The 3 Musketeers: PARP, PROC and Platinum

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Presenter disclosure

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- Not applicable

Objectives

- Understand the difference between platinum sensitive versus platinum resistant as it relates to the treatments for Gynecological Cancers
- Review the use of bevacizumab in Gynecological Cancers
- Review AUC dosing of carboplatin in Gynecological Cancers
- Review the use of PARP inhibitors in ovarian cancer

Platinum sensitive versus platinum resistant

Definition of platinum-sensitive: response lasting greater than 6 months from last platinum dose (recurrence occurs after at least 6 months of platinum-based chemotherapy)

Definition of platinum-resistant: response lasting less than 6 months from last platinum dose (recurrence occurs less than 6 months from the platinum-based chemotherapy)

Current landscape for ovarian cancer - BRCA positive

1st line	• Carboplatin + Paclitaxel X 6 rounds (dose dense or regular)
2nd line (more than 6 months after 1st line)	• Repeat with carboplatin + paclitaxel or • Carboplatin + liposomal doxorubicin
Maintenance	• If partial or complete response to 2nd line therapy and BRCA mutation positive then olaparib twice daily until disease progression or unacceptable toxicity

Current landscape for ovarian cancer – BRCA mutation negative

1st line

- Carboplatin + Paclitaxel x 6 cycles (dose dense or regular)

2nd line (greater than 6 month respoonse from 1st line)

- Repeat carboplatin + paclitaxel
- Carboplatin + liposomal doxorubicin
- Once chemo complete, observation.

3rd line

- Platinum sensitive: repeat carboplatin + paclitaxel
- Platinum resistant: bevacizumab + chemo (liposomal doxorubicin, topotecan or paclitaxel)

Bevacizumab for cervix

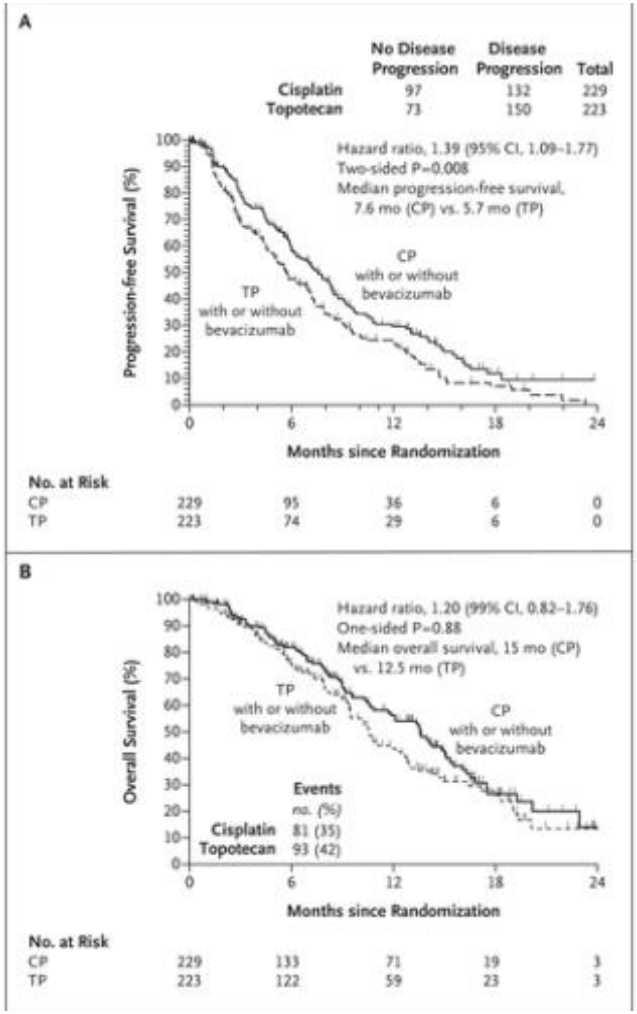
- In combination with CARBOplatin and PACLitaxel for the treatment of patients with:

i) Metastatic, persistent or recurrent cervical carcinoma AND

ii) An Eastern Cooperative Group Performance Status of 0 or 1 AND

iii) Adequate renal, hepatic and bone marrow function.

