NCCN Virtual Nursing Program:
Advancing Oncology Nursing™

Wednesday, March 17, 2021
2:15 PM – 3:00 PM EDT

Navigating Treatment Selection for Patients with Advanced Ovarian Cancer

Paula Anastasia, RN, MN, AOCN
UCLA Health

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

Learning Objectives

- Describe to a patient some of the key factors to consider when selecting among the recommended options for treatment of recurrent/refractory ovarian cancer.
- Describe considerations when choosing between chemotherapy options versus targeted therapies for treatment of persistent/recurrent disease.
- Outline for a patient the signs and symptoms associated with recurrent and/or progressive disease versus toxicity from different types of treatment, and explain option for management to improve quality of life.

Epithelial Ovarian Cancer (EOC) (including Fallopian Tube and Primary Peritoneal Carcinoma):

Prolonging Survival in the Setting of Recurrent/Refractory Disease

Ovarian Cancer: Surgery and Chemotherapy is not Enough ~ The need for targeted therapy

- Ovarian cancer 2021 statistics
  - 21,410 estimated new cases; 13,770 estimated deaths
  - Leading cause of death from gynecologic cancer
  - New cases decreasing 2.5% each year from 2008-2017 (SEER)
  - Death rates decreasing by 2.3% from 2009-2018 (SEER)
  - Overall 5-year survival rate ~48.6% from 2010-2016 (SEER)
  - Survival in patients with distant disease, 30%; localized disease, 92%
  - ~80% diagnosed stage II-IV; Majority have serous histology
- Standard of care
  - Surgical debulking with optimal cytoreduction and combination platinum-taxane–based therapy
  - Majority of patients will have multiple recurrences resulting in lack of chemo-sensitivity.

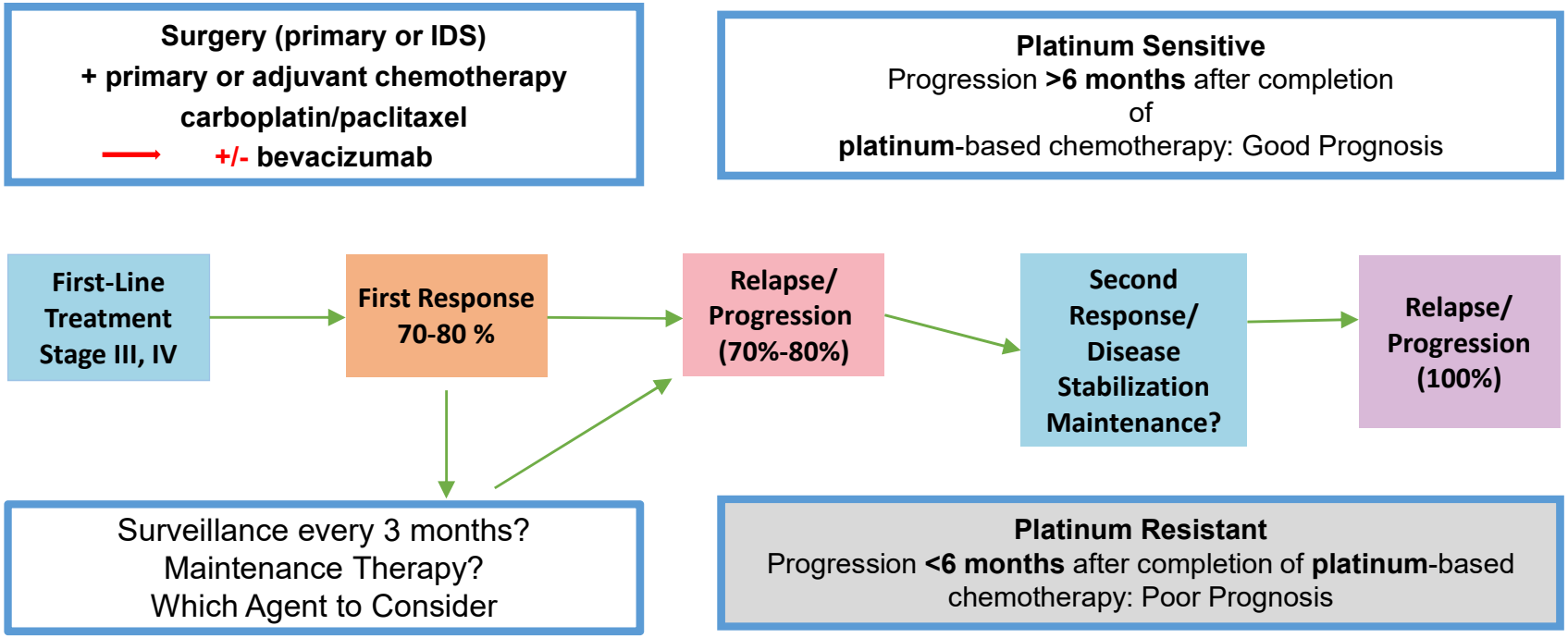
SEER: Surveillance, Epidemiology, and End Results Program. https://doi.org/10.3322/caac.21654; National Cancer Institute 2021 https://seer.cancer.gov/statfacts/html/corp.html.
Siegel RL, et al. CA Cancer J Clin 2021;71:7-33.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer (Version 1.2021). Available at: NCCN.org.
Lheureux S, et al. Lancet 2019;393:1240-1253.

Diagnostic Procedures

- Requires tissue or cytology for diagnosis.
  - Imaging does not determine diagnosis
- Paracentesis (ascitic fluid)
- Thoracentesis (pleural effusion)
- Laparoscopy or exploratory laparotomy to obtain tissue for diagnosis
- CA-125 blood test is not diagnostic but if elevated at time of pathology confirmed diagnosis, often used as one measure of treatment response

Cancer.org ovarian cancer 2021

Typical Course of Advanced Ovarian Cancer



Approximately 5% of patients are primary treatment refractory, meaning disease progressed during therapy or within 4 weeks after the last dose.
IDS, interval debulking surgery.

