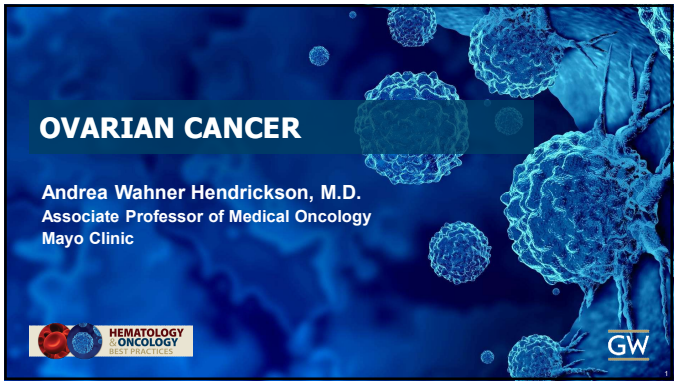


Disclosures

Interests

- Advisory Board: Clovis, Epsila Bio

Off Label Usage

- I **WILL** include discussion of investigational or off-label use of a product in my presentation.

Ovarian Cancer
Outline

- Epithelial carcinoma (90%)
  - Epidemiology and Screening
  - Initial therapy
    - Surgery
    - Adjuvant chemotherapy
    - Maintenance therapy
  - Disease recurrence
    - Platinum sensitive vs. platinum resistant
- Non-epithelial malignancies (10%)
  - Sex cord-stromal tumors (7%)
  - Germ cell neoplasms (2%)

Ovarian Cancer
Epidemiology and Screening

GW

Ovarian Cancer
Key Statistics

- Highest mortality rate of all gynecologic malignancies
  - Fifth in cancer deaths among women
    - 21,410 diagnoses
    - 13,770 deaths
- Overall 5 year survival rate: 46%
  - Confined to the ovary: 95%
  - Stage IV: 18%
- 75% are detected at advanced stage

ACS, CA Cancer J Clin 2009; 59(4): 225-249

GW

Screening for ovarian cancer

No effective screening test
for the general population!

Risk reducing BSO for women at highest risk for epithelial ovarian/fallopian tube cancer

Menon U, et al. Lancet Oncol, March 10, 2009
Menon U et al: Obstet Gynecol 131:909-927, 2018

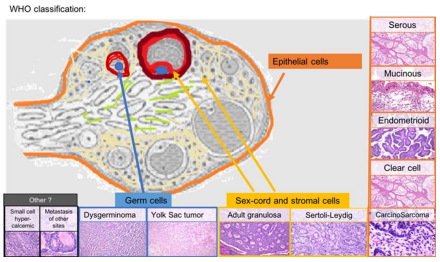
GW

Risk of Ovarian Cancer

Protective factors and Risk factors

Protective Factors	Risk Factors
Oral Contraceptives • Relative risk of 0.7 for 2 year use • Relative risk of 0.5 for >5 year use	Advancing age • < 40 incidence 1.4/100,000 • > 50% are over age 63 • 80% occur after age 40
Pregnancy, 1st full term < age 25	Infertility/Low parity
Multiple pregnancies	Family History
Breast Feeding	Early menarche (<12), late menopause (>52)
Tubal ligation	* Endometriosis (endometrioid,clear cell carcinoma)

Ovarian Cancer Classification



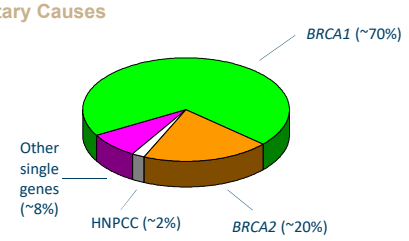
Int J Gynecol Cancer 202;30:879-887

Hereditary Syndromes

Syndrome	Gene	Tumor
Hereditary breast and ovarian syndrome	*BRCA1/2*	Epithelial carcinoma
HNPCC (Lynch)	Mismatch repair	Epithelial carcinoma
Peutz-Jeghers	*STK11*	Sex cord tumors
Nevoid basal cell carcinoma (Gorlin)	*PTCH1*	Ovarian fibromas Fibrosarcomas (rare)
Ollier Disease (Enchondromatosis)	EXT1,2,3	Juvenile Granulosa Cell

All women with ovarian cancer should undergo genetic testing for hereditary breast and ovarian cancer syndrome

Ovarian Cancer
Hereditary Causes



American Society of Clinical Oncology. Hereditary Breast and Ovarian Cancer. ASCO Curriculum guidelines. Alexandria, Va. 1999.

GW 10

BRCA Mutations

	Germline	Somatic
Origin	Inherited	Acquired
Prevalence	18%	7%

1. Pennington et al. Clin Cancer Res. 2014;20(3):764-75
2. Hennessy et al. J Clin Oncol. 2010;28(22):3570-6. 3. Petrucelli et al. In:
3. Pagon et al, eds. *GeneReviews® [Internet]*. https://www.ncbi.nlm.nih.gov/books/NBK1247/. Updated September 26, 2013.
4. Robson et al. J Clin Oncol. 2015;33(31):3660-7.

