Oncology Grand Rounds
Ovarian Cancer
Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Friday, May 5, 2017
12:15 PM – 1:45 PM

Faculty

Kimberly Camp, RN, BSN, MSN, ANP-BC, ONC
Ursula A Matulonis, MD
Michele Peetz, FNP-C
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds Series

Wednesday	**Non-Small Cell Lung Cancer** 6:00 PM – 8:00 PM
Thursday	**Cancer Immunotherapy** 6:00 AM – 7:30 AM
	Breast Cancer 12:15 PM – 1:45 PM
	Lymphomas and CLL 6:00 PM – 8:00 PM
Friday	**Myeloproliferative Neoplasms** 6:00 AM – 7:30 AM
	Ovarian Cancer 12:15 PM – 1:45 PM
	Gastrointestinal Cancers 6:00 PM – 8:00 PM

Oncology Grand Rounds: Themes

Identifying and understanding oncology clinical scenarios

- Key determining factors; natural history and treatment
- Evaluating and managing clinical symptoms
- Patient and caregiver education

Integrating new agents and treatment strategies into practice

- Benefits and risks
- Prevention, identification and management of side effects/toxicity
- Identifying patients at high risk for toxicity

Psychosocial issues in clinical oncology

- Caring for family and loved ones, including minor children and grandchildren
- Job satisfaction and disappointment
- The bond that heals

Novel Agents Approved by the FDA in the Past 9 Weeks

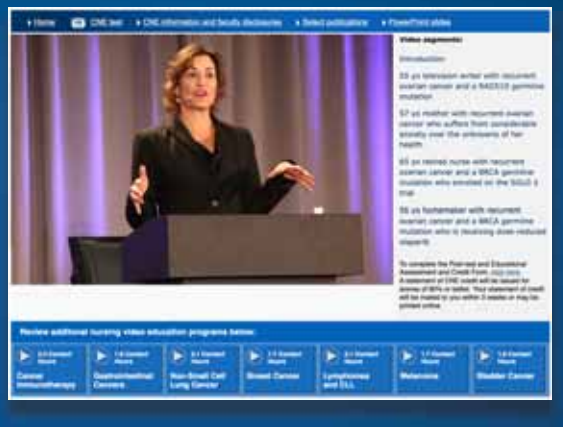
Agent	Approval Date	FDA-Approved Use on Approval Date
Telotristat ethyl (tryptophan hydroxylase inhibitor)	February 28th	In combination with somatostatin analogue (SSA) therapy for the treatment of adults with carcinoid syndrome diarrhea inadequately controlled by SSA therapy alone
Ribociclib (CDK4/6 inhibitor)	March 13th	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer
Avelumab (anti-PD-L1 antibody)	March 23rd	For the treatment of patients (≥12 years) with metastatic Merkel cell carcinoma, including those who have not received prior chemotherapy
Niraparib (PARP inhibitor)	March 27th	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer whose tumors have completely or partially shrunk in response to platinum-based chemotherapy
Brigatinib (ALK inhibitor)	April 28th	For the treatment of patients with ALK-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
Midostaurin (FLT3 inhibitor)	April 28th	For the treatment of adults with newly diagnosed FLT3-positive acute myeloid leukemia in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Durvalumab (anti-PD-L1 antibody)	May 1st	For the treatment of patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer that has progressed during or after one standard platinum-based regimen

https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm

- Pre-PARP Era: OC confined to abdomen
- Pre-PARP Era: Recurrent disease (Platinum-sensitive and resistant)
- PARP Era: Integration of PARP inhibitors
- PARP Era: Recurrent disease (Platinum-sensitive and resistant)

About the Enduring Program

- The proceedings from this 7-part CNE series will be video recorded and used in a virtual meeting archive including a downloadable version of the slides.



- An email will be sent to all attendees when the web activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

Download the RTPLive app on your smartphone or tablet to access program information, including slides being presented during the program:

www.ResearchToPractice.com/RTPLiveApp

Make the Meeting Even More Relevant to You

Submit a challenging case or question for discussion during the program.

Email to **DrNeilLove@ResearchToPractice.com**

Text to **(786) 759-1458**

(Your phone number will remain confidential and will not be disclosed.)

If you are unable to text or email, please complete a question/comment card located on your conference table and drop it in one of the designated bins located throughout the meeting room.

Make the Meeting Even More Relevant to You

Join the conversation by sharing photos and videos using the hashtag #RTPLive

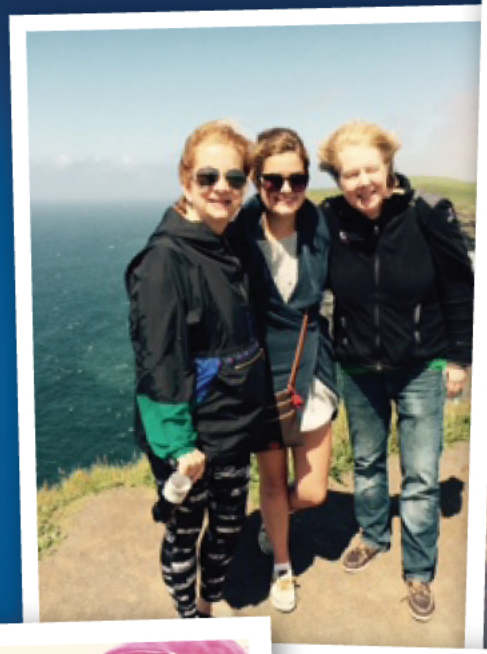
Facebook **@researchtopractice**

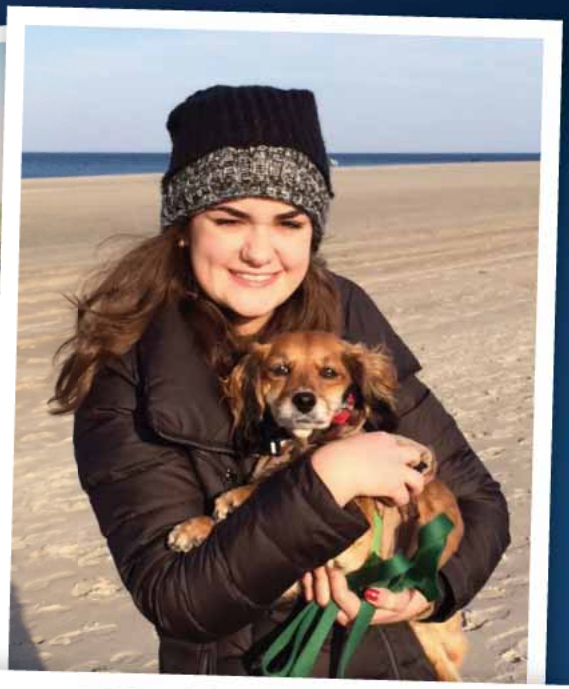
Twitter **@DrNeilLove**

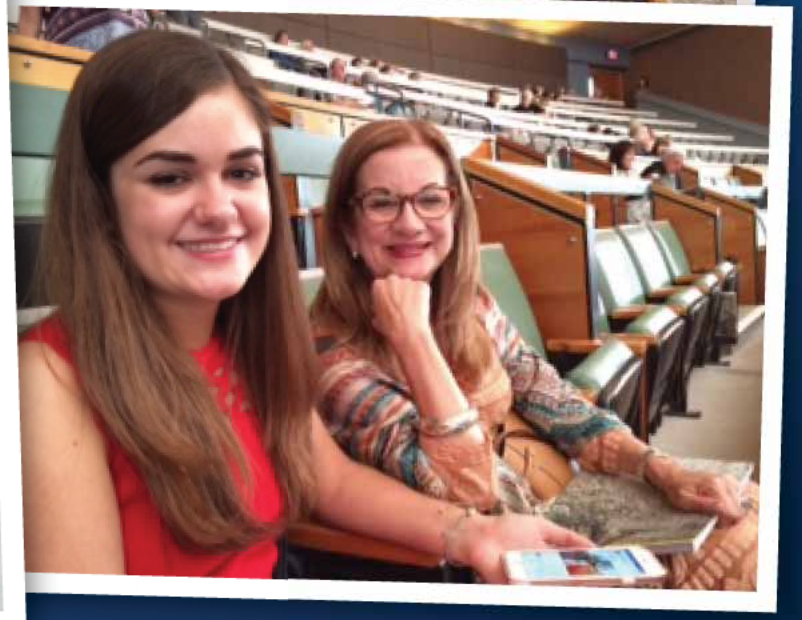
Instagram **@researchtopractice**

And get here early to participate in a brief video interview, where you can tell us about your experiences with oncology nursing. You may even see your post on the big screen during the events!