1. Ledermann JA, et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S, et al. *Ann Oncol.* 2017;28(suppl_8):viii51-viii56.
4. du Bois A, et al. *Cancer*. 2009;115(6):1234-1244. 5. Wilson MK, et al. *Ann Oncol*. 2017;28(4):727-732.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

Primary Systemic Therapy Recommended Dosing

IV/IP Paclitaxel/cisplatin
- Paclitaxel 135 mg/m² IV continuous infusion[i] 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/carboplatin q3weeks[j]
- Paclitaxel 175 mg/m² IV followed by carboplatin[k] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[j]

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)[h]

Docetaxel/carboplatin[j]
- Docetaxel 60–75 mg/m² IV followed by carboplatin[k] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[j]

Carboplatin/liposomal doxorubicin[j]
- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m² IV
- Repeat every 28 days for 3–6 cycles[j]

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (ICON-7)
- Paclitaxel 175 mg/m² IV followed by carboplatin[k] 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[g] (GOG-218)
- Paclitaxel 175 mg/m² IV followed by carboplatin[k] 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[9]
- Paclitaxel 135 mg/m² IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles[j]

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)

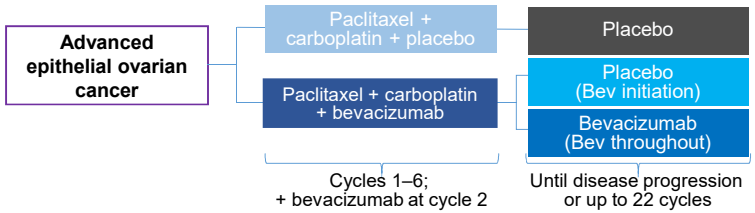
Carboplatin[9]
- Carboplatin AUC 5 IV given every 21 days

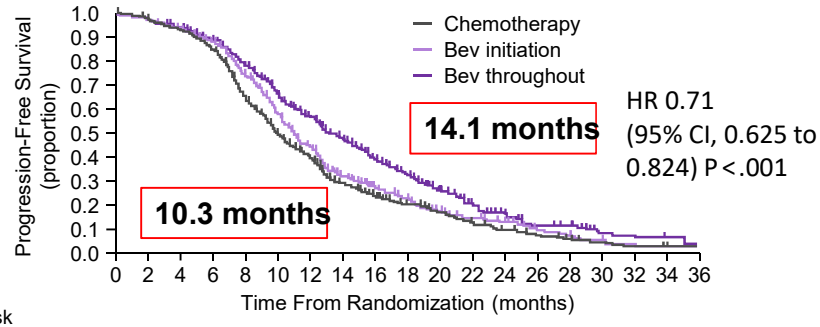
Most common regimens

In what scenario would bevacizumab be considered in front-line setting with paclitaxel/carboplatin?

Frontline Bevacizumab: Progression-Free Survival

GOG 218[1]

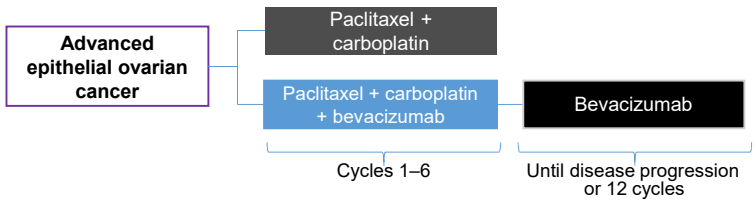


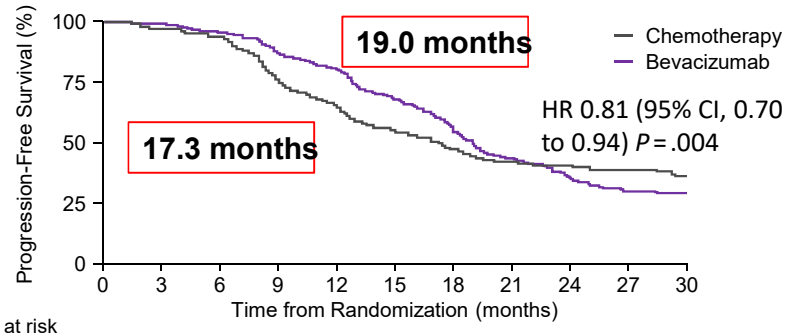


No. at risk

Chemotherapy	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

ICON7[2]





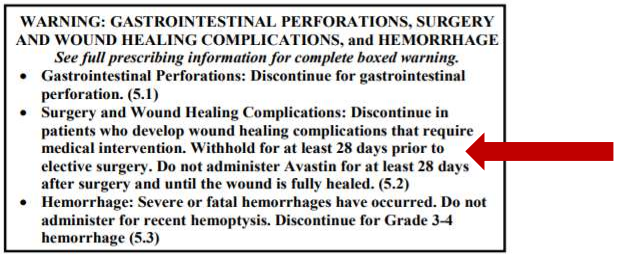
No. at risk

Chemotherapy	764	693	464	216	91	25
Bevacizumab	764	715	585	263	73	19

Burger RA, et al. *N Engl J Med.* 2011; Perren TJ et al. *N Engl J Med.* 2011

What common side effects do you educate your patients regarding bevacizumab?

- Hypertension (what are your parameters)
- Proteinuria
- Headache
- Epistaxis
- Rhinitis/Sinusitis
- Do you need to consider any modifications for bevacizumab administration prior to or after surgery ?



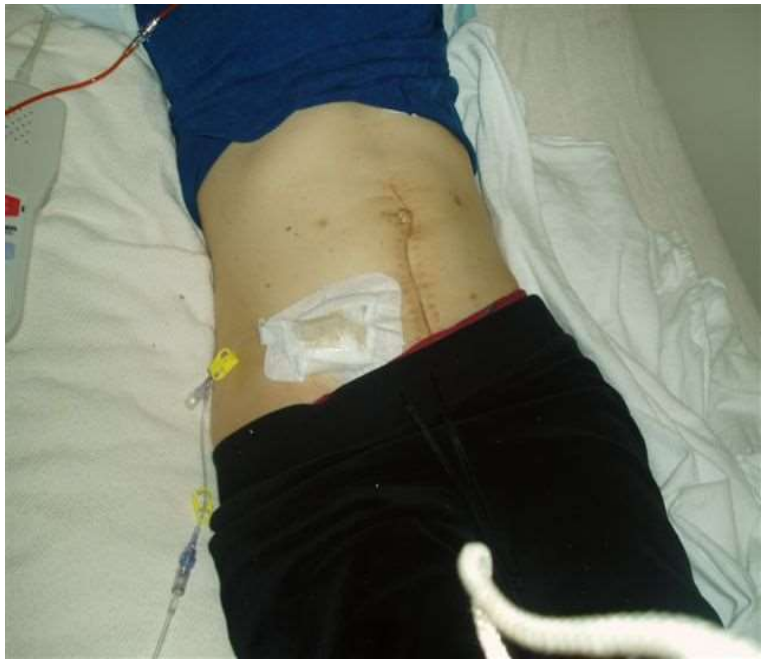
WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Gastrointestinal Perforations: Discontinue for gastrointestinal perforation. (5.1)**
- **Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery and until the wound is fully healed. (5.2)**
- **Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)**