GW

Ovarian Cancer
Staging and Diagnosis

GW

Ovarian Cancer
FIGO Staging 2014

STAGE I: Tumour confined to ovaries	
IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings
IB	Tumour involves both ovaries otherwise like IA
IC: Tumour limited to 1 or both ovaries	
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumour on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings

STAGE II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues

STAGE III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		
IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)		
IIIA1	Positive retroperitoneal lymph nodes only	
	IIIA1(i)	Metastasis ≤ 10 mm
	IIIA1 (ii)	Metastasis > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extrapelvic, peritoneal metastasis < 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	

STAGE IV: Distant metastasis excluding peritoneal metastasis	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Ovarian Cancer
Classic Presentation

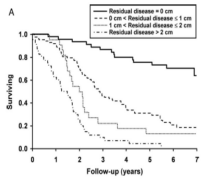
- Symptoms
  - Pelvic/abdominal pain
  - Abdominal bloating
  - Early satiety
  - Urinary changes
- Evaluation
  - Exam to assess for pelvic mass
  - Imaging of abdominal cavity
  - CA-125

Ovarian Cancer Treatment
Initial Diagnosis

Ovarian Cancer
Primary Surgical Cytoreduction

- Should be done by a gynecologic oncologist
- Goal: no residual disease
  - Significant survival advantage
  - Optimal: less than 1 cm residual deposits
  - Suboptimal: More than 1 cm deposits remaining at completion of surgery

Stage IIIC



Obstet and Gynecol. 2006;107(1) 77-85

Timing of the debulking surgery
Upfront surgery vs neoadjuvant chemotherapy?

- PFS similar in both groups
- Neoadjuvant chemotherapy (NACT)
  - Candidates for NACT
    - Poor operative candidates
    - Unlikely to be optimally cytoreduced
  - Poor operative candidates
- NACT treatment plan
  - 3-4 cycles of chemotherapy
    - Carboplatin/paclitaxel +/- bevacizumab
  - Assess for surgery
  - Additional chemotherapy after completion of surgery

J Clin Oncol. 2016;34(28):34600
Lancet 2015;386(9990)249-257
Lancet 2018; 19(12)1680-1687
NEJM 2010 363(10):943-53

Initial therapy recommendations

- Quality of the surgery is critical
  - Well trained gynecologic oncologist
  - Survival advantage
- Primary debulking
  - Generally favored *unless*:
    - Optimal debulking unlikely
    - Poor surgical candidate
  - Followed by 6* cycles of adjuvant platinum/taxane
    - Maintenance therapy (bevacizumab and/or PARPi)
- Neoadjuvant chemotherapy (NACT)
  - Reassess after 3-4 cycles
  - Continue chemotherapy after the interval surgery
  - If disease progression, no surgery
  - Consider maintenance in these patients as well

Bottom line. . .

- Assuming no contraindication, every patient should have one attempt/evaluation at surgical debulking
  - Goal should be no gross residual disease
  - Can be up front or interval (NACT)
  - Surgical quality is critical to outcome
    - Well trained gynecologic oncologist
    - Quality of the surgery impacts OS

Brief note on borderline and low grade ovarian tumors. . .

Borderline and low grade tumors

- Borderline tumors
  - Surgery
  - Excellent prognosis even with intra-abdominal spread (85% 5 yr OS)
  - Observation after surgery
- Low grade
  - Better prognosis than high grade
  - Adjuvant platinum based chemotherapy if advanced stage
    - Consider maintenance hormonal therapy after chemotherapy
    - Ongoing trial of chemotherapy versus hormonal therapy in LGS (Phase III; NRG-GY019)

J Clin Oncol 2017;35(10):1103-1111

Initial Management of Ovarian Cancer

Adjuvant Chemotherapy

Ovarian Cancer

Adjuvant chemotherapy (platinum/taxane)

- In everyone **except**:
  - Stage 1A/B grade 1
    - Tumor limited to inside the ovary
    - >95% 5 yr. relapse free survival
- Platinum/taxane
  - Usually carboplatin and paclitaxel
- Response rate: 60-80%
  - As many as 50% have a complete response
  - 75% of these patients will relapse
- Maintenance therapy
  - Bevacizumab
  - PARP inhibitors (Olaparib, niraparib)

Administration of carboplatin/paclitaxel

- Generally, regimen of choice (6-9 cycles)
  - Carboplatin AUC6/Paclitaxel 175 mg/m^2
- IP Chemotherapy
  - GOG172
    - Stage III, optimally debulked
    - More toxicity
    - Quality of life decreased in IP arm until 12 m

	IV	IP
Regimen	• Paclitaxel 135 mg/m^2/24h • Cisplatin 75mg/m^2 IV	• Paclitaxel 135 mg/m^2/24 hr D1 • Cisplatin 100mg/m^2 IP d2 • Paclitaxel 60mg/m^2 IP d8
PFS	24 m	18 m
OS	66 m	50 m

NEJM 2006;354:34-43.

Ovarian Cancer
IV or IP?

- GOG252 – (optimal debulking to 1 cm or less)

		PFS	P value HR (95% CI)
IV Carboplatin	Paclitaxel 80mg/m2/1h d1,8,15 Carboplatin AUC6 IV D1 Bevacizumab 15mg.kg/IV d1 starting cycle2	26.8 m	Reference arm
IP carboplatin	Paclitaxel 80mg/m2/1h d1,8,15 Carboplatin AUC6 IP D1 Bevacizumab 15mg.kg/IV d1 starting cycle 2	28.7m	0.416 0.947 (0.808-1.11)
IP cisplatin	Paclitaxel 135mg/m2/1h IV d1 Cisplatin 75mg/m2 IPd2 Paclitaxel 60mg/m2 IP d8 Bevacizumab 15mg/m2 d1 starting cycle 2	27.8m	0.727 1.01 (0.858-1.18)

Evidence for superior efficacy is not clear
IP chemotherapy causes more toxicity and has a greater impact on QOL
Careful patient selection, less commonly used now

