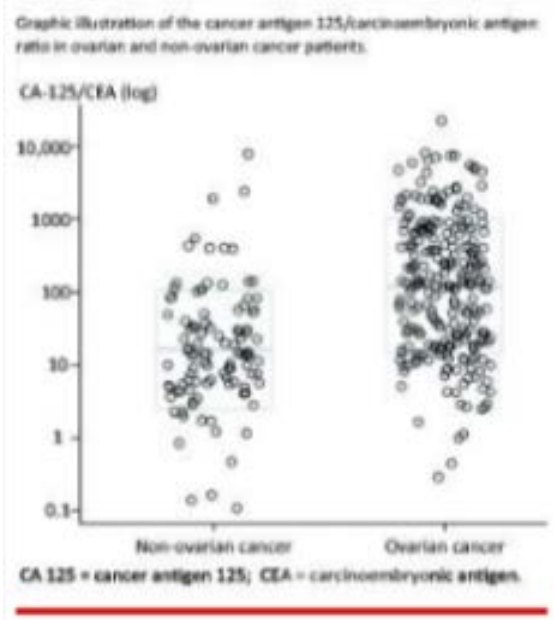
- Expressed by cells of coelomic (pleura, peritoneum) and Mullerian (gyn) epithelia
- Sensitivity 70%, specificity 80% (lower in premenopausal)
- Not as useful in mucinous or clear cell tumors
- If find a pelvic mass/abnormal ovary – order CA125



HE-4 (human epididymis protein 4) (normal <150 pM/mL)

- FDA Approved for monitoring recurrent or progressive EOC
- Part of ROMA (Risk of malignancy algorithm) score
  - CA125, HE4 & menopausal status
  - Assess likelihood of malignancy in women undergoing surgery for adnexal mass
- Generic price at UW: $184

Modes of Diagnosis



- Biopsy-proven (preferable)
- If biopsy specimen unavailable, FNA specimen acceptable if:
- presence of pelvic (ovarian) mass
- presence of metastases outside pelvis measuring ≥2 cm
- regional lymph node metastasis or proof of stage IV disease (+ pleural effusion, + parenchymal liver mets)
- Ratio of CA 125:CEA ≥ 25

Ratio of CA 125:CEA <25 requires evaluation for primary gastrointestinal malignancy

Surveillance?

Modalities

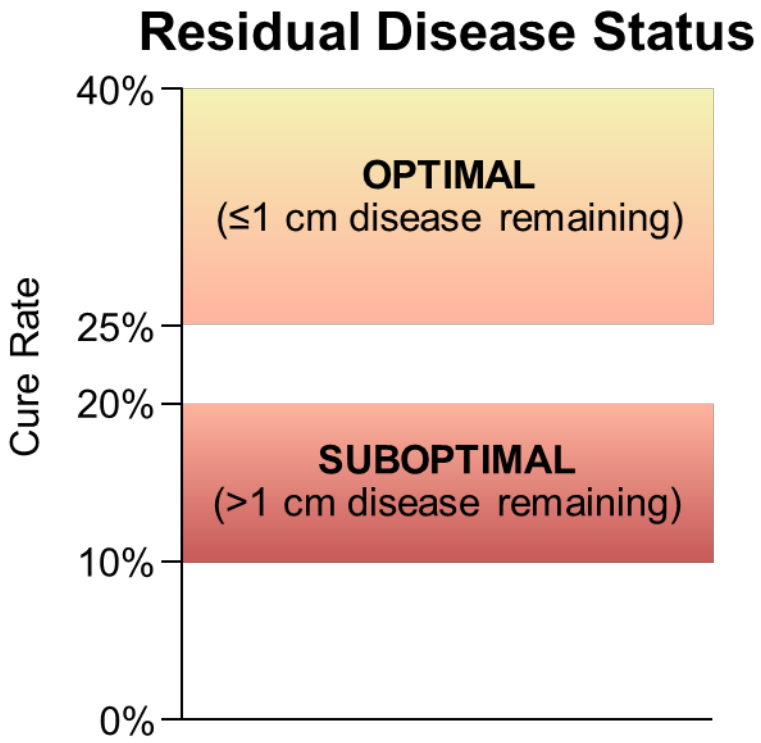
- Clinical exam, including pelvic, q 3-6 mos
- CA 125 every visit, if initially elevated
- Imaging, as clinically indicated
- HE4 - newly discovered glycoprotein, overexpressed by serous and endometrioid adenocarcinomas
  - FDA-approved marker to monitor for recurrence