Burger, R.A., Brady, M.F., Bookman, M.A, et al, NEJM 2011: 365: 2473-2483. http://www.ncbi.nlm.nih.gov/pubmed/22204724

IP/IV Chemotherapy



IP/IV: Intraperitoneal /Intravenous
OS: overall survival
PFS: progression free survival

Although there are three randomized studies showing improved PFS/OS survival with IP/IV therapy compared to IV therapy, most physicians are not using due to:

1. Offering clinical trial as front line therapy (trial has no IP arm)
2. IP/IV therapy is time intensive with increased side effect profile

Photos courtesy of Paula Anastasia RN, MN, AOCN ; 2007

Armstrong, DK, et al., NEJM 2006;354:34:34-43; NCCN Guidelines for Ovarian Cancer, V1.2021

Importance of Genetics in Ovarian Cancer

- All women with a (pathologically confirmed) *diagnosis* of ovarian cancer ***should*** have genetic counseling and testing (panel testing)
  - Recommended by NCCN, SGO, ASCO, ESMO
  - Facilitates treatment decisions; cascade testing for cancer prevention
- Up to 40% of patients with germline *BRCA*1/2 (g*BRCA1/2*) pathogenic variants have no known family history
- Most commonly associated genes: *BRCA*1 and *BRCA*2
  - 10%-15% of patients with ovarian cancer may have *BRCA1/2* pathogenic variants
  - *BRCA*1 associated with ~44% risk of ovarian cancer (up to age 80)
  - *BRCA*2 associated with ~17% risk of ovarian cancer (up to age 80)
  - Other genes identified as high risk: *BARD1*, *BRIP1*, *MLH1*, *MSH2*, *MSH*6, *PALB2*, *PMS2*, *RAD51C*, *RAD51D*

NCCN Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic Guidelines, V2.2021
www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer 2020; www.asco.org/practice-guidelines/genetics-toolkit 2020; Konstantinopoulos, et al. 2015; Kuchenbaecker, et al. 2017; Norquist, et al. 2016.

Mutations Are a Feature of All Cancers

Germline

- Present in egg or sperm
- Can be inherited from mom or dad
- Cause family cancer syndrome

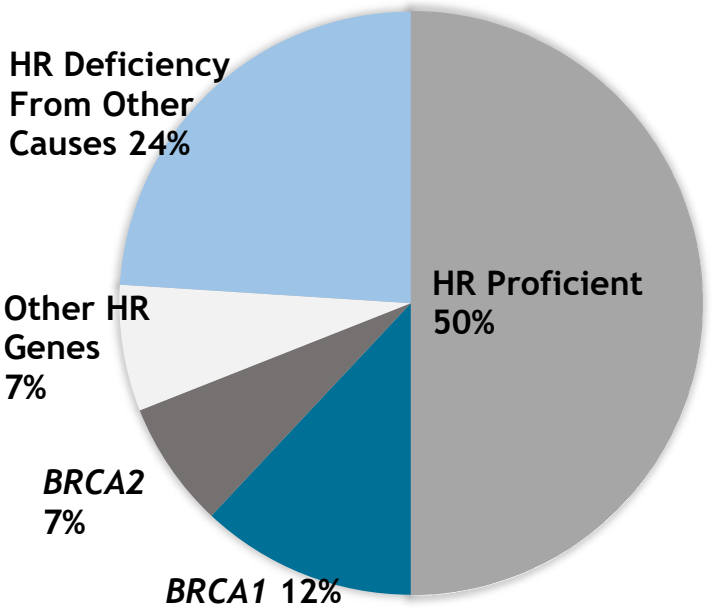
Somatic

- Occur in tumor tissues
- Cannot be inherited
- "Acquired"

Moschetta M, et al. Ann Oncol 2016;27:1449-1455; Petrucelli N, et al. In: GeneReviews. Seattle (WA): U of Washington, Seattle © 1993-2021.