NEJM 2006; 354:34-43

GW

Trial Design
JGOG 3016- "dose dense"

- Ovarian epithelial, primary peritoneal, or fallopian tube cancer
- FIGO Stage II-IV
- Stratified: residual disease, stage, and histology

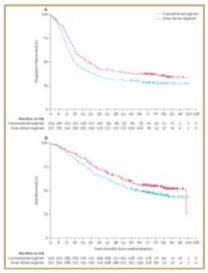
RANDOMIZE

Standard Arm: c-TC
Paclitaxel 180 mg/m^2, day 1
Carboplatin AUC 6,day 1
Q21 days for 6-9 cycles

Experimental Arm: dd-TC
Paclitaxel 80 mg/m^2 days 1,8, 15
Carboplatin AUC 6 day 1
Q21 days for 6-9 cycles

GW

JGOG 3016
Results



- PFS: 28.2 vs. 17.5m
  - 10.7m PFS benefit
    (HR 0.76, p=0.0037)
- OS: 100.5 vs. 62.2m
  - 38.3m PFS benefit
    (HR 0.79, p=0.039)

Lancet Oncol 14(10) 1020-1026.2013.

GW

GOG 262

Stage III/IV Disease: Large Volume Residual

RANDOMIZE

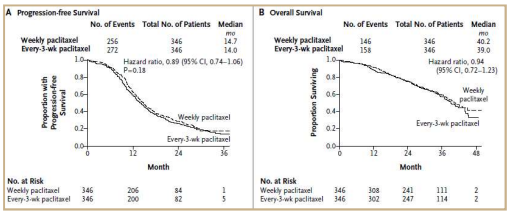
- Paclitaxel 80 mg/m2 IV every week + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression
- Paclitaxel 175 mg/m2 IV + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression

n = 625
Primary Endpoint = Progression free survival
Activated: Sep 27 2010
Study Chair: J Chan

ClinicalTrials.gov identifier: NCT01167712

GOG 262

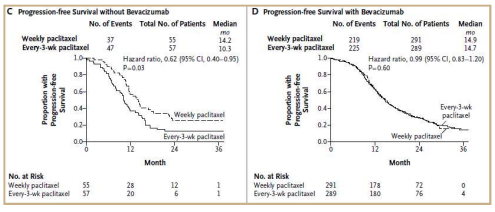
Results



NEJM 2016;374:738-748

GOG 262

Subgroup analysis



NEJM 2016;374:738-748

Trial Design

MITO-7

- FIGO IC-IV
- ECOG PS 0-2
- No prior chemotherapy
- Stratified: Center, PS, Residual disease

RANDOMIZE

Control arm: (403 pts.)
Carboplatin AUC 6 d1 q21
Paclitaxel 175 mg/m^2 d1 q21
6 cycles

Experimental arm: (405 pts.)
Carboplatin AUC 2 d1,8,15 q21
Paclitaxel 60 mg/m^2 d1,8,15 q21
6 cycles

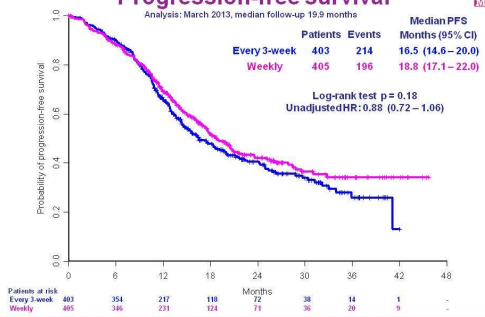
Primary endpoint: PFS , QoL
Secondary endpoints: QoL, OS, Toxicity, RR

Progression-free survival

Analysis: March 2013, median follow-up 19.9 months

	Patients	Events	Median PFS Months (95% CI)
Every 3-week	403	214	16.5 (14.6 – 20.0)
Weekly	405	196	18.8 (17.1 – 22.0)

Log-rank test p = 0.18
Unadjusted HR: 0.88 (0.72 – 1.06)



Presented by: S.Pignata

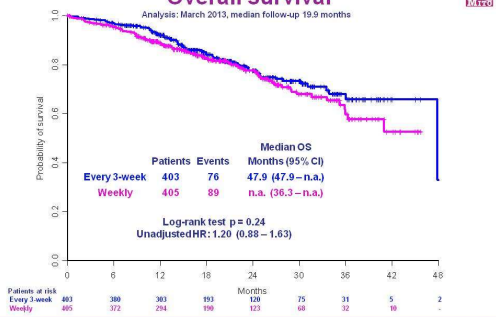
PRESENTED AT: ASCO Annual '13 Meeting

Overall survival

Analysis: March 2013, median follow-up 19.9 months

	Patients	Events	Median OS Months (95% CI)
Every 3-week	403	76	47.9 (47.9 – n.a.)
Weekly	405	89	n.a. (36.3 – n.a.)