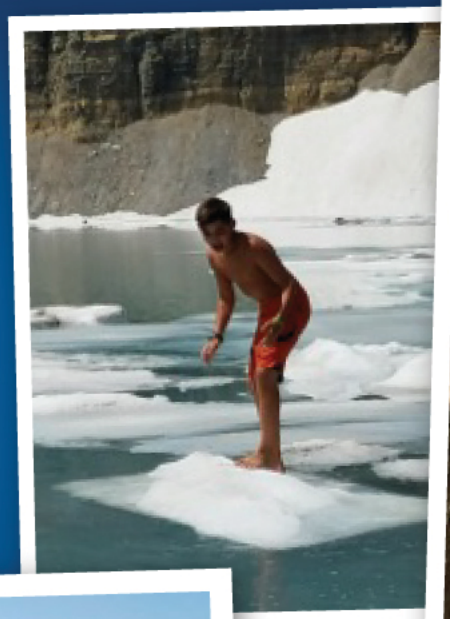
Ursula A Matulonis, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

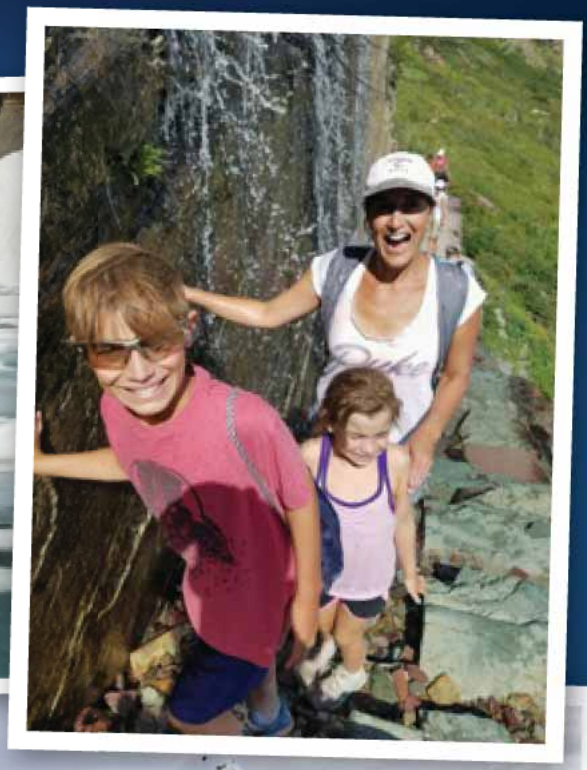


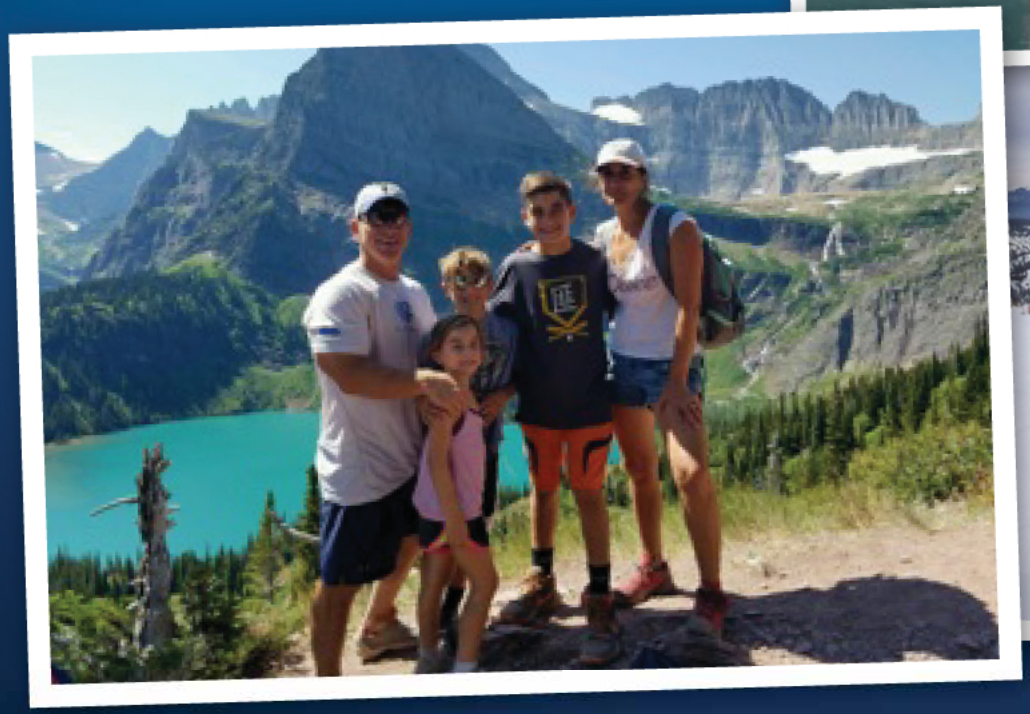


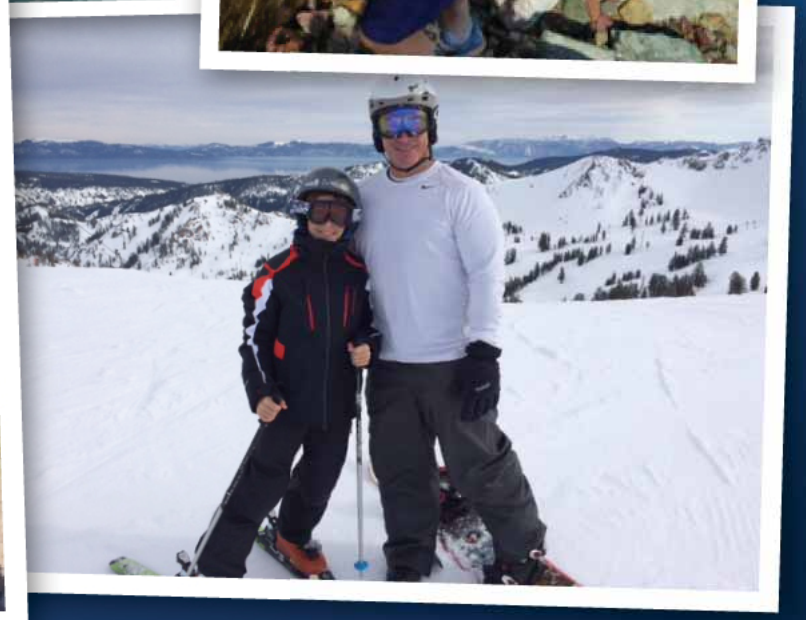


Angeles Alvarez Secord, MD, MHSc
Duke Cancer Institute
Durham, North Carolina

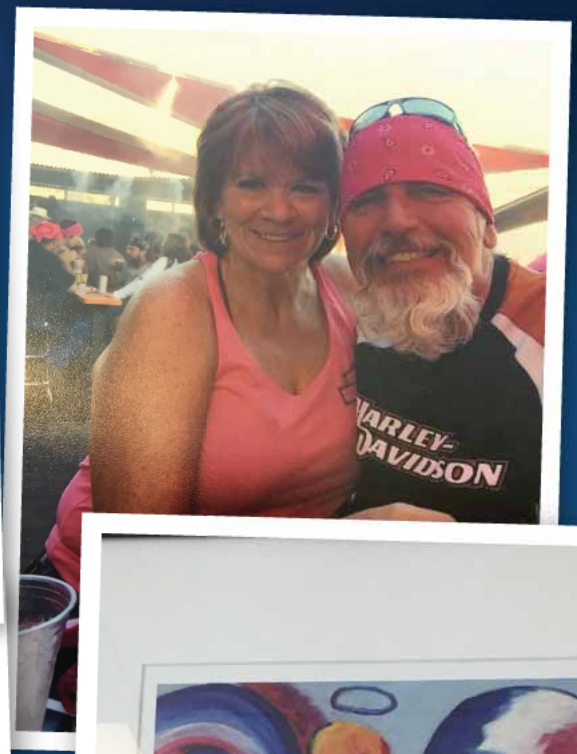


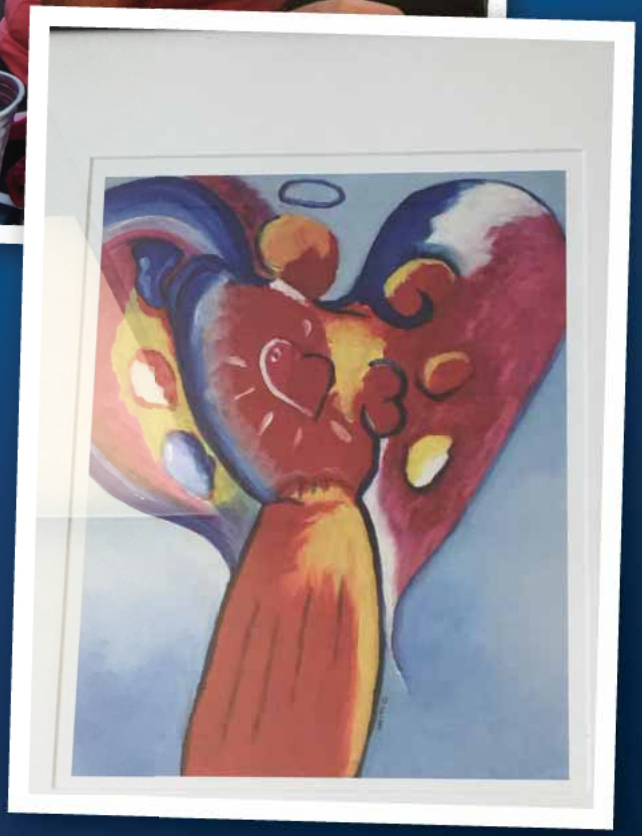






Michele Peetz, FNP-C
Biltmore Cancer Center
Phoenix, Arizona





Kimberly Camp, RN, BSN, MSN, ANP-BC, ONC
Duke Cancer Institute
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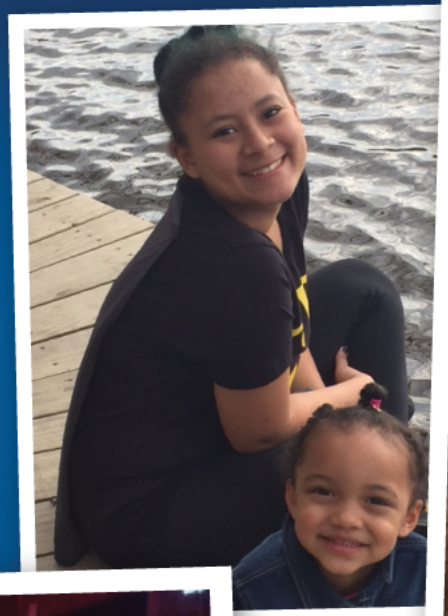

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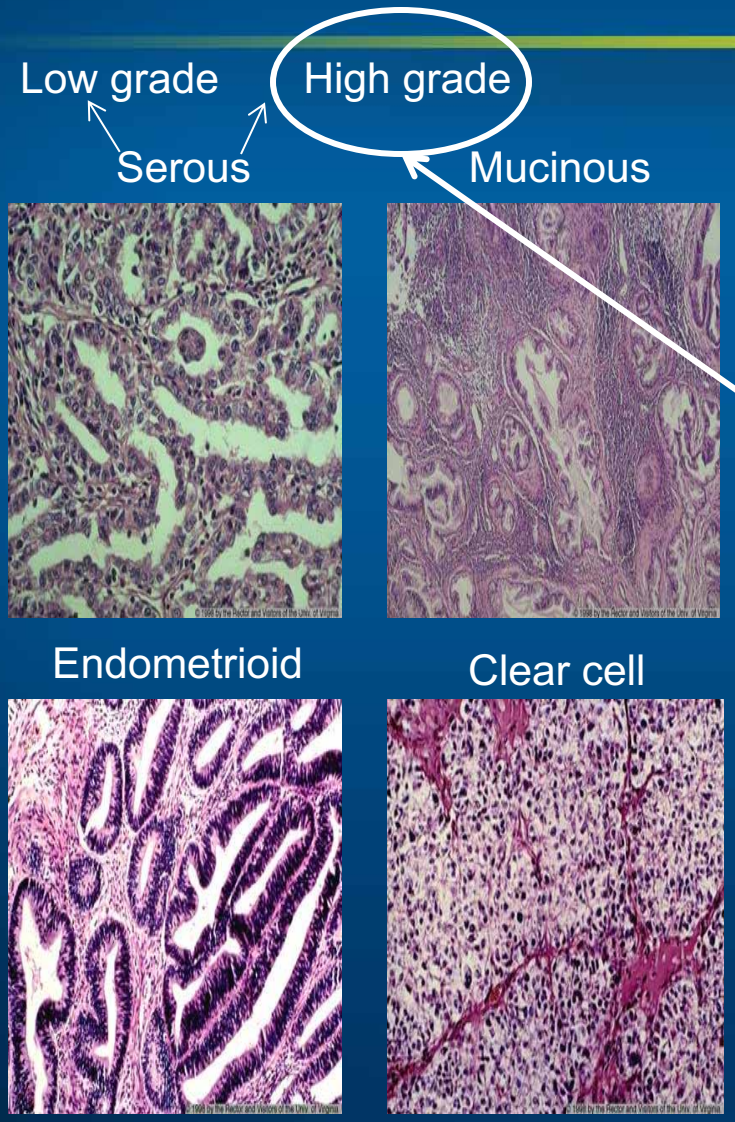
Module 1: Overview of Ovarian Cancer (OC)

- Pre-PARP Era: OC confined to abdomen
- Pre-PARP Era: Recurrent disease (Platinum-sensitive and resistant)
- PARP Era: Integration of PARP inhibitors
- PARP Era: Recurrent disease (Platinum-sensitive and resistant)

Overview

- Biology of OC and specific histologic and clinical subtypes
- Clinical presentation and staging