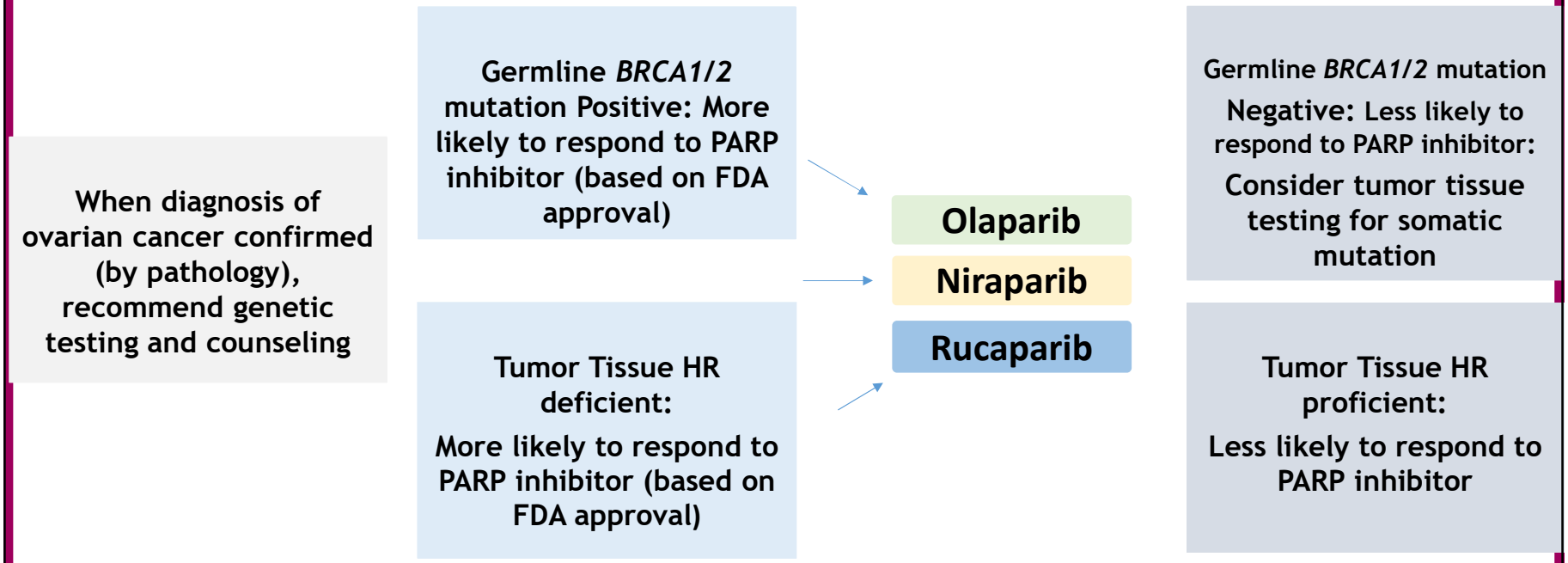
Homologous Recombination (HR) Pathway

- Homologous recombination pathway
  - One of the 2 primary pathways that repair double-strand breaks in DNA
- Deficiency in this pathway (aka, HR deficiency) leads to error-prone repairs that lead to an accumulation of mutations Resulting in cell death and risk for ovarian cancer
- 50% of high-grade serous ovarian cancers (HGSOC) are HR deficient



Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1187-1154. TCGA. *Nature*. 2011;474(7353):609-615. Norquist, et al. SGO 2016.

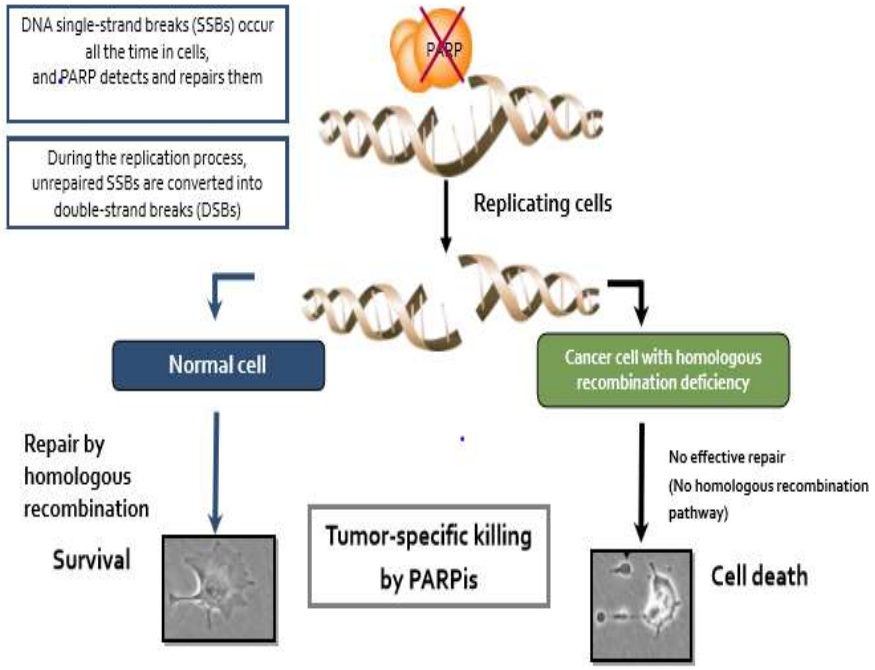
Genetics: When to Test and When to Treat



Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf
www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer 2020; www.asco.org/practice-guidelines/genetics-toolkit 2020

Rationale for Molecular Tumor Profile

- Molecular tumor profiling through next-generation sequencing (NGS) can determine genomic and molecular alterations in ovarian cancer and identify patients for targeted therapy
- Ovarian cancer tumors with deficient homologous recombination (HR) repair represent such a group and have demonstrated sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPi)



1. Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. 2. NCCN Guidelines for Ovarian Cancer. V1.2020.
3. Audeh MW, et al. *Lancet.* 2010;376(9737):245-251. 4. Ledermann J, et al. *Lancet Oncol*. 2014;15:852-861.

PARP Inhibitors: Real Time Reminders

- **Genetic testing** for all women with pathologically confirmed OC. Obtain family history and refer to genetic counselling to determine whether family members should be tested. Knowledge of family cancer syndrome and/or pathogenic variant can help with prevention and early diagnosis in family members.
- **Oral adherence**
  - PARPi: Review Patients Biomarker status; Review prior Hematologic Trends during chemotherapy prior to dosing. Is daily vs BID dosing relevant to your patient's adherence to taking a PARPi. Patients with multiple prior lines of chemotherapy may need to begin at a reduced dose. Proactive anti-emetics to prevent nausea, remind patient that symptoms improve 2-4 weeks.
  - Experiment with different dosing times of day/evening to mitigate nausea or insomnia if oral medications
  - No grapefruit or Seville oranges for patients taking olaparib
- **Accountability**: Who is in charge of reviewing patient lab results (especially if weekly labs), documentation and determining dose hold and or reductions?

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

Recurrent Disease: Majority of women with advanced ovarian cancer will have multiple recurrences

- May remain asymptomatic but rising CA-125: follow trends
  - if only rising CA-125 may opt to monitor until symptoms
- May manifest with abdominal pain, early satiety, bloating.
- May manifest as bowel obstruction: constipation, nausea and vomiting, abdominal distension (differentiate symptoms from treatment side effects)
- Confirming Recurrence:
  - Exam/Pelvic Exam (palpable mass)
  - CT or PET/CT (consider disease-free interval (DFI): if <1 year usually assume recurrence)
  - Biopsy (pathology confirmed)

NCCN Guidelines for Ovarian Cancer, V1.2021

Recurrent Ovarian Cancer: Treatment Decisions

- Determine disease free interval (DFI) since last platinum-based chemotherapy
- Prior adverse effects from prior chemotherapy: myelosuppresion, growth factor support? Transfusion? Residual Side effects
  - Comorbidities (Diabetes, hypertension, kidney disease)
- Performance status, life style, quality of life
- Measurable disease? Eligible for clinical trial
- Biomarkers: confirm germline genetic testing performed. Confirm tumor profiling sent.
- Patient goals: frequency of treatments (weekly, every other week, every 3 weeks, monthly) Oral vs IV. What side effects are they unwilling to consider (some may say alopecia)