Evidence

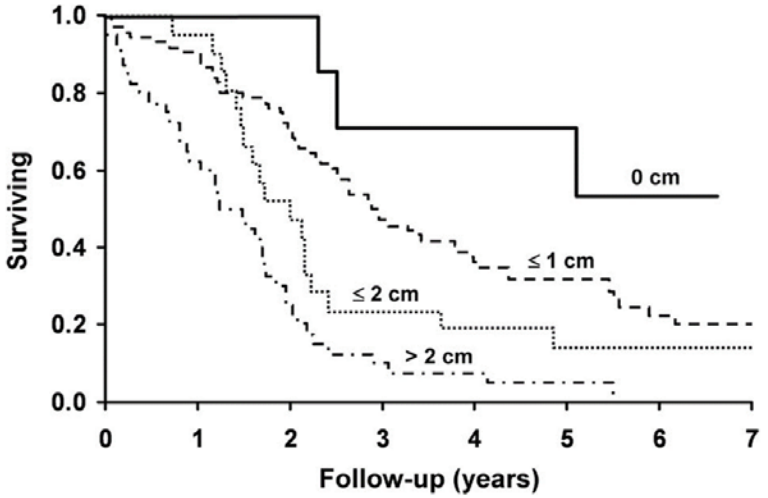
- Detection of early recurrence may extend lifespan; however, that benefit not derived from routine F/U Exams
- Randomized EORTC trial: No survival benefit when Rx on basis of CA 125 alone vs clinical recurrence

NCCN Guidelines. Ovarian Cancer. V1.2019
Geurts SM et al. Int J Gynecol Cancer 2011
Rustin GJ et al. Lancet 2010.

Importance of Cytoreduction



Survival by volume of residual disease remaining after surgery



Questions?

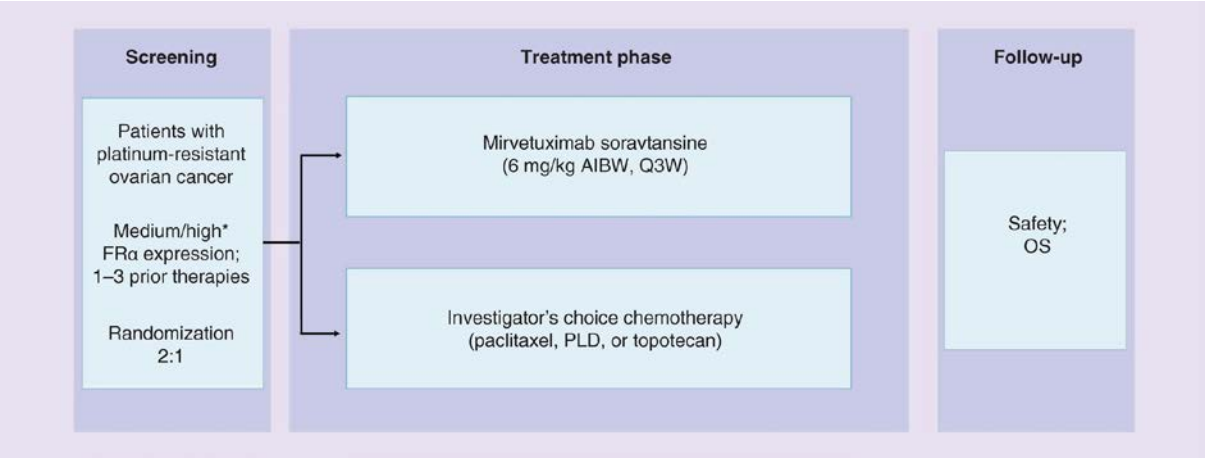
Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Platinum Resistant Disease
Future Directions

Folate receptor (FR)

- Capacity to internalize large molecules
- Mirvetuximab (coupled to DM4)
- FORWARD I: Mirvetuximab vs IC chemo in patients with tumors having FRα expression



Encourage clinical trial participation!