- Role of tumor markers (CA-125)

Ovarian Cancer Is Separated into Histological Categories



Specific molecular features define these categories and shape clinical trial design:

Mucinous tumors
KRAS mutations

High-grade serous cancers
Homologous recombination deficiency (HRD) is common and thus displays a high rate of platinum sensitivity

Low-grade serous cancers
KRAS mutations; usefulness of MEK inhibitors

Clear cell cancers
Chemotherapy insensitivity, PIK3CA mutations and sensitivity to VEGFR-2 inhibitors

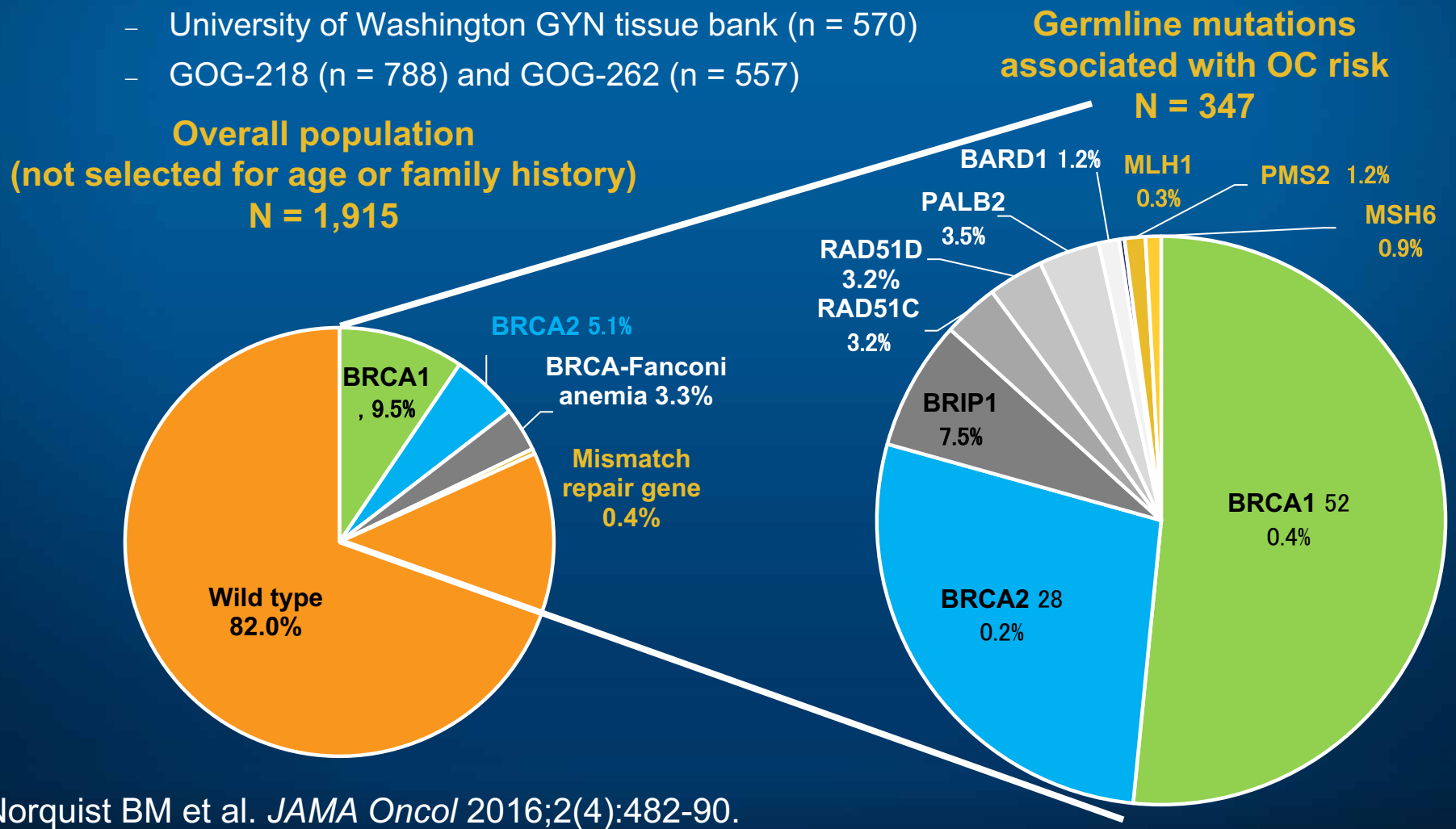
Courtesy of Ursula Matulonis, MD

Key Considerations for BRCA Mutation Testing for Patients with Ovarian Cancer

- Frequency and clinical significance of BRCA germline and somatic mutations
- Selection of patients with OC for genetic testing
- Options for BRCA germline mutation testing: “One-off” versus multiplex assays
- Significance of “BRCA-like” and other genomic signatures (eg, homologous recombination deficiency)
- Indications for genetic counseling for patients with OC and their family members