NCCN Guidelines for Ovarian Cancer, V1.2021

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

RECURRENT Platinum Sensitive

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[l]/Fallopian Tube/Primary Peritoneal Cancer[m]

Recurrence Therapy for Platinum-Sensitive Disease[n] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[t]	Useful in Certain Circumstances
Carboplatin/gemcitabine[10] ± bevacizumab[g,o,p,11] Carboplatin/liposomal doxorubicin[12] ± bevacizumab[g,13] Carboplatin/paclitaxel[14] ± bevacizumab[g,o,p,15] Cisplatin/gemcitabine[16] Targeted Therapy (single agents) Bevacizumab[g,o,17,18] Niraparib[q,19] Olaparib[r,20] Rucaparib[s,21]	Carboplatin/docetaxel[22,23] Carboplatin/paclitaxel (weekly)[24] Capecitabine Carboplatin[u,10] Cisplatin[14] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine Targeted Therapy Niraparib/bevacizumab[g,25] Pazopanib (category 2B)[26] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[g,o] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[g,o] Carboplatin/paclitaxel, albumin bound (for confimed taxane hypersensitivity) Carboplatin/paclitaxel[u] (for age >70) Irinotecan/cisplatin (for clear cell carcinoma)[27] Targeted Therapy (single agents) Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[v] Trametinib (for low-grade serous carcinoma)[28] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Immunotherapy Pembrolizumab (for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors, or patients with tumor mutational burden-high [TMB-H] tumors ≥10 mutations/megabase and no satisfactory alternative treatment options)[v,29]

Recurrent Platinum Sensitive Ovarian Cancer

- Platinum Sensitive: defined as complete remission and recurrence ≥6 months since completing last platinum based therapy (good prognosis)
- Surgery may be option if have a good performance status, have no ascites, and have an isolated focus or limited foci of disease amenable to complete resection; would still require adjuvant chemotherapy
- Determine Clinical Trial Option
- Retreatment with Platinum Combination:
  - Choice determined by prior side effects and residual side effects from prior treatment (myelosuppression, peripheral neuropathy)
- Retreatment with carboplatin has higher incidence of hypersensitivity reaction than primary use

NCCN Guidelines for Ovarian Cancer, V1.2021; Koul, et al., Gynecology Oncology 2018, 148: 363-367

Pivotal Studies of PARPi Maintenance After Response to Platinum-based Chemotherapy For Recurrent OC

Study:	Study 19[1] N = 265	SOLO-2[2] g*BRCA*m N = 295	NOVA[3,4] g*BRCA*m N = 203	NOVA[3,4] Non-g*BRCA*m N = 350	ARIEL-3[5] *BRCA*m N = 196	ARIEL-3[5] ITT N = 564
Agent	**Olaparib**	**Olaparib**	**Niraparib**	**Niraparib**	**Rucaparib**	**Rucaparib**
PFS, test vs control (months)	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR (investigator assessed)	**0.35** (95% CI, 0.25 - 0.49; *P* < .001)	**0.30** (95% CI, 0.22-0.41; *P* < .0001)	**0.27** (95% CI, 0.18-0.40)	**0.53** (95% CI, 0.41-0.68)	**0.23** (95% CI, 0.16-0.34; *P* < .0001)	**0.36** (95% CI, 0.30-0.45; *P* < .0001)
PFS HR (BICR)	**0.39** (95% CI, 0.27-0.55; *P* < .001)	**0.25** (95% CI, 0.18-0.35; *P* < .0001)	**0.27** (95% CI, 0.17-0.41; *P* < .0001)	**0.45** (95% CI, 0.34-0.61; *P* < .0001)	**0.20** (95% CI, 0.13-0.32; *P* < .0001)	**0.35** (95% CI, 0.28-0.45; *P* < .0001)

BICR, blinded independent central review; gBRCAm, germline *BRCA1/2* mutation; HR, hazard ratio; ITT, intent-to-treat population. Note: In the absence of head-to-head data comparing PARP inhibitors, efficacy and safety comparisons between PARP inhibitors are not to be made or communicated.

1. Ledermann J et al. *N Engl J Med*. 2012;366(15)1382-1392. 2. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18(9):1274-1284. 3. FDA NDA review ref 4074987, application no 208447. 4. Mirza MR, et al. *N Engl J Med*. 2016;375(22)2154-2164. 5. Coleman RL et al. *Lancet*. 2017;390(10106):1949-1961.

PARP Inhibitors: FDA Approvals for Maintenance After Platinum-based Chemotherapy for Recurrent OC

Olaparib

Maintenance treatment for adult patients with **recurrent** OC in CR/PR to platinum-based chemotherapy.

(Regardless of germline mutation or HR status)

8/2017

Niraparib

Maintenance treatment for adult patients with **recurrent** OC in CR/PR to platinum-based chemotherapy.

(Regardless of germline mutation or HR status)

3/2017

Rucaparib

Maintenance treatment for adult patients with **recurrent** OC in CR/PR to platinum-based chemotherapy.

(Regardless of germline mutation or HR status)

4/2018

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

PARP Inhibitor Adverse Effects

Toxicity	Description	PARP Inhibitor (PARPi)
GI	Nausea, constipation, vomiting, diarrhea, ↑ LFT	All PARPi LFT: Rucaparib
Renal	Increase in creatinine (inhibits MATE inhibitors)	Rucaparib
Fatigue	Universal for all PARPi	ALL PARPi
Neurologic	Headaches/insomnia	ALL PARPi
Respiratory	Dyspnea/cough/pneumonitis	Olaparib
Cardiac	Hypertension/tachycardia	Niraparib
Skin	Photosensitivity	Rucaparib
Muscle	Arthralgia/back pain	ALL PARPi

GI, gastrointestinal; LFT, liver function tests.