Why is bevacizumab used for cervix cancer?



Tewari, K.S..; Sill M.W. er al. Improved Survival with Bevacizumab in Advanced Cervical Cancer. NEJM 2014; 370:734-43.

What is the dose?

- Bevacizumab dosing in cervix is 15 mg/kg IV on day 1 in combination with paclitaxel 135 to 175 mg/m2 IV on day 1 and carboplatin with AUC = 5 IV on day 1
- Given every 21 days
- Note: bevacizumab is given last
- Continues until disease progression or unacceptable toxicity

What monitoring is required?

- Blood pressure prior to each infusion
- Monitoring for proteinuria (urinalyis or dipstick)
- CBC, biochemistry, hepatic and renal function tests prior to each cycle

Risks?

Table 1. Selected Adverse Events among the Study Patients, According to Treatment Group.*

Event	Chemotherapy Alone (N=219)	Chemotherapy plus Bevacizumab (N=220)	Odds Ratio (95% CI)	P Value
	no. of patients (%)			
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)§	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)§	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

Tewari, K.S..; Sill M.W. er al. Improved Survival with Bevacizumab in Advanced Cervical Cancer. NEJM 2014; 370:734-43.

Bevacizumab for ovarian – focusing on the PROC patients

- Bevacizumab in combination with liposomal doxorubicin, topotecan or paclitaxel for the treatment of patients with:

i) Advanced stage recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer AND

ii) Disease recurrence within 6 months after completing a platinum-based chemotherapy regimen AND

iii) Who have received no more than 2 prior lines of anticancer regimens AND

iv) ECOG performance status of 2 or less.

What are the advantages of using bevacizumab in the platinum-resistant ovarian cancer setting?

Table 1. Key efficacy outcomes of bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer[2]

		Bevacizumab plus Chemotherapy (n=179)	Chemotherapy Alone (n=182)
Progression-Free Survival (PFS)	Median (95% CI) [months]	6.7 (5.7-7.9)	3.4 (2.2-3.7)
	Unstratified HR (95% CI)	0.48 (0.38-0.60; log-rank p<0.001)	
Objective response rate (ORR)	RECIST and/or GCIG CA-125 criteria (350 evaluable patients)	30.9%	12.6%
		Two-sided X^2 p<0.001	
	RECIST (287 evaluable patients)	27.3%	11.8%
		Two-sided X^2 p=0.001	
	GCIG CA-125 (297 evaluable patients)	31.8%	11.6%
		Two-sided X^2 p<0.001	
Overall survival (OS)	Median (95% CI) [months]	16.6 (13.7-19.0)	13.3 (11.9-16.4)
	Unstratified HR (95% CI)	0.85 (0.66-1.08; log-rank p<0.174)	

Notes: GCIG-CA-125 = Gynecologic Cancer Intergroup HR= Hazard Ratio

https://cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_proc_fn_rec.pdf

Quality of life improved

Quality of life: improvement in HRQoL

Health-related quality of life (HRQoL) was assessed at baseline and every two or three cycles until disease progression, using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Ovarian Cancer Module (QLQ-Ov28) and the Functional Assessment of Cancer Therapy-Ovarian Cancer symptom index (FOSI). The primary HRQoL endpoint was that a higher proportion of patients in the bevacizumab plus chemotherapy arm would achieve at least a 15% (≥15-point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline. At week 8/9, a higher proportion of patients in the bevacizumab plus chemotherapy arm had achieved a ≥15% improvement in QLQ-OV28 abdominal/GI symptom scores compared with the chemotherapy arm (21.9% versus [vs.] 9.3%, respectively; difference 12.7%, 95% CI 4.4 to 20.9; p=0.002). pERC also noted that in a subgroup analysis of 99 evaluable patients with ascites at baseline who were expected to have considerable pain and GI symptoms, 44% of patients who received bevacizumab plus chemotherapy experienced a ≥15% improvement in pain and GI symptoms compared with 4.1% in the chemotherapy alone arm (difference 39.9%, 95% CI 23.9% to 55.9%; p<0.001). pERC was impressed by the effort in the data collection and reporting of HRQoL from the AURELIA trial.

https://cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_proc_fn_rec.pdf

What is the dose of bevacizumab used?