Summary of Germline DNA Mutations in OC

- Germline DNA sequenced from women with OC (N = 1,915) using a targeted capture and multiplex sequencing assay
  - University of Washington GYN tissue bank (n = 570)
  - GOG-218 (n = 788) and GOG-262 (n = 557)



Norquist BM et al. *JAMA Oncol* 2016;2(4):482-90.

Genetic Testing in Patients with Ovarian Cancer

SGO Position Paper on Risk Assessment for Inherited Gynecologic Cancer Predispositions, 2015

- Patients with an increased likelihood of having an inherited predisposition to breast and ovarian/tubal/peritoneal cancer who should receive genetic counseling and be offered genetic testing
  - Women affected with high-grade epithelial ovarian/tubal/peritoneal cancer

NCCN Ovarian Cancer Guidelines, v1.2017

- All patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should be referred for genetic risk evaluation

Lancaster JM et al. *Gyn Oncol* 2015;136:3-7. NCCN Ovarian Cancer Guidelines v1.2017

Examples of Assays for Genetic Testing

Test	Companion diagnostics	Turnaround time
BRACAnalysis CDx®	Olaparib companion diagnostic test	2 weeks
FoundationFocus™ CDxBRCA test	Rucaparib companion diagnostic test — somatic and germline BRCA1/2	2 weeks
	Breast/ovarian panels	
Ambry Genetics BRCAplus™	6-gene panel	1-2 weeks
Ambry Genetics OvaNext™	25-gene panel	2-4 weeks
Invitae Breast/Gyn guidelines-based panel	19-gene panel	1-3 weeks
Color Genomics™	19-gene panel	4-8 weeks
GeneDx Breast/Ovarian	21-gene panel	3 weeks
	Comprehensive panels	
Ambry Genetics CancerNext™	32-gene panel	2-3 weeks
GeneDx Comprehensive	32-gene panel	3 weeks
Myriad myRisk®	28-gene panel	2-4 weeks
Invitae Multi-Cancer	80-gene panel	1-3 weeks

GeneTests (www.genetests.org); Lynce F, Isaacs C. ASCO 2016 Education Book

Panel Testing

Advantages:

- More “diagnoses”
- Often cost effective

Disadvantages:

- Unexpected results
  - Noncorrelative high-penetrant gene(s)
  - Mosaicism
- Low and moderate penetrance genes
- High uncertain variant rate
- Slower turnaround time

Courtesy of Kathleen N Moore, MD

Even Wider Catch: BRCAness "Profile"

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gene Expression Profile of *BRCA*ness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer

Panagiotis A. Konstantinopoulos, Dimitrios Spentzos, Beth Y. Karlan, Toshiyasu Taniguchi, Elena Fountzilas, Nancy Francoeur, Douglas A. Levine, and Stephen A. Cannistra

See accompanying article doi: 10.1200/JCO.2010.28.5791

From the Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Cedars-Sinai Medical Center, Los Angeles, CA; Howard Hughes Medical Institute, Chevy Chase, MD; Fred Hutchinson Cancer Research Center, Seattle, WA; and Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted December 16, 2009; accepted March 12, 2010; published online ahead of print at www.jco.org on June 14, 2010.

Supported in part through the Ovarian Cancer Specialized Program of Research Excellence (SPORE) Grant

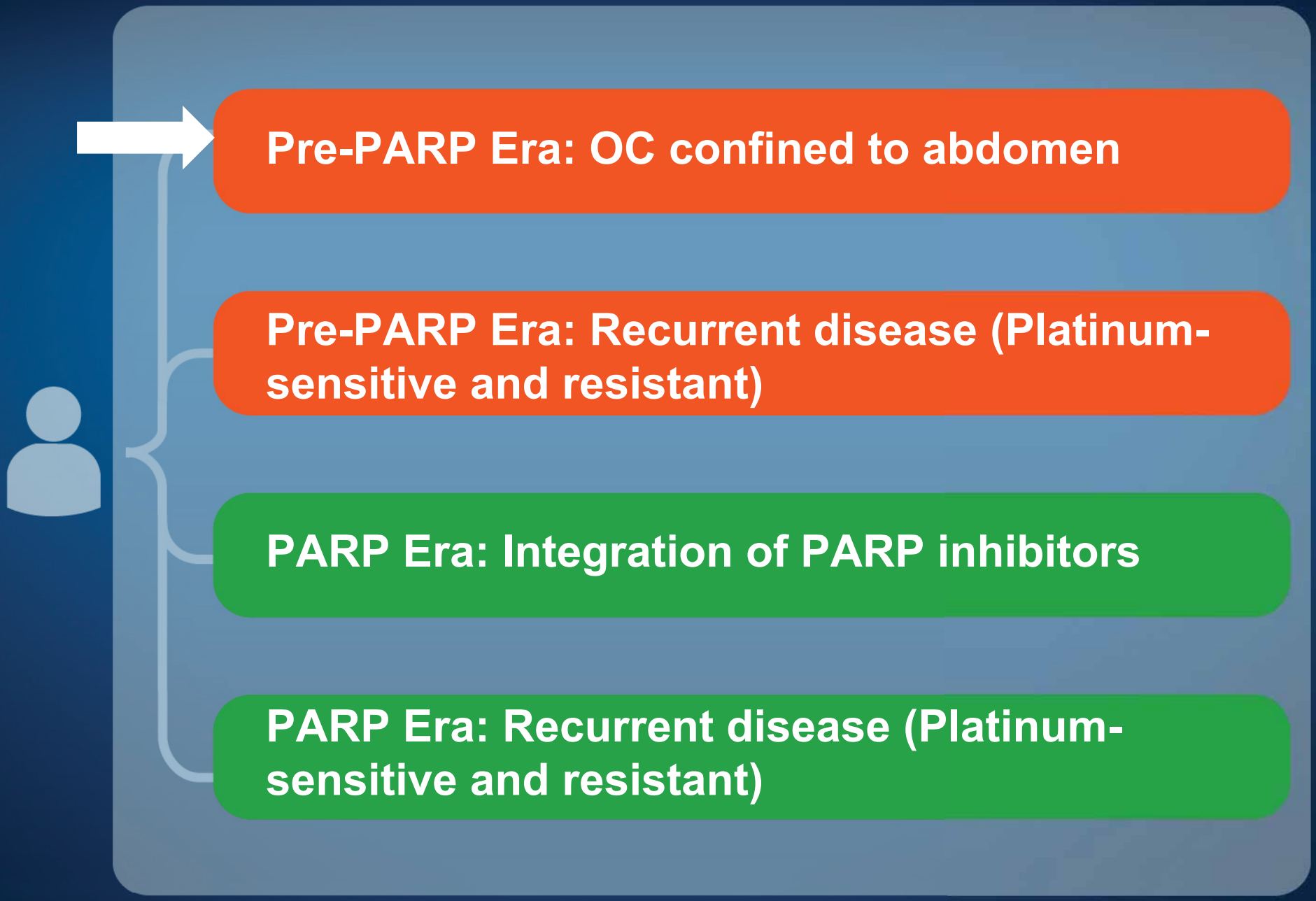
A B S T R A C T

Purpose
To define a gene expression profile of *BRCA*ness that correlates with chemotherapy response and outcome in epithelial ovarian cancer (EOC).

Methods
A publicly available microarray data set including 61 patients with EOC with either sporadic disease or *BRCA1/2* germline mutations was used for development of the *BRCA*ness profile. Correlation with platinum responsiveness was assessed in platinum-sensitive and platinum-resistant tumor biopsy specimens from six patients with *BRCA* germline mutations. Association with poly-ADP ribose polymerase (PARP) inhibitor responsiveness and with radiation-induced RAD51 foci formation (a surrogate of homologous recombination) was assessed in Capan-1 cell line clones. The *BRCA*ness profile was validated in 70 patients enriched for sporadic disease to assess its association with outcome.