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

PARP Inhibitor Dosing Guidelines Per FDA

	Olaparib	Rucaparib	Niraparib
Recommended dose (All Oral)	**300 mg BID (two 150-mg tablets) (total 600 mg daily)**	**600 mg BID (two 300-mg tablets) (total 1200 mg daily)**	**300 mg once daily (three 100-mg capsules)**
Dose level 1 reduction	250 mg BID (one 150-mg tablet and one 100-mg tablet) (total 500 mg daily)	500 mg BID (two 250-mg tablets) (total 1000 mg daily)	200 mg once daily (two 100-mg capsules)
Dose level reduction 2	200 mg BID (two 100-mg tablets) (total 400 mg daily)	400 mg BID (two 200-mg tablets) (total 800 mg daily)	100 mg once daily (one 100-mg capsule)
Dose level reduction 3		300 mg BID (one 300-mg tablet) (total 600 mg daily)	

BID, twice daily

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
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Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

PARP Inhibitor Hematologic Adverse Effects: Anemia Most Common for All PARPi

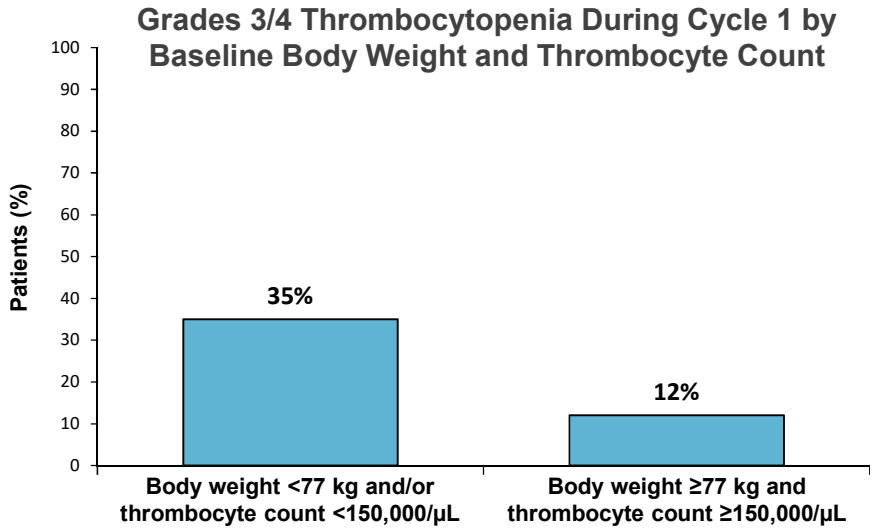
Percent %	Grade	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Decrease in hemoglobin	All Grades	90	67	50
	Grade 3 and 4	15	23	25
Decrease in platelets	All	30	39	**61**
	Grades 3 and 4	3	6	34
Decrease in neutrophil count	All	25	35	30
	Grades 3 and 4	7	10	20

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

The Rapid Adjustment of Dose to Reduce Adverse Reactions (RADAR) Analysis

Exploratory analysis of NOVA trial that examined predictive factors for the development of grades 3/4 thrombocytopenia

Niraparib: NOVA Phase 3 Maintenance Study in Platinum-Sensitive OC



The patients deemed to be most likely to develop thrombocytopenia had:

Baseline body weight <77 kg

and/or

Baseline thrombocyte count <150,000/µL

Berek JS, et al. Ann Oncol. 2018 May 14. Mirza MR, et al. *N Engl J Med*. 2016;375:2154-2164

Incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia with Parp Inhibitors

- Low risk, but patients need to be informed
- Know your patient's prior chemotherapy adverse event response, oncology history (eg, breast cancer, alkylating agent, pathogenic variant)
- Hematologic: persistent anemia or thrombocytopenia
  - Refer patients to hematologist if blood counts do not return to ≤ grade 1 within 4 weeks after holding drug or dose reduction; diagnosed by bone marrow aspiration
  - Other symptoms: weakness, fatigue, fever, weight loss
- Do not initiate a PARPi until lab values have recovered to grade <1 from prior chemotherapy

Agent	Trial	PARPi n (%)	Placebo n (%)
Niraparib	NOVA	8/367 (2.2)	2/179 (1.1)
Rucaparib	ARIEL 3	3/375 (0.8)	0/189 (0)
Olaparib	Study 19	2/136 (1.5)	1/129 (0.8)
	SOLO2 (initial)	4/195 (2.1)	4/99 (4.0)
	SOLO2 (final)	16/195 (8.2)	4/99 (4.0)

Prescribing information: olaparib tablets, for oral use 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf
Pujade-Lauraine E, et al. *Lancet Oncol.* 2017; 18(9): 1274-1284; Mirza MR, et al. *N Engl J Med.* 2016;375:2154-2164. Coleman RL, et al. *Lancet.* 2017;390:1949-1961.

Recurrent Platinum Resistant Ovarian Cancer

~**Platinum Resistant** is defined as complete remission and recurrence <6 months since completing last platinum-based therapy, or Platinum Refractory.

~**Platinum Refractory** is defined as progression while receiving initial platinum-based chemotherapy or progression after two consecutive regimens without clinical benefit or stable or persistent disease.

~Patients have poorer prognosis and should be counseled on Goals of Care, Clinical Trials

- If not already performed, may consider tumor tissue molecular markers for *BRCA1/2* mutation, HR deficiency: for PARP inhibitor. Identifying microsatellite instability, mismatch repair deficiency, or tumor mutational burden may determine possible response to immunotherapy.
- Patients with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without known acquired resistance mutation may respond to larotrectinib or entrectinib

NCCN Guidelines for Ovarian Cancer, V1.2021; Prescribing information for larotrectinib tablets 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf; Prescribing information for entrectinib capsules, 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

RECURRENT Platinum Resistant Disease

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy	**Cytotoxic Therapy**[t]	**Immunotherapy**
Cyclophosphamide (oral)/bevacizumab[g,30] Docetaxel[31] Etoposide, oral[32] Gemcitabine[33,34] Liposomal doxorubicin[33,34] Liposomal doxorubicin/bevacizumab[g,o,35] Paclitaxel (weekly)[36] Paclitaxel (weekly)/bevacizumab[g,o,35] Topotecan[37,38] Topotecan/bevacizumab[g,o,35]	Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[39] Vinorelbine	Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase and no satisfactory alternative treatment options)[v,29]
		Hormone Therapy
		Fulvestrant (for low-grade serous carcinoma)
Targeted Therapy (single agents)	**Targeted Therapy (single agents)**	**Targeted Therapy (single agents)**
Bevacizumab[g,o,17,18] Niraparib[q,19] Olaparib[r,20] Rucaparib[s,21]	Pazopanib (category 2B)[26]	Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[v] Trametinib (for low-grade serous carcinoma)[28]
	Hormone Therapy	
	Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	

Molecular Profiling of Tumor May suggest a gene deficiency or overexpression and guide treatment decisions

PARP Inhibitors: FDA Approvals for Monotherapy for Multiple Relapsed Disease

Olaparib

Treatment for adult patients with **g*BRCA*m** advanced OC who have been treated with **≥3 prior lines** of chemotherapy.