Log-rank test p = 0.24
Unadjusted HR: 1.20 (0.88 – 1.63)



Presented by: S.Pignata

PRESENTED AT: ASCO Annual '13 Meeting

Board Pearls

Initial therapy

- Combination of surgery and chemotherapy
  - Usually initial debulking unless contraindication
  - Platinum/taxane doublet unless stage IA grade 1
  - Generally at least 6 cycles
    - Can consider 3 in earlier stage
- Platinum doublet
  - Generally every three week carboplatin/paclitaxel
    - Abraxane if paclitaxel reaction
  - IP can be considered
    - Look for a contraindication
  - Weekly regimens also an option
    - Dose dense (more cytopenias)
    - MITO-7 (tends to be better tolerated in elderly)
- Consider maintenance therapy

Initial Maintenance Therapy

Maintenance Therapy

- Two main options
  - Bevacizumab
    - Given with the chemotherapy and continued
      - Initial therapy
      - Platinum sensitive recurrence
      - Platinum resistant recurrence
  - PARP inhibitors
    - Given after completion of platinum based chemotherapy
      - After initial therapy
        - Need to respond to initial platinum doublet
      - After platinum sensitive recurrence
        - Need to respond to most recent platinum therapy

Maintenance Therapy
Paclitaxel

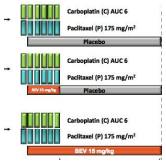
- Paclitaxel maintenance
  - GOG 178/SWOG 9701
    - 262 women
    - CR after plt/taxane
    - 175 mg/m2 paclitaxel q 28d for 3 vs. 12m
    - PFS 22 vs. 14m p=0.006
    - OS 53 vs. 48m p=0.34
    - Significant neurotoxicity, alopecia etc.

J Clin Oncol 2003;21:2460-2465; Gynecol Oncol 2009;114:195-198.

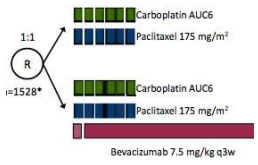
Bevacizumab in Ovarian Cancer
Initial Therapy

Bevacizumab

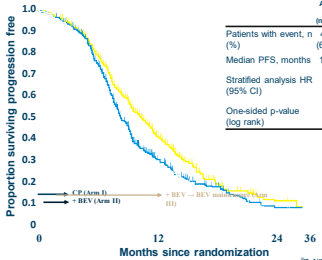
GOG 218



ICON 7



GOG-0218: PFS



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]

No OS benefit

[a]p-value boundary = 0.0116

NEJM 2011; 365:2473-2483

ICON 7 Results

Parameter	Protocol defined analysis	Post hoc analysis High risk disease
PFS	HR= 0.87; p=0.039	
CP	17.4m	
CP + Bev and Bev maintenance	19.8m	
OS	HR=0.84, p=0.099	HR=0.64; p=0.002
CP	45.5m	34.5m
CP + Bev and Bev maintenance	44.6m	45.5m

High risk: Stage IV, suboptimally debulked (>1cm) stage III, inoperable stage III

Lancet Oncol. 2015;16:928-36

Bevacizumab in front line therapy

- FDA approved June 2018
  - Front line in combination with carboplatin/paclitaxel and maintenance therapy in stage III and IV debulked ovarian/fallopian/primary peritoneal cancer
- Recent update:
  - Can also use PARPi maintenance therapy (will discuss in few slides)
  - FDA approval of adding olaparib to the maintenance therapy after front line treatment based on PAOLA-1 clinical data (if HRD)
    - (PFS advantage, but no olaparib only arm on the trial)

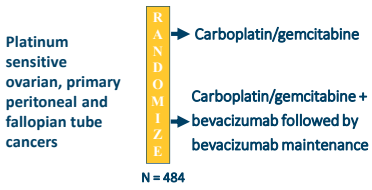
NEJM 2019; 381:2416-2428

Bevacizumab
Platinum Sensitive Disease

Platinum sensitive recurrence

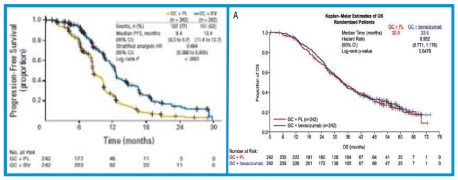
- Recurrence of 6 months or more after completion of prior platinum regimen
- Retreat with a platinum doublet
  - Carboplatin/paclitaxel
  - Carboplatin/liposomal doxorubicin
  - Carboplatin/gemcitabine
- Generally a minimum of 6 cycles

Ovarian Carcinoma
OCEANS Trial



Proc ASCO 2011: LBA 5007; J Clin Onc 2012:30(17):

OCEANS
Addition of bevacizumab



J Clin Oncol 2012 10;30(17):20392045

OCEANS
Addition of bevacizumab

Parameter	Gem/Carbo	Gem/Carbo Bev	
Patients	242	242	
Response Rate	57.4%	78.5%	P<0.0001
Median PFS	8.4 mos	12.4 mos	HR 0.484, p<0.001
Median OS	29.9 mos	35.5 mos	HR 0.751, p=0.094

J Clin Oncol 2012 10;30(17):20392045

Bev after Bev?

Ovarian Carcinoma

MITO16B – MaNGO OV2B – ENGOT OV17

- Stages IIIB-IV in first relapse after frontline chemo/bev
- PFI ≥6 mos
- PS 0-2
- RECIST progression +/- measurable disease
- Normal organ function
- Tumor samples for molecular analysis

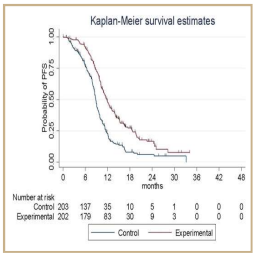
RANDOMIZE

- Platinum-Based Chemotherapy
- Chemotherapy plus Bevacizumab Bevacizumab Maintenance

- Primary Endpoint: PFS
- Patients: 400 (265 events)

Ovarian Carcinoma (PFS)