Konstantinopoulos PA et al. *J Clin Oncol* 2010;28:3555.

Module 2: Treatment of OC in the Pre-PARP Era


Pre-PARP Era: OC confined to abdomen
Pre-PARP Era: Recurrent disease (Platinum-sensitive and resistant)
PARP Era: Integration of PARP inhibitors
PARP Era: Recurrent disease (Platinum-sensitive and resistant)

Scenario 1: A patient with disease confined to the abdomen

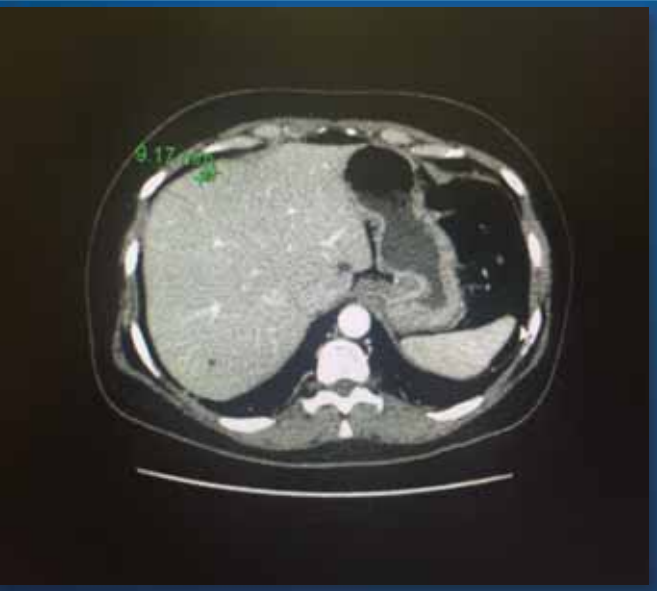
Key considerations

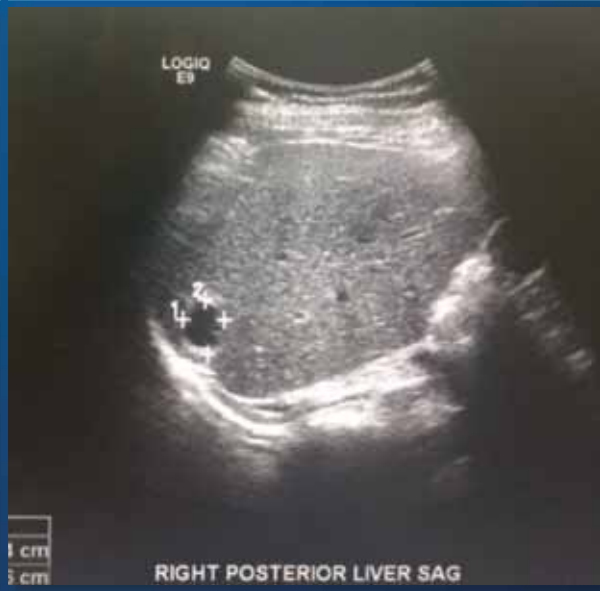
- Patient selection for neoadjuvant systemic therapy and choice of neoadjuvant regimen
- Risks and benefits of intraperitoneal chemotherapy; indications for its use in clinical practice
- Supportive management considerations for patients receiving intraperitoneal chemotherapy
- Available data and ongoing Phase III trials with bevacizumab in the setting of primary OC

44-year-old woman with Stage IIIC high-grade ovarian cancer (Ms Camp)

- March 2016: Exploratory laparotomy, TAH/BSO, omentectomy, optimal debulking, placement of IP catheter
- April 2016: Paclitaxel 135 mg/m^2, cisplatin 75 mg/m^2 IP and paclitaxel 60 mg/m^2 IP
  - July 2016: Completed 6 cycles
- OncoGeneDx custom breast/ovarian cancer panel
- NGS genomic analysis is negative for mutation
- Single mother with adult children, currently works in school system
  - Children adapting to life-threatening illness of parent
  - Patient concerned with body image changes

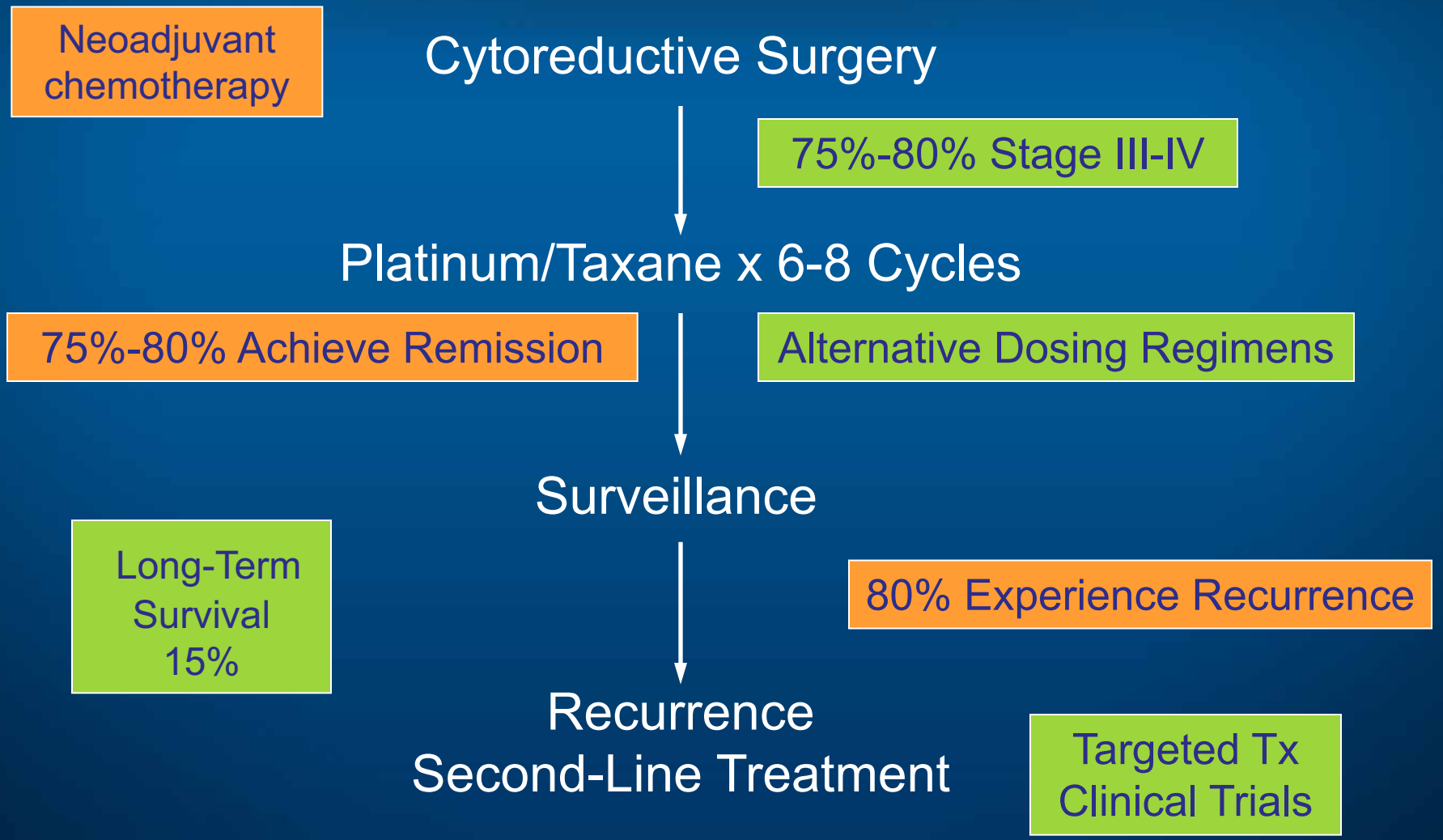
A 44-year-old Woman with Stage IIIC High-Grade Ovarian Cancer (Ms Camp)