Based on companion diagnostic approved for olaparib.

12/2014

Niraparib

Treatment of adult patients with advanced OC who have been treated with **≥3 prior** lines of chemotherapy whose cancer is HRD positive

Based on companion diagnostic approved for niraparib.

10/2019

Rucaparib

Treatment for adult patients with **g*BRCA*m or s*BRCA*m** advanced OC who have been treated with **≥2 prior lines** of chemotherapy.

Based on companion diagnostic approved for rucaparib.

4/2018

gBRCAm, germline *BRCA1/2* mutation; sBRCAm, somatic *BRCA1/2* mutation

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Prescribing information: niraparib capsules, for oral use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
Prescribing information: rucaparib tablets, for oral use. 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf

Treatment for Recurrent Ovarian Cancer: Common Side Effects: May increase if given in combinations

Drug	Side Effects
Carboplatin OR Cisplatin	Carboplatin: Low Blood Counts; Allergic reactions can occur with later cycles and retreatment. Mild Nausea. Fatigue. Constipation Cisplatin: Nausea and Vomiting Common, Potential Dehydration, Kidney Problems; Constipation, Fatigue, Ear Ringing
Paclitaxel OR Docetaxel	Low Blood Counts, Hair loss, Allergic reactions can occur; Joint/Body Aches; Peripheral Neuropathy, Fatigue
Bevacizumab (monoclonal antibody, VEGF inhibitor)	High Blood Pressure, Protein in Urine, Joint aches, Delayed Wound Healing, Nosebleeds, Bowel Perforation (Rare)
Liposomal Doxorubicin (antibiotic agent/anthracycline-type chemotherapy)	Low Blood Counts, Nausea (may be delayed), Fatigue (may be delayed), Mouth sores, Hand-Foot syndrome (redness on hands/ feet can lead to blisters - ice packs on hands/feet during infusion helpful; can have Rash on body, Sensitive to Sun Burning
Pazopanib (kinase inhibitor)	Hepatotoxicity, Diarrhea, Hypertension, Neutropenia, Thrombocytopenia, Nausea,
Entrectinib (kinase inhibitor) Larotrectinib (kinase inhibitor)	Fatigue, edema, diarrhea, cognitive changes, dyspnea , lung infection, myalgia's, hypotension, weight gain Fatigue, nausea, anemia, increase AST/ALT, diarrhea

www.accessdata.FDA.gov

Fatigue

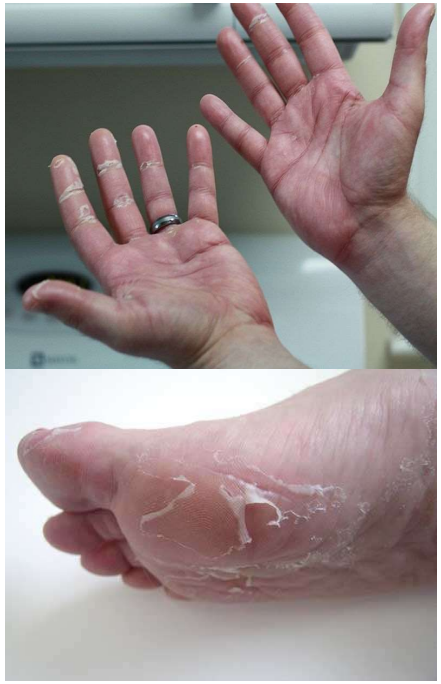
- LISTEN to your patient's weekly/monthly 'self report'.
  Educate that fatigue is common with PARPi, but often improves/plateaus by 2-4 weeks
  - Ask patient to rate their fatigue level and their level of function; may be two different answers. What are they unable to do this week/month that they were able to do last week/month? Ask partner/caregiver for their observation
  - If interferes with ADLs, consider holding drug one week, re-evaluate if dose reduction needed.
    Rule out other causes: anemia, insomnia, depression, hypothyroid, dehydration
- If other medical etiology ruled out, encourage exercise and staying active

NCI Common Terminology Criteria for Adverse Events v4.0

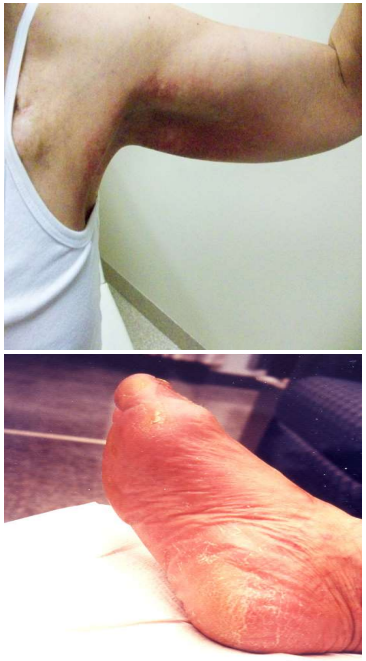
Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limited self care ADL

Grade 1, 2, 3 respectively

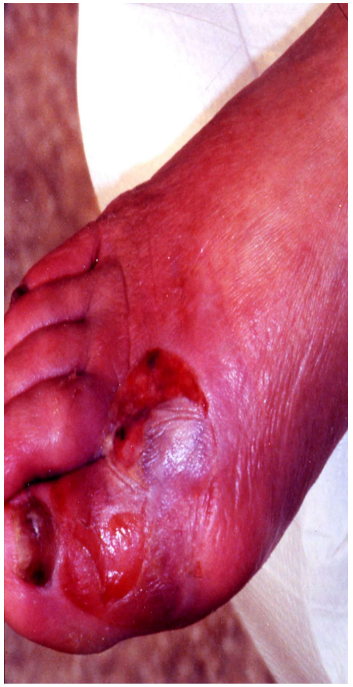
Palmar Plantar Erythrodysesthesia (PPE) or Hand-Foot Syndrome: Liposomal Doxorubicin