MITO16B – MaNGO OV2B – ENGOT OV17

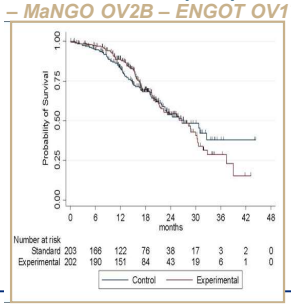


	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Ovarian Carcinoma (OS)

MITO16B – MaNGO OV2B – ENGOT OV17



	Chemo	Chemo/Bev	Log Rank P
Event	68	79	
Med OS	27.1 mo	26.6 mo	0.98
HR (95% CI)			0.97 (.70-1.35)

Bev after Bev: Response

MITO16B – MaNGO OV2B – ENGOT OV17

	Chemo	Chemo/Bev	P value
Patients	143	130	
Responders	94 (65.7%)	97 (74.6%)	0.14
CR	9 (6.3%)	20 (15.4%)	
PR	85 (59.4%)	77 (59.2%)	

Summary

Bevacizumab

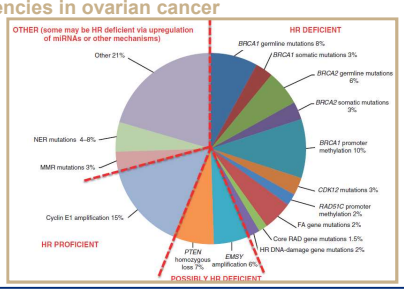
- Bevacizumab an active agent in ovarian carcinoma
- Induces responses and improves PFS
- Can be used in front line and platinum sensitive and resistant recurrences
- Can be used repeatedly

PARP Inhibitors

PARP inhibitors (PARPi)
Background

- PARPi prevent repair of ssDNA breaks in tumors with HR deficiencies, leading to cell death
- 10-15% of epithelial ovarian cancer are deficient in HR due to germline BRCA1 or BRCA2 mutations
- Up to 50% of patients with high grade serous ovarian cancer could have deficient HR

PARP inhibitors
HR deficiencies in ovarian cancer



Cancer Discovery 5(11):1137, 2015

PARP inhibitors
Agents and Indications in Ovarian Cancer

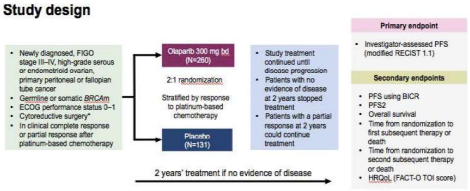
Agent	Maintenance therapy*	Monotherapy
Olaparib (Lynparza)	• Front line (BRCAm) • Front line HRD positive in combination with bevacizumab • Recurrent platinum sensitive	Third recurrence with gBRCA
Rucaparib (Rubraca)	• Recurrent platinum sensitive	Second recurrence gBRCA or sBRCA
Niraparib (Zejula)	• Front line (all women) • Recurrent platinum sensitive	Third recurrence with HRD

* Must have had a response on current therapy

PARPi in Front Line Therapy

SOLO 1

Study design

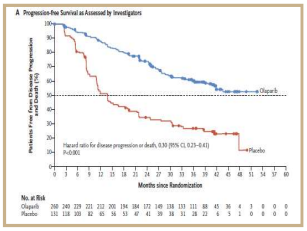


Moore K, NEJM 2018

Olaparib

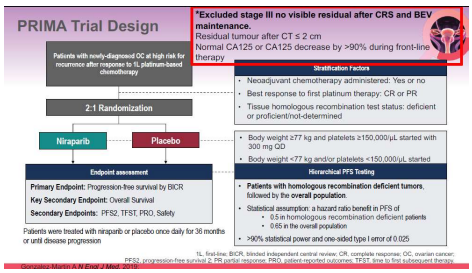
Front line maintenance

- FDA APPROVAL 12/2018
- Maintenance treatment of adult patients with *gBRCAm or sBRCAm* advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy
- Not given during the chemotherapy (unlike bev)



NEJM 2018; 376:26

PRIMA

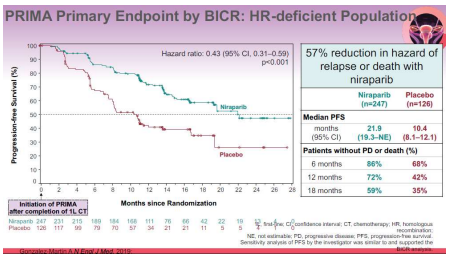


50% had tumors with HR deficiency

NEJM 2019 381;2391-2402

PRIMA

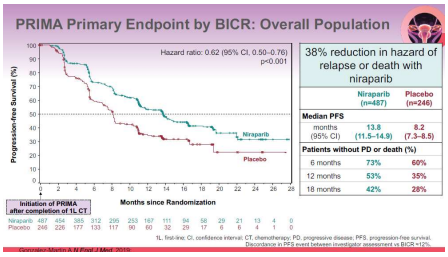
Niraparib maintenance



NEJM 2019 381;2391-2402

PRIMA

Niraparib maintenance



NEJM 2019 381;2391-2402

PRIMA subgroups

Exploratory analyses

- *BRCA* mutation
  - 22.1m versus 10.9m (HR 0.40 CI:0.27-0.62)
- *BRCA*wt/HRD+
  - 19.6m versus 8.2m (HR 0.50 CI:0.31-0.83)
- *BRCA*wt/HRD-
  - 8.1m versus 5.4m (HR 0.68 CI:0.49-0.94)
- PR to platinum
  - 8.3m vs 5.3m (HR 0.60)
- CR to platinum
  - 16.4m vs 5.6m (HR 0.60)