Hip Hip Hooray
CHEMO ENDS TODAY!
Be BRCAware

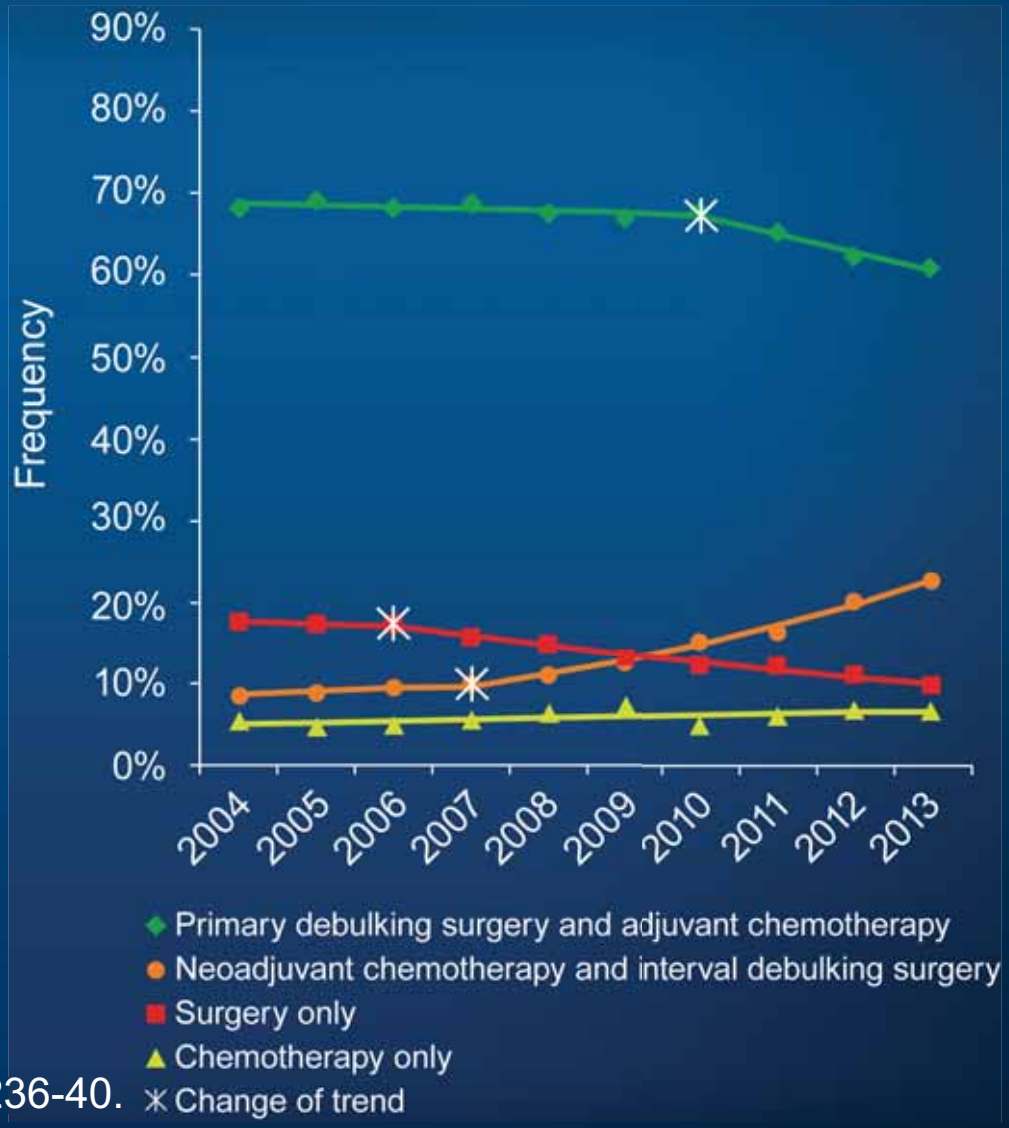
Ovarian Cancer Standard of Care



NCCN Clinical Practice Guidelines for Ovarian Cancer Version 1, 2017; NCCN 2012; NCI 2012

Trends in the Use of NACT for Advanced Ovarian Cancer in the United States

- Time trend analysis of the National Cancer Database
- Women with Stage IIIC and IV epithelial ovarian cancer diagnosed between 2004 and 2013 (N = 40,694)
- The proportion of women receiving neoadjuvant chemotherapy and surgery increased from 8.6% to 22.6% between 2004 and 2013 ($p < 0.001$)



Melamed A et al. *Gynecol Oncol* 2016;143:236-40.

Key Phase III Studies of Intraperitoneal Therapy for Up-Front Therapy

Study	N	Eligibility	Median OS	Hazard ratio	*p*-value
SWOG 8501/ GOG 104[1]	546	Stage III, ≤2 cm residual	IP: 49 mo IV: 41 mo	0.76	0.02
GOG 114/ SWOG 9227[2]	462	Stage III, ≤1 cm residual	IP: 63.2 mo IV: 52.2 mo	0.81	0.05
GOG 172[3]	415	Stage III, ≤1 cm residual	IP: 65.6 mo IV: 49.7 mo	0.75	0.03

Retrospective analysis of GOG 114 and 172[4]

- N = 876, median follow-up 10.7 years
- Median OS for IP vs IV: 61.8 mo vs 51.4 mo, HR = 0.77, $p = 0.002$

[1] Alberts DS et al. *N Engl J Med* 1996;335:1950-5; [2] Markman M et al. *J Clin Oncol* 2001;19:1001-7; [3] Armstrong DK et al. *N Engl J Med* 2006;354:34-43; [4] Tewari D et al. *J Clin Oncol* 2015;33:1460-6.

Patient Teaching for Primary Platinum/Taxane Chemotherapy

IV Chemotherapy

- Alopecia
- Neutropenia
- Anemia
- Nausea
- Constipation
- Myalgias
- Cumulative peripheral neuropathy
- Fatigue

IP Chemotherapy

- Alopecia
- Abdominal bloating/anorexia discomfort up to 7 days
- Neutropenia
- Delayed nausea and vomiting
- Dehydration
- Constipation
- Myalgias
- Cumulative peripheral neuropathy
- Fatigue

Armstrong DK et al. *N Engl J Med* 2006;354:34-43; Katsumata N et al. *Lancet* 2009;374(9698):1331-8; Landrum LM et al. *Gynecol Oncol* 2011;122(3):527-31; Markman M, Walker JL. *J Clin Oncol* 2006;24(6):988-94.

IP Extravasation, Complications

- Pain during infusion is not normal
- Erythema post infusion not normal
- Bloating, discomfort due to abdominal “expansion” can last 2-5 days: normal
- Fatigue, malaise, loss of appetite, nausea all common post IP and interfere with daily life
- IP cisplatin is administered after IV paclitaxel day 1; IP paclitaxel is administered on day 8

Courtesy of Paula J Anastasia, RN, MN, AOCN

A 65-year-old woman with ovarian cancer (Ms Peetz)

- May 2008: Diagnosis of pT2c pMX with 3/7 positive metastatic right pelvic nodes
- Administered paclitaxel/cisplatin IV/IP
  - Tolerated well, though has experienced lasting peripheral neuropathy
- Remains disease free
- No genetic testing performed
  - Daughter tested negative for BRCA 1/2 mutation
- Married and retired elementary school teacher
  - Radioactive contamination
  - Issues with survivor's remorse as son-in-law succumbed to brain cancer during her recovery

A 65-year-old woman with ovarian cancer (Ms Peetz)


BUBBA GUMP
SHRIMP
66

- Pre-PARP Era: OC confined to abdomen
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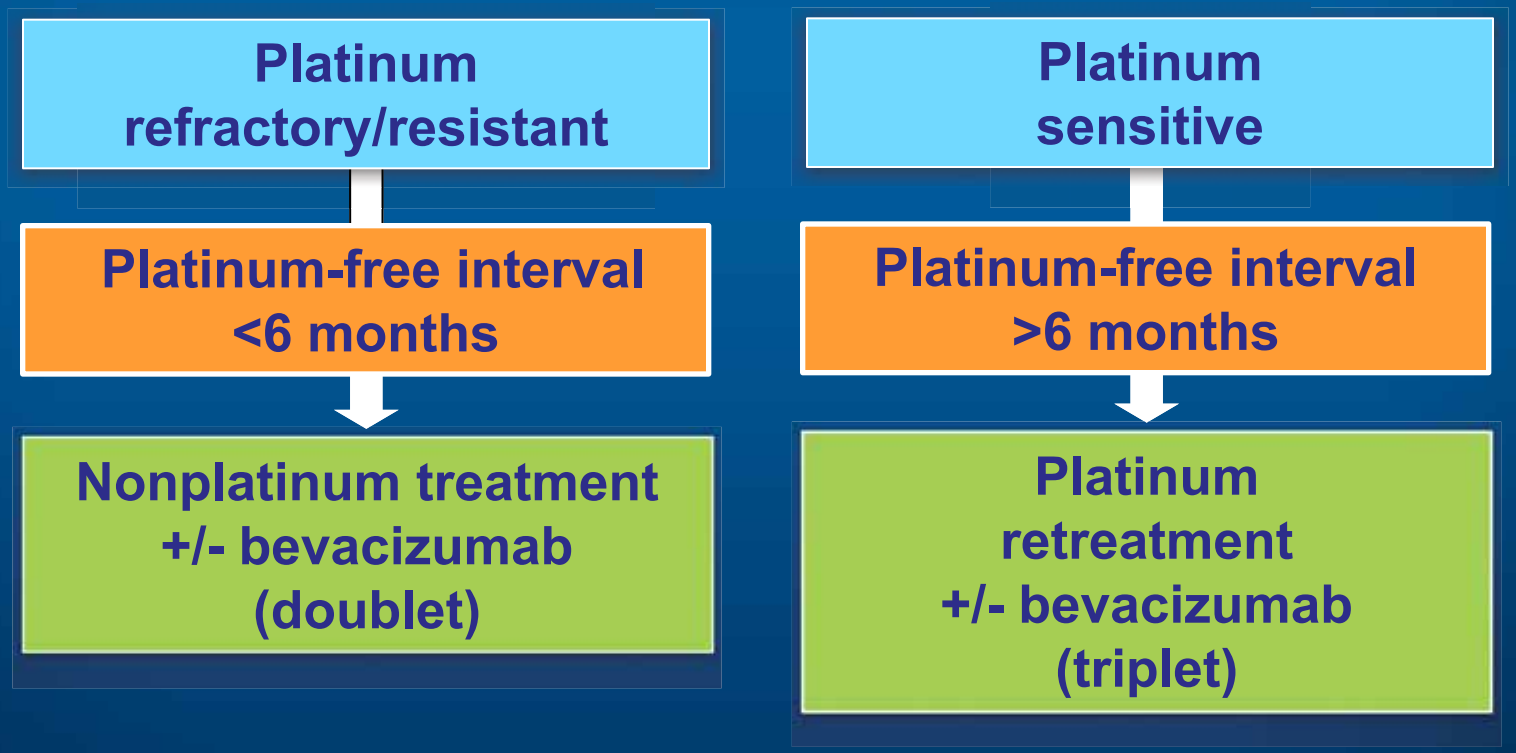
- PARP Era: Integration of PARP inhibitors
- PARP Era: Recurrent disease (Platinum-sensitive and resistant)