GRADE 1



GRADE 2



GRADE 3

Photos Courtesy of Paula Anastasia RN, Used with Permission

58-year-old with Stage IIIC High Grade Serous Ovarian Cancer

- 2017: Optimal debulking surgery and 6 cycles Paclitaxel and Carboplatin: Complete Response. Residual grade 1 neuropathy.
  - Germline panel testing negative
- 2019: Rising CA-125, CT scan reveals new pelvic mass and carcinomatosis.
  - Not a candidate for secondary cytoreductive surgery
- Original tumor sent for molecular profile
- Receives 6 cycles Carboplatin (over 3 hours and pre-medicated with oral dexamethasone day prior, to decrease hypersensitivity risk) and Liposomal Doxorubicin: Complete response.
  - Grade 1 fatigue, neuropathy, neutropenia

58-year-old with Stage IIIC High Grade Serous Ovarian Cancer: Now Platinum-Resistant Disease

- Molecular Profile Result: somatic BRCA2 mutation, no mismatch repair deficiency, no PD-L1 overexpression
- Maintenance Olaparib BID x 7 months
  - Dose reduced after 4 weeks due to grade 2 fatigue and grade 2 anemia
  - Rising CA-125, CT reveals carcinomatosis, new mass
- Cisplatin and Gemcitabine x 3 cycles
  - Gemcitabine dose reduced due to grade 2 neutropenia
  - Rising CA-125 and abdominal pain. CT reveals disease progression and new ascites
- Discuss clinical trials and standard of care treatments for platinum-resistant disease
- Bevacizumab and oral cyclophosphamide x 4 months (grade 2 hypertension)
  - Rising CA-125 and disease progression
- Currently: Weekly paclitaxel with stable disease, decrease in ascites

PD-L1 = Programmed death-ligand 1

Treatment Considerations for your Practice

- Individualized/Personalized Care: Reassure and Discuss Patient Goals
- Biomarkers: germline/somatic mutations: Patient with a *BRCA1/2* mutation or HR deficiency are more likely to respond to a PARP inhibitor than those with no biomarker variant
- **Patient Education:** Multiple recurrences and multiple chemotherapy regimes, therefore long term residual side effects
  - **Patient Lifestyle**
    - **Performance Status, home life, comorbidities, treatment frequency and follow up**
    - Side effects interfering with ADLs and body image: alopecia, nausea, neuropathy, dermatologic conditions
  - Prior Treatment and Comorbidities
  - Maintenance Therapy vs Recurrent Disease: In recurrent setting patients may have more hematologic side effects: Anemia, Neutropenia, Thrombocytopenia
  - Targeted therapy/Biologics vs Chemotherapy: Clinical trial option for patients who have no pathogenic variant or have HR proficiency. Review and discuss patient goals
  - Best Supportive Care Option
- Surveillance
  - Physical Exam every 3 months (NCCN recommends every 2-4 mo for 2 y, then 3-6 mo for 3 y, then annually after 5 y)
  - CA-125 monitoring if initially elevated
  - Imaging as clinically indicated (signs or symptoms at clinical exam)
  - Refer for genetic risk evaluation, if not previously done (eg, genetic test done for other cancer risks)
- Oral Adherence
  - Patient Accountability
  - Patient should know whom to call and when

Challenges with Chronic Disease

- Fear of recurrence often expressed by patient with ovarian cancer
  - Continue open ended questions
  - Maintain honesty and hope
- Advanced OC: Often not curable, but new treatments may prolong survival
- Advance Directives: Discuss with all newly diagnosed patients
- Ask patients about their short-term and long-term goals; focus on what matters to them, answers may change over time
- Discuss Best Supportive Care as treatment option: quality vs length of life. Involve Multi-disciplinary Team

There is Always Hope, even if goal is Comfort

National Comprehensive Cancer Network®

- **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education
- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally

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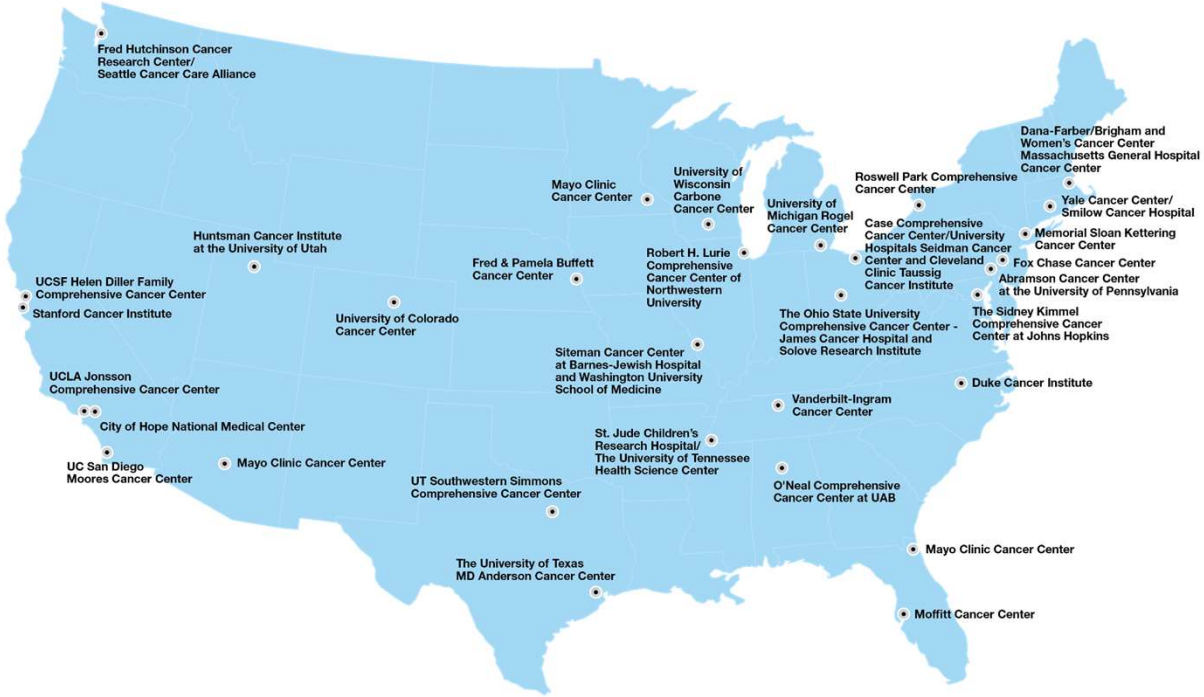

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