NEJM 2019 381;2391-2402

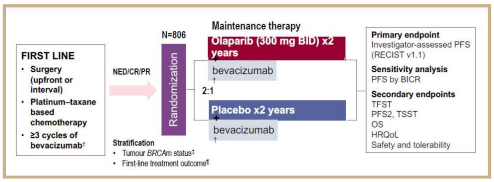
Niraparib Maintenance Therapy

- April 29, 2020
  - Niraparib approved for the maintenance treatment of adult patients with advanced epithelial, fallopian tube, primary peritoneal cancer who are in complete or partial response to first-line platinum base chemotherapy.
  - The recommended niraparib dose for first-line maintenance treatment of advanced ovarian cancer is based on body weight or platelet count. For patients weighing less than 77 kg (170 lbs) OR with a platelet count of less than 150,000/µL, the recommended dose is 200 mg taken orally once daily. For patients weighing greater than or equal to 77 kg (170 lbs) AND who have a platelet count greater than or equal to 150,000/µL, the recommended dose is 300 mg taken orally once daily.

www.fda.gov

PAOLA-1

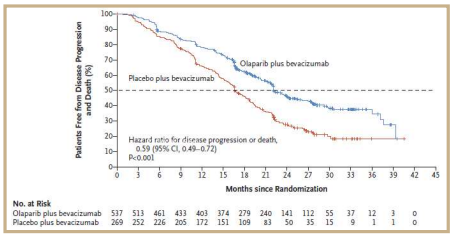
Olaparib and bevacizumab



No olaparib only arm

ESMO 2019; NEJM 2019; 381:2416-2428

PAOLA-1
Primary endpoint: PFS in ITT Population



NEJM 2019; 381:2416-2428

PAOLA-1
Olaparib and bevacizumab

	PFS	HR (95% CI)
ITT	22.1m v. 16.6m	0.59 (0.49-0.72)
BRCA	37.2m v. 21.7m	0.31(0.20-0.47)
HRD (w/o BRCA)	28.1m v. 16.6m	0.43 (0.28-0.66)
HRP	16.6m v. 16.2m	HR 1.00 (0.75-1.35)

NEJM 2019; 318:2416-2428

PAOLA-1
Conclusions

- Bevacizumab and olaparib can safely be given together
- Improvement in PFS (22.1m vs. 16.6m; HR 0.59)
  - Most notable in BRCAm
- No olaparib only arm
- No OS results available yet

- May 8, 2020
  - FDA approval of the combination who have had a CR/PR after platinum based adjuvant therapy associated with HRD positive status

www.fda.gov

PARP Inhibitors

Front line maintenance clinical data summary

Trial	Subgroup	PFS	HR (95% CI)
SOLO-1	BRCA 1/2	56.0m vs.13.8m	0.3 (0.23-0.41)
PRIMA	ITT	13.8m v. 8.2m	0.62 (0.5-0.76)
	HRD	21.9m v. 10.4m	0.43 (0.31-0.59)
	HRP	8.1m v. 5.4m	0.68 (0.49-0.94)
PAOLA-1	ITT	22.1m v. 16.6m	0.59 (0.49-0.72)
	gBRCA	37.2m v. 21.7m	0.31(0.20-0.47)
	HRD	37.2m v. 17.7m	0.33 (0.25-0.45)
	HRP	16.6m v. 16.2m	HR 1.00 (0.75-1.35)

PARPi in first line therapy

- Two options
  - Olaparib
    - FDA approved for BRCAm (germline or somatic) who have responded to first line therapy
    - Twice daily dosing
    - Also in combination with bevacizumab in HRD
  - Niraparib
    - FDA approved for all women who have responded to first line therapy
    - Once daily dosing
- Not without side effects. . .
  - Nausea, fatigue
  - AML/MDS

PARPi Maintenance: Recurrent platinum sensitive

Olaparib, Rucaparib, and Niraparib

SOLO 2
Olaparib

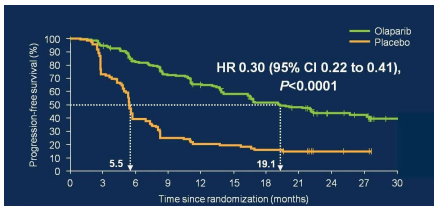
- •gBRCA1/2m
- •platinum sensitive recurrent EOC
- • ≥ 2 prior lines of plt tx
- •CR or PR to most recent therapy

RANDOMIZE

- **Olaparib 300 mg BID** (n=196)
- **Placebo** (n=203)

Primary Endpoint: PFS
Secondary Endpoints: OS

SOLO 2
PFS Results



SGO 2017; Lancet 18(9):1274-1284 2017

SOLO 2
Overall survival

	Olaparib n=196	Placebo n=99
Cumulative exposure of ≥ 5 years	43 (22.1%)	9 (9.1%)
OS events	116 (59%)	65 (65%)
Median OS, months	51.7	38.8
HR (95% CI)	0.74 (0.54-1.00)	
P value	0.0537	

Journal of Clinical Oncology 2020 38:15_suppl, 6002-6002

ARIEL 3
Trial Design

- Platinum sensitive recurrent EOC
- HGS and endometrioid histology
- ≥ 2 prior lines of plt tx
- CR or PR to most recent therapy

RANDOMIZE 2:1

- Rucaparib 600 mg BID
- Placebo

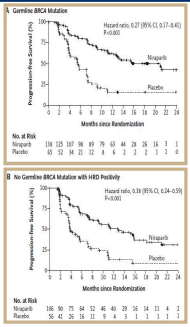
Primary Endpoint: PFS
Secondary Endpoints: OS