Protocol	Dosing
Bevacizumab in combination with liposomal doxorubicin	Bevacizumab 10mg/kg IV on days 1 and 15 and liposomal doxorubicin 40mg/m2 IV on day 1 ONLY (every 28 days) – continue until disease progression
Bevacizumab in combination with topotecan	Bevacizumab 15 mg/kg IV on day 1 and topotecan 1.25 mg/m2 IV on days 1 to 5 (every 21 days) – continue until disease progression
Bevacizumab in combination with paclitaxel	Bevacizumab 10 mg/kg IV on days 1 and 15 and paclitaxel 80mg/m2 IV on days 1, 8, 15 and 22 (28 days cycle) – continue until disease progression or unacceptable toxicity

What monitoring needs to occur for bevacizumab?

- Urine protein (when urinalysis is not possible, then dipstick is acceptable. If lab urinalysis for protein is greater than or equal to 1g/L or dipstick proteinuria shows 2+ or 3+, then prescriber should be notified).
- Blood pressure prior to each bevacizumab dose
- Signs and symptoms of fistulization

Risks?

Table 6. Summary of Adverse Events of selected grade ≥2 & Grade ≥3 & AEs of special interest[2,7]	Bevacizumab plus Chemotherapy (n=179) [%]	Chemotherapy Alone (n=181) [%]
Hypertension		
Grade ≥2	20	7
Grade ≥3	7	1
Proteinuria, Grade ≥3	2	0
GI Perforation		
Grade ≥2	2	0
Grade ≥3	2	0
Fistula/abscess		
Grade ≥2	2	0
Grade ≥3	1	0
Bleeding, Grade ≥3	1	1
Thromboembolic event, Grade ≥3	5	4
Arterial, Grade ≥3	2	0
Venous, Grade ≥3	3	4
Wound-healing complication, Grade ≥3	0	0
Reversible posterior leukoencephalopathy syndrome, Grade ≥3	1	0
CHF, Grade ≥3	1	1
Cardiac disorders, Grade ≥3 (excluding CHF)	0	0
Notes: AEs= Adverse Events Only grade 2-5 AEs were collected in the AURELIA trial. CHF= congestive heart failure; GI=gastrointestinal.		

https://cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_proc_fn_rec.pdf

Area under the curve dosing for CARBOplatin

Calvert equation:

Carboplatin dose (mg) = Target AUC X (GFR + 25)

GFR uses Cockcroft-Gault Equation:

$$\text{CrCl (female; mL/min)} = \frac{N \times (140 - \text{age}) \times (\text{weight in kg})}{\text{serum creatinine}}$$

N = 1.04 in females

Gyne Oncology uses actual body weight for all their carboplatin dosing procotols.

Maximum dose = 900mg (cap at 900mg dose)

Example 1

- 42 year old with metastatic cervix cancer in which physician wants to start carboplatin in combination with paclitaxel and bevacizumab with the following information

Actual body weight = 120kg

Height = 158 cm

Serum creatinine = 68 mmol/L

GFR = [N X (140-age) X body weight]/scr = [1.04 X (140-42) X 120kg]/68 = 180mL/minute

Carboplatin dose = AUC X (GFR+25) = 5 X (180 + 25) = 1025mg

However, **in real life cap dose at 900mg** in Gyne-Onc clinic.