Scenario 2: A patient with disease recurrence after treatment with a platinum/taxane

- Duration of response to initial platinum-based therapy
- Selection of chemotherapeutic regimen
- Indications for the use of maintenance therapy; impact of response to current treatment
- Incorporation of bevacizumab with chemotherapy or as monotherapy

General Approach to Treatment of First or Second Recurrence



NCCN Clinical Practice Guidelines for Ovarian Cancer Version 1, 2017.

Classes of Approved Systemic Treatments: Pre-PARP Era

Platinum Sensitive

Chemotherapy

Platinums, taxanes, gemcitabine, liposomal doxorubicin

Biologics

Bevacizumab

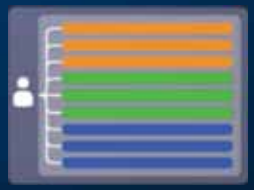
Platinum Resistant

Chemotherapy

Taxanes, gemcitabine, liposomal doxorubicin, etoposide, topotecan

Biologics

Bevacizumab



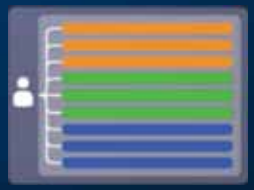
Bevacizumab – FDA Approvals

November 14, 2014:

- In combination with paclitaxel, pegylated liposomal doxorubicin or topotecan for *platinum-resistant*, recurrent EOC

December 6, 2016:

- Either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine chemotherapy, followed by bevacizumab alone, for the treatment of *platinum-sensitive* recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer



Phase III Studies of Bevacizumab in Combination with Chemotherapy for EOC: Platinum-Sensitive, Recurrent Setting

Study	Randomization	N	Median PFS (mo)	HR, *p*-value	Median OS (mo)	HR, *p*-value
OCEANS[1]	C/gem + placebo	242	8.4	HR = 0.48 <0.0001	32.9	HR = 0.952
	C/gem + bev until progression	242	12.4		33.6	*p* = 0.6479
GOG-0213[2]	C/P	374	10.4	HR = 0.61 <0.0001	37.3	HR = 0.827
	C/P + bev	374	13.8		42.2	*p* = 0.056

[1] Aghajanian C et al. *J Clin Oncol* 2012;30(17):2039-45; *Gynecol Oncol* 2015;139(1):10-6.
[2] Coleman RL et al. *Proc SGO* 2015;Abstract 3.

Bevacizumab Toxicities

- Hypertension (maintain < 140/90)
- Rhinitis
- Proteinuria (maintain < 2+, → UPR or 24h CCI)
- Epistaxis
- Headache
- Vascular: GI perforation, delayed wound healing, hemorrhage (28-day wait before or after surgery)

Courtesy of Paula J Anastasia, RN, MN, AOCN

Module 3:
Integration of PARP Inhibitors into OC Management

Pre-PARP Era: OC confined to abdomen

Pre-PARP Era: Recurrent disease (Platinum-sensitive and resistant)

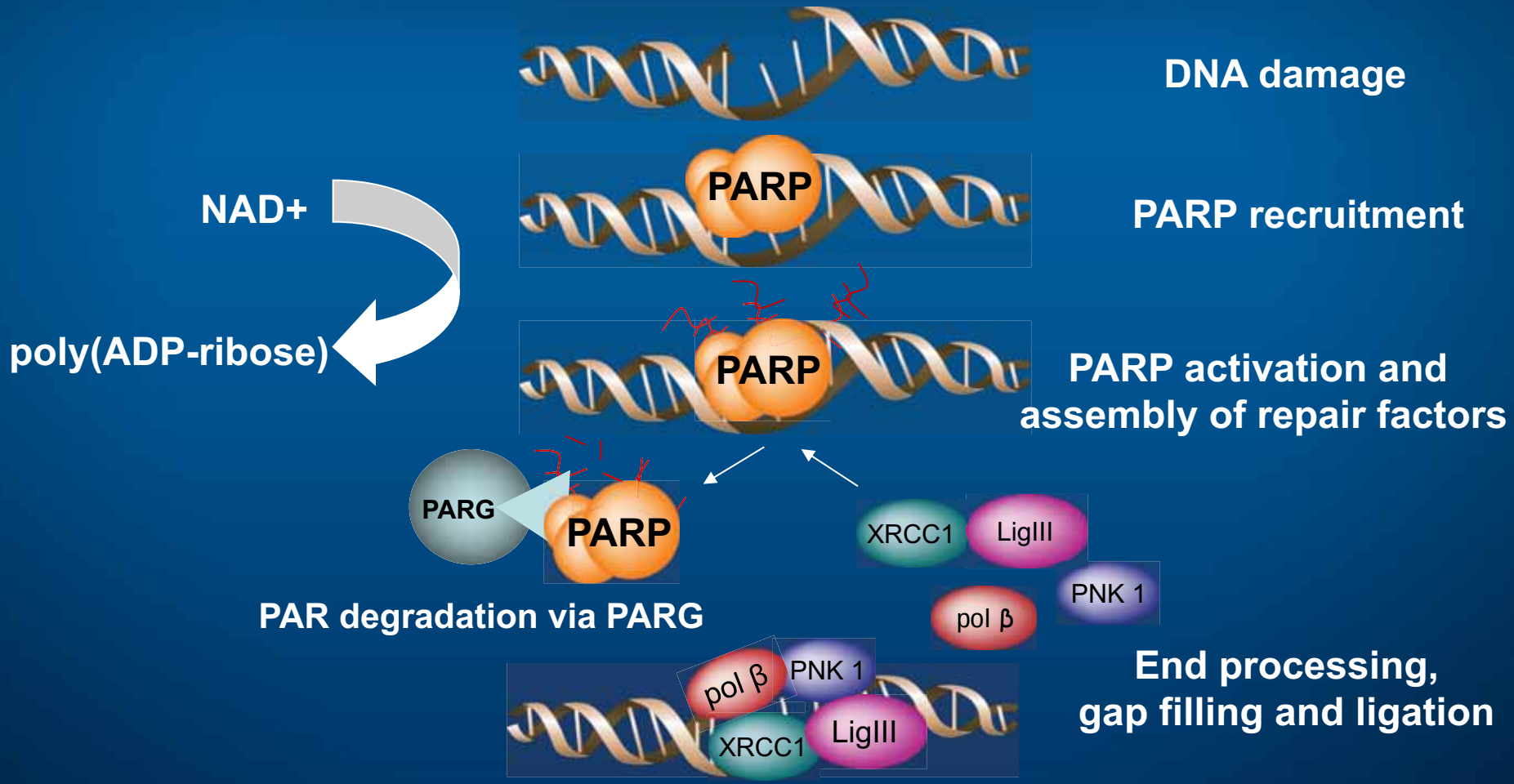
PARP Era: Integration of PARP inhibitors

PARP Era: Recurrent disease (Platinum-sensitive and resistant)