PARPi Maintenance therapy
ARIEL 3 (Rucaparib)

ARIEL3 Analysis Population	PFS by Investigator Review *(Primary Endpoint)*		PFS by Blinded Independent Central Review *(Key Secondary Endpoint)*	
Primary Analyses				
	Hazard Ratio	Median PFS (months) Rucaparib vs. Placebo	Hazard Ratio	Median PFS (months) Rucaparib vs. Placebo
tBRCAmut (n=196)	0.23; p<0.0001	16.6 vs. 5.4	0.20; p<0.0001	26.8 vs. 5.4
HRD-positive (n=354)	0.32; p<0.0001	13.6 vs. 5.4	0.34; p<0.0001	22.9 vs. 5.5
Intent-to-Treat (n=564)	0.36; p<0.0001	10.8 vs. 5.4	0.35; p<0.0001	13.7 vs. 5.4
Exploratory Analyses				
BRCA# / HRD-positive (n=158)	0.44; p<0.0001	9.7 vs. 5.4	0.55; p=0.0135	11.1 vs. 5.6
BRCA# / HRD-negative (n=161)	0.58; p=0.0049	6.7 vs. 5.4	0.47; p=0.0003	8.2 vs. 5.3

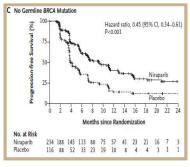
Lancet 390(10106)1949-1961. 2017
ESMO 2017, ESGO 2017

Niraparib Maintenance Therapy



21.0 vs 5.5 mo

12.9 vs 3.8 mo



9.3 vs 3.9 mo

HRD-negative: 6.9 mo vs 3.8 mo

Mirza MR, et al. *N Engl J Med*. 2016;375:2154-64

PARP inhibitors in recurrent platinum sensitive ovarian cancer

- Three FDA approved options:
  - Olaparib
  - Rucaparib
  - Niraparib
- Should see a response to the platinum regimen prior to the maintenance therapy
- PFS advantage seen with all three agents

PARPi as Treatment

PARP inhibitors

Agents and Indications in OVARY

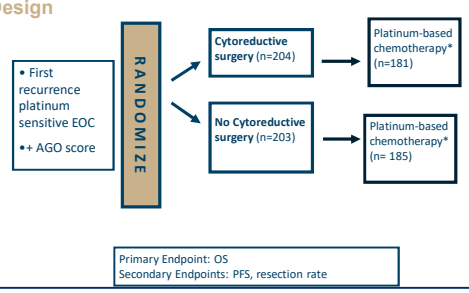
Agent	Maintenance therapy*	Monotherapy
Olaparib (Lynparza)	• Front line (BRCAm) • First recurrence, platinum sensitive	**Third recurrence with gBRCA**
Rucaparib (Rubraca)	• First recurrence, platinum sensitive	**Second recurrence gBRCA or sBRCA**
Niraparib (Zejula)	• Front line (all women) • First recurrence, platinum sensitive	**Third recurrence with HRD**

Secondary Debulking

Recurrent Platinum Sensitive Disease

DESKTOP III

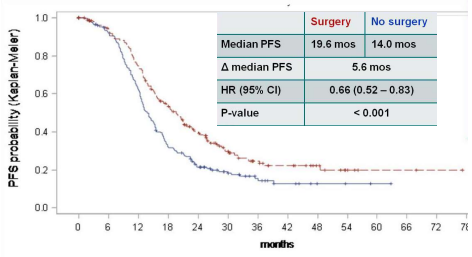
Trial Design



Primary Endpoint: OS
Secondary Endpoints: PFS, resection rate

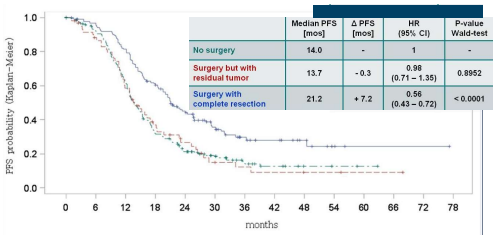
DESKTOP III

Results: Progression Free survival



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

DESKTOP III
PFS by surgical outcome



	Median PFS [mos]	Δ PFS [mos]	HR (95% CI)	P-value Wald-test
No surgery	14.0	-	1	-
Surgery but with residual tumor	13.7	- 0.3	0.98 (0.71 – 1.35)	0.8952
Surgery with complete resection	21.2	+ 7.2	0.56 (0.43 – 0.72)	< 0.0001

DESKTOP III
Conclusions

- Secondary cytoreductive surgery in PSROC resulted in a PFS and TTNT advantage
  - Benefit only seen in women who had complete resection
- Stresses the importance of selecting the appropriate patients and institution
- OS results presented at ASCO 2020
  - Survival advantage
  - (Not seen with GOG213) N Eng J Med 2019; 381:1929-1939.
- Consider secondary debulking in a platinum sensitive recurrence (referral to a gynecologic surgeon for evaluation)

Platinum sensitive disease recurrence

- Consider secondary debulking in select population
- Platinum doublet
  - Taxane,gemcitabine, PLD
  - Consider bevacizumab
- Maintenance therapy
  - Bevacizumab (if started with the chemotherapy)
  - PARPi (if not had prior, start after response seen with platinum doublet)
    - Olaparib, rucaparib, niraparib