Example 2

- 64 year old female with stage IV serous ovarian cancer being treated with carboplatin + paclitaxel in the first line setting.
- Values as follows

Cycle #	Body weight	Scr	Calculated carboplatin dose	Ordered carboplatin dose
1	74	68	555 mg	555 mg
2	73.4	72	530mg	555mg
3	72.8	81	466mg	555mg

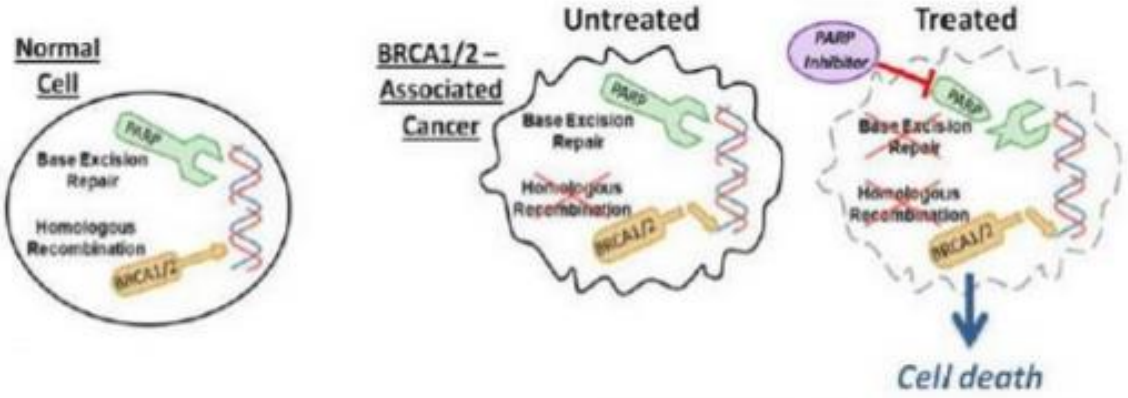
Question often asked: Do we need to change the carboplatin dose with each cycle – general rule of thumb is if carboplatin dose stays with 10 % of patient's previous dose, then okay to keep same dose as previous cycle. In this case, ordered carboplatin dose with cycle #2 is okay (within 4.5%). Cycle 3 dose should be adjusted as 16% difference from previous cycle.

PARP inhibitors – Focusing on olaparib (Lynparza)

- ~20 to 30% of high-grade serous ovarian cancers have the BRCA mutation.
- BRCA are human genes that produce tumor suppressor proteins (important to help repair damaged DNA).
- Olaparib is used for BRCA mutated **platinum sensitive** relapsed ovarian cancer
- Platinum sensitive = retreatment with paclitaxel and carboplatin only if patient had at least 6 months response with initial treatment.

Mechanism of action slide here

PARP Inhibitors: Mechanism



- PARP and BRCA1/2 normally function to repair daily DNA damage
- Allows cells to grow in a healthy way
- Too much DNA damage-> cell death

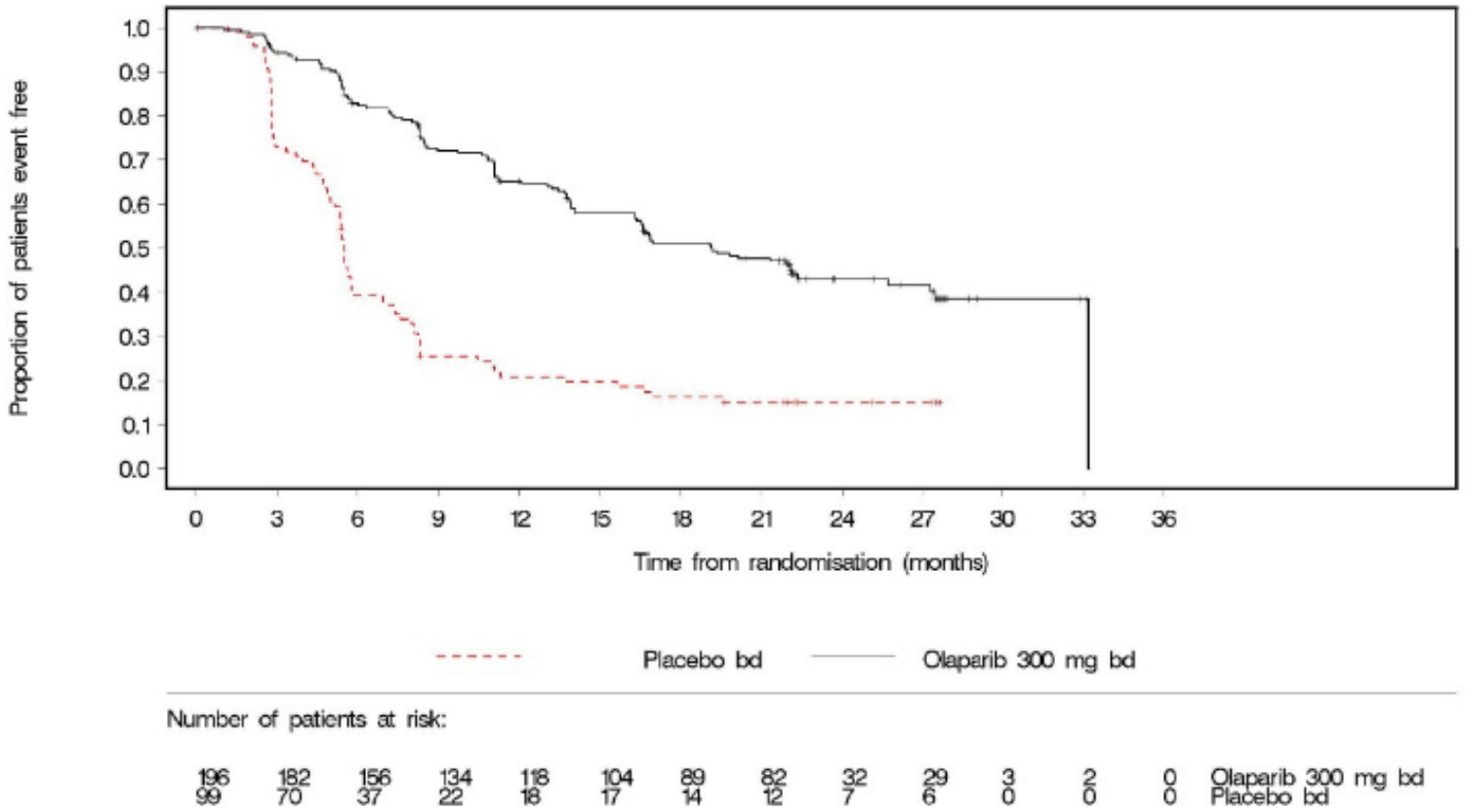
- If BRCA1/2 is damaged or not working, the cell is dependent on PARP for all DNA repair
- PARP inhibitors prevent DNA repair in cancer cells
  - May increase cancer cell death
  - May help chemo and radiation work better

Ellisen, Cancer Cell 2011; Tutt et al, Lancet 2010

https://www.google.com/search?q=olaparib+mechanism+of+action+slide&client=firefox-b&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjnpP

SOLO-2

Figure 2 **SOLO2: Kaplan-Meier Plot of PFS in Patients with g*BRCA*mutated PSR Ovarian Cancer[a]**



Tablets versus capsules

- Tablet and capsules are NOT interchangeable: that means that a 300mg dose using capsules is NOT equivalent to a 300mg dose using tablets

- Dose should starts no later than 8 weeks after completion of their final dose of the platinum-containing regimen and continues until disease progression or unacceptable toxicity.

Formulation	Dosing
Tablets	300mg (2 tablets of 150mg) twice daily
Capsules	400mg (8 capsules of 50mg) twice daily

Bioavailability

- Bioavailability of the tablet formulation is higher than the capsule formulation.
- Population PK showed that steady-state exposure (AUC) following 300mg tablet twice daily was 77% higher compared to that following 400mg capsule twice daily.
- Important to note that all new patients start on ***TABLET*** formulation.