Platinum Resistant Disease

Platinum Resistant Ovarian Cancer

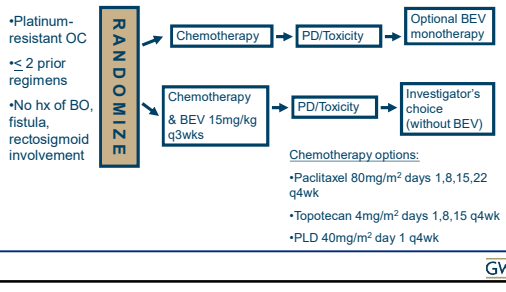
Overview

- Disease recurrence within 6 months of completion of platinum therapy
- Often use single agent therapy with an average response rate of 15-20%*
  - Gemcitabine
  - Topotecan
  - Liposomal Doxorubicin (PLD)
  - Docetaxel
  - Etoposide

*Current Oncology Reports 2006;6:448-54

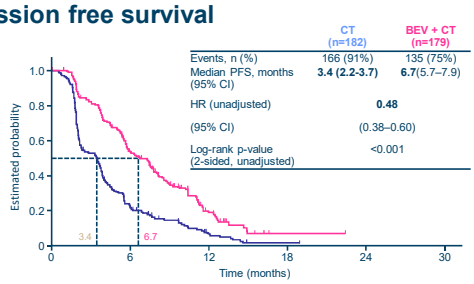
Trial Design

AURELIA



Progression free survival

AURELIA



	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)	**0.48**	
(95% CI)	(0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

Ovarian Cancer Recurrence

Key Take home points

- Disease recurrence
  - CA-125 usually goes up prior to disease on imaging
    - No benefit in OS or QOL to treat a rising CA-125
  - Assess the treatment free interval (initial chemotherapy)
    - Platinum sensitive (more than 6 months)
      - Consider secondary debulking
      - Platinum based chemotherapy
        - Carboplatin
        - Paclitaxel, gemcitabine, liposomal doxorubicin
        - Consider bevacizumab or PARPi maintenance
    - Platinum resistant (less than 6 months)
      - Single agent therapy
        - PLD, topotecan, etoposide, gemcitabine, docetaxel
      - Consider addition of bevacizumab
  - No current approval for immunotherapy (RR 8%-KEYNOTE100)

Nonepithelial Cancers of the Ovary

- 10% of ovarian cancers
- Two major subtypes
  - Germ cell
  - Sex cord stromal

Malignant Germ Cell Tumors

Malignant Germ Cell Tumors

- Account for 1-2% of ovarian cancers
  - Rare, most benign
- Younger women (median age 16-20)
- Often diagnose early stage
  - Rapid growth with associated symptoms
- Excellent prognosis overall 5yr OS 85%
- Fertility sparing surgery appropriate in most cases
- Elevated HCG or AFP in some cases, can follow

Ovarian germ cell tumors

NON-DYSGERMINOMAS

- Endodermal sinus tumor
  - (yolk sac)
- Immature teratomas
- Mixed germ cell
- Choriocarcinoma
- High risk of recurrence if not stage I , but chemosensitive

- Management
  - Surgery
  - Systemic therapy*
    - BEP

Observation for stage 1, grade 1 immature teratoma

DYSGERMINOMAS

- More likely to be bilateral
  - Usually stage 1 at diagnosis

- Management
  - Stage I, completely resected
    - Consider observation
  - Adjuvant chemotherapy
    - BEP

Management

- Consider fertility sparing procedure
- No adjuvant chemotherapy
  - Stage 1 dysgerminomas
  - Stage 1, grade 1 immature teratomas
- All others: adjuvant chemotherapy
  - BEP (3-4 cycles)
  - Adjuvant and no gross residual disease:3 cycles
  - Gross residual disease: 4 cycles

J Clin Oncol. 1994 Apr;12(4):701-6

GW

Sex Cord-Stromal Tumors

GW

Ovarian sex cord-stromal tumors (MSCST)

- Develop from the sex cord
  - Sertoli cell tumor
  - Granulosa cell tumor
- Develop from stromal cells
  - Fibroma
  - Thecoma
  - Leydig
- Both
  - Sertoli-leydig
- Generally, lower grade, lower stage at diagnosis
- Account for less than 8% of ovarian cancers
- Some secrete androgens or estrogens or other steroid hormones

GW

Granulosa cell tumor

- Most common type of MSCST
  - 2-5% of all ovarian cancers
  - 90% of malignant SCSTs
  - Usually an indolent growth pattern
  - Inhibin, particularly inhibin B may be elevated
  - Frequently produce estrogen
    - Endometrial bx, if uterus not removed
- 2 subtypes
  - Adult type: 95% (*FOXL2 somatic mutation*)
  - Juvenile type: 5%
- Adult type
  - Median age 52
  - 80-90% diagnosed stage I
  - 10-30% recur

Treatment
MSCST

- Surgery
  - Hysterectomy and bilateral salpingo-oophorectomy
  - Early stage
    - Can consider fertility sparing procedure if confined to ovary
- Post operative management
  - Observation (can recur late)
  - Stage II-IV (category 2B)
    - BEP versus carboplatin/paclitaxel (ongoing phase II trial; NCT02429700)
    - Hormonal therapy
    - Radiation therapy for limited disease
  - Can follow inhibin levels

Recurrence
MSCST

- Potential surgery
- Cisplatin based chemotherapy
- Hormone therapy
  - Granulosa cell tumors
- Angiogenesis inhibitors
  - Bevacizumab (GOG Phase 2 RR 16.7%)
- Radiation therapy

Cancer 2014: Feb;120(3):334-51

Thank You!