Main side effects

- Blood work needs to be checked as it can cause anemia, neutropenia and thrombocytopenia. Suggested monitoring of CBC is once a month for 12 months and then periodically.
- Generally well tolerated.
- Small risk of MDS/leukemia
- Small risk of pneumonitis

Side effects on trial

System Organ Class/ Preferred Term	LYNPARZA 300 mg tablets twice daily N = 195	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Blood and Lymphatic System Disorders		
Anemia[a]	85 (43.6)	38 (19.5)
Neutropenia[a]	38 (19.5)	10 (5.1)
Thrombocytopenia[a]	27 (13.8)	2 (1.0)
Leukopenia[a]	31 (15.9)	5 (2.6)
Lymphopenia[a]	2 (1.0)	1 (0.5)
Gastrointestinal Disorders		
Nausea	148 (75.9)	5 (2.6)
Vomiting	73 (37.4)	5 (2.6)
Diarrhea	64 (32.8)	2 (1.0)
Dyspepsia	22 (11.3)	0
Upper Abdominal Pain	21 (10.8)	0
Stomatitis	20 (10.3)	2 (1.0)

Side effects on trial continued

System Organ Class/ Preferred Term	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Fatigue (including asthenia)	128 (65.6)	8 (4.1)
Investigations		
Increase in creatinine	21 (10.8)	1 (0.5)
Mean corpuscular volume elevation	1 (0.5)	0
Metabolism and nutrition disorders		
Decreased appetite	43 (22.1)	0
Nervous system disorders		
Headache	49 (25.1)	1 (0.5)
Dysgeusia	52 (26.7)	0
Dizziness	26 (13.3)	1 (0.5)
Respiratory, thoracic and mediastinal disorders		
Cough	35 (17.9)	1 (0.5)
Skin and Subcutaneous Tissue Disorders		
Rash[a]	16 (8.2)	0
Dermatitis[a]	2 (1.0)	0

Other important points

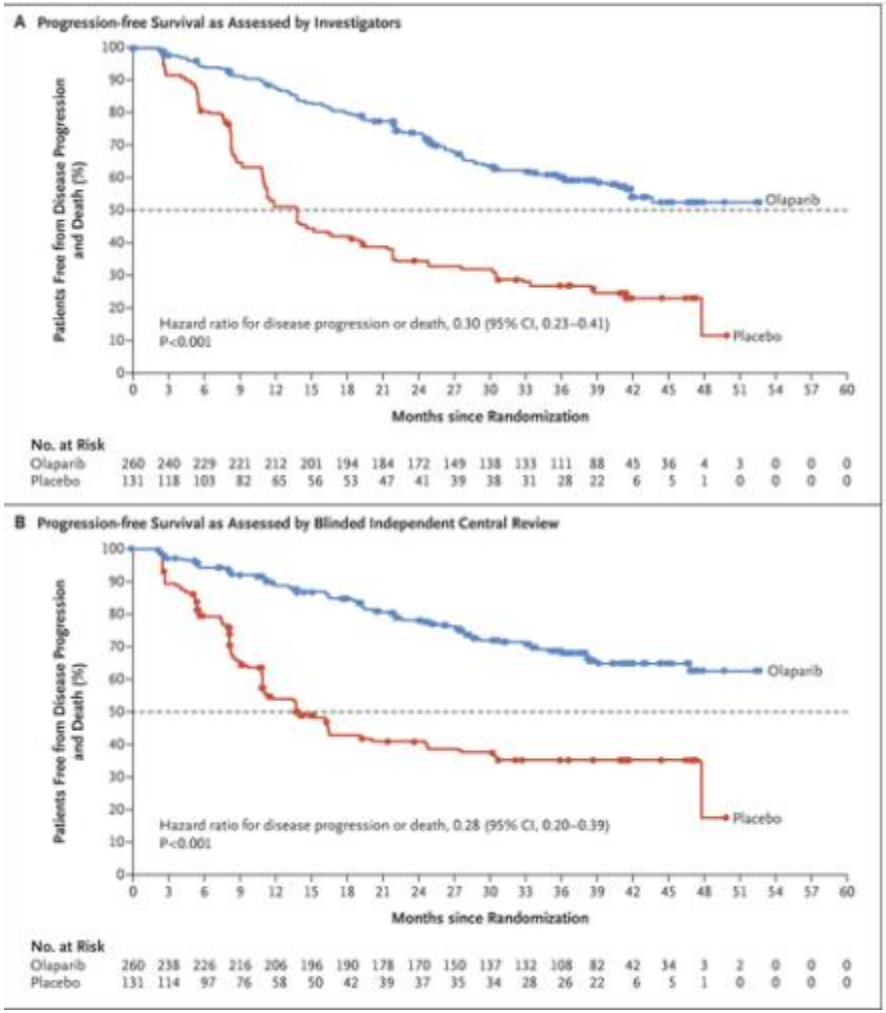
- Grapefruit/grapefruit juice needs to be avoided while on olaparib.
- Drug-drug interactions: need to check before starting a new medication.
- Tablets should be swallowed whole and can be taken with or without food.
- Olaparib should start no later than 8 weeks after completion of the patient' final dose of platinum-containing regimen.
- Capsules are stored in refrigerator and tablets are stored at room temperature.

Sneak peak ahead….(SOLO-1)

- SOLO-1 trial was a phase 3 trial that evaluates olaparib as maintenance therapy in patients with newly diagnosed advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer with BRCA mutation who had a complete or partial clinical response after platinum-based chemotherapy.

Moore, K.. Colombo, N. et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. NEJM (October 21st, 2018)

Progression free survival



Moore, K.. Colombo, N. et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. NEJM (October 21st, 2018)

Adverse events

Table 2. Summary of Adverse Events.*

Adverse Event	Olaparib (N = 260)		Placebo (N = 130)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any	256 (98)	102 (39)	120 (92)	24 (18)
Nausea	201 (77)	2 (1)	49 (38)	0
Fatigue or asthenia	165 (63)	10 (4)	54 (42)	2 (2)
Vomiting	104 (40)	1 (<1)	19 (15)	1 (1)
Anemia†	101 (39)	56 (22)	13 (10)	2 (2)
Diarrhea	89 (34)	8 (3)	32 (25)	0
Constipation	72 (28)	0	25 (19)	0
Dysgeusia	68 (26)	0	5 (4)	0
Arthralgia	66 (25)	0	35 (27)	0
Abdominal pain	64 (25)	4 (2)	25 (19)	1 (1)
Neutropenia‡	60 (23)	22 (9)	15 (12)	6 (5)
Headache	59 (23)	1 (<1)	31 (24)	3 (2)
Dizziness	51 (20)	0	20 (15)	1 (<1)
Decreased appetite	51 (20)	0	13 (10)	0
Upper abdominal pain	46 (18)	0	17 (13)	0
Dyspepsia	43 (17)	0	16 (12)	0
Cough	42 (16)	0	28 (22)	0
Back pain	40 (15)	0	16 (12)	0
Dyspnea	39 (15)	0	7 (5)	0
Thrombocytopenia§	29 (11)	2 (1)	5 (4)	2 (2)
Led to discontinuation of intervention	30 (12)	NA	3 (2)	NA
Led to dose reduction	74 (28)	NA	4 (3)	NA
Led to dose interruption	135 (52)	NA	22 (17)	NA

Moore, K.. Colombo, N. et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. NEJM (October 21st, 2018)

Take home messages

- Treatments in the recurrent setting are usually dictated by the platinum status (sensitive versus resistant setting)
- Bevacizumab does have its benefits in metastatic cervix cancer and in the platinum resistant ovarian cancer, but is not for everyone (some women may decline due to risk of fistulization)
- Carboplatin AUC dosing is important in the Gynecological setting and ACTUAL body weight should be used in calculating the CARBOplatin dosing
- Maximum carboplatin dose is 900mg in Gyne Onc regimens
- PARP inhibitors are here and the first one is olaparib. There are other PARP inhibitors coming to Canada. BRCA mutation dictates the olaparib treatment and in the future will be given to women after 1st line treatment (at the current time, only funded in the recurrent platinum sensitive setting)