Key Considerations in the Integration of PARP Inhibitors into OC Management

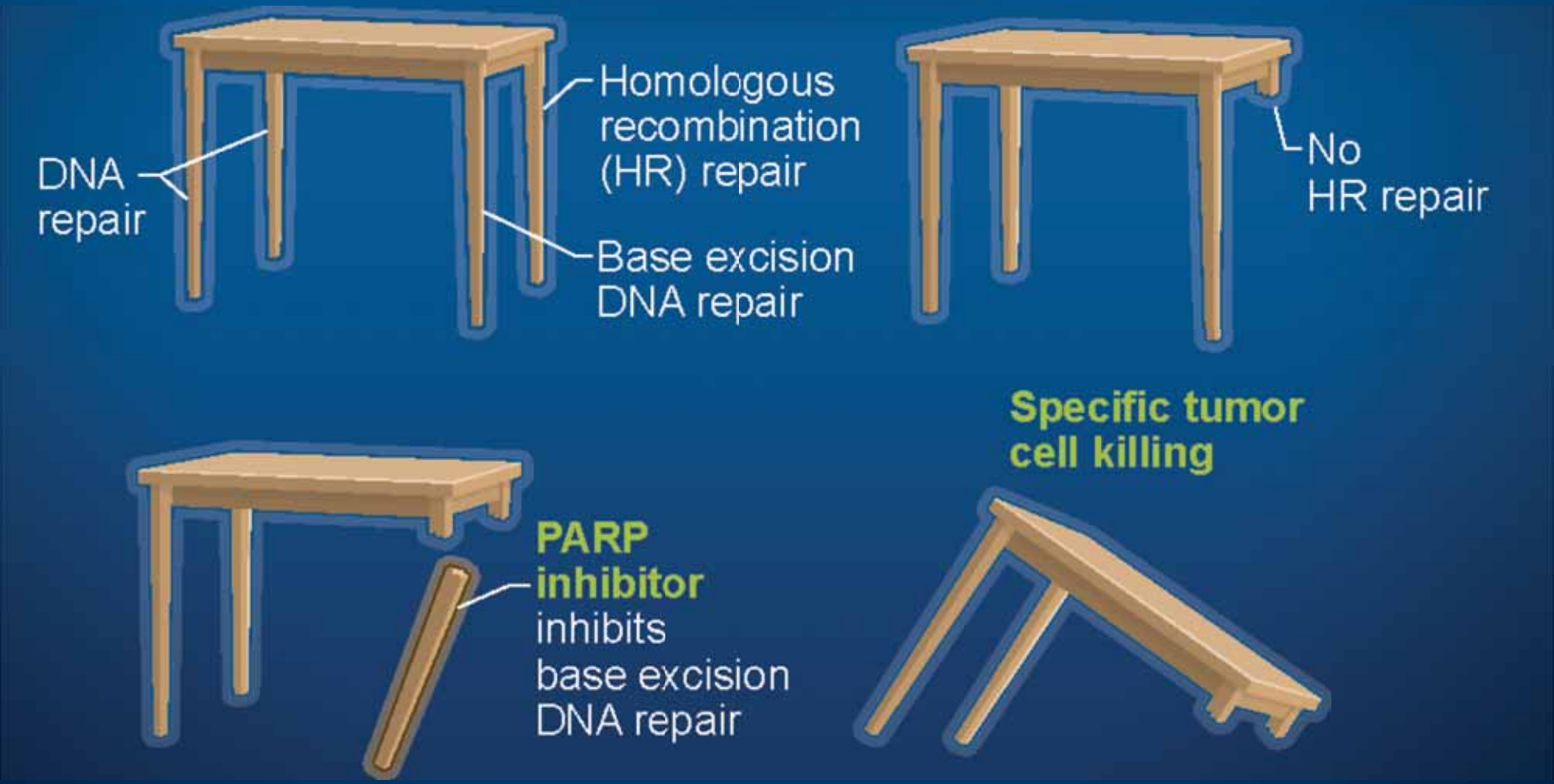
- Effect of BRCA mutation status on activity
- Similarities and differences among companion diagnostics developed for FDA-approved PARP inhibitors
- FDA-approved indications for and optimal integration of olaparib, rucaparib and niraparib
- Dosing and administration of olaparib, rucaparib and niraparib
- Recognition and management of PARP inhibitor side effects
- Risk of AML/MDS for patients receiving PARP inhibitors
- Current role of PARP inhibitors for patients without BRCA mutations

PARP and Base Excision Repair



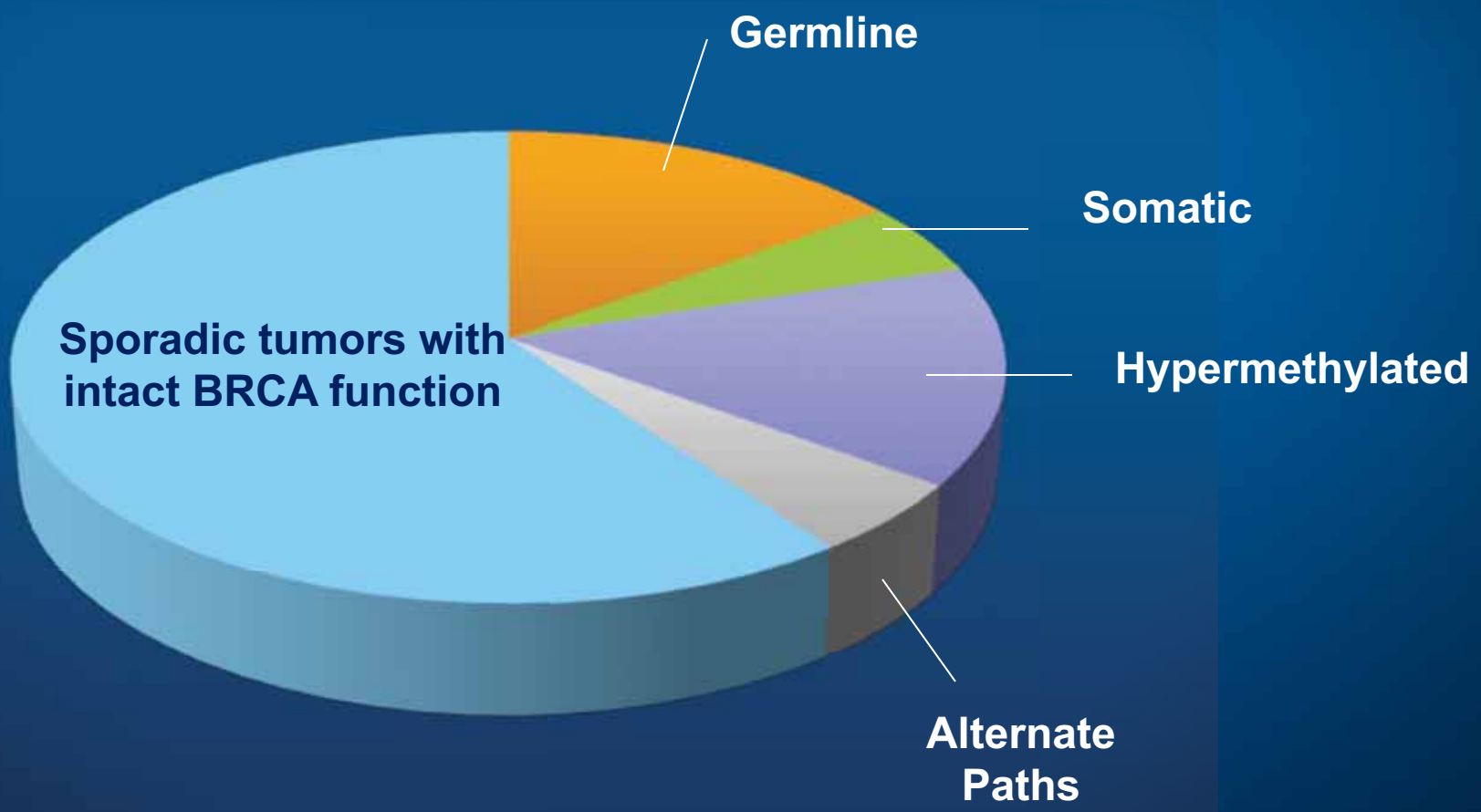
Vergote ND; Khanna et al, 2001; Sanchez-Perez, 2006; Kennedy et al, 2006.

Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition



Courtesy of Jenny C Chang, MD

Who Will Benefit from PARP Inhibitor Treatment?



Adapted from Coleman, 2009.

Courtesy of Robert Coleman, MD.

Pre-PARP Era: OC confined to abdomen

Pre-PARP Era: Recurrent disease (Platinum-sensitive and resistant)

PARP Era: Integration of PARP inhibitors

PARP Era: Recurrent disease (Platinum-sensitive and resistant)

71-year-old woman with Stage IIIB ovarian cancer (Ms Peetz)

- 1995: Diagnosis of Stage IIIB serous ovarian cancer
  - Oophorectomy → Paclitaxel/carboplatin x 6 cycles
  - Discharged after 5 years of surveillance
- 2012: CT scan shows 18-cm pelvic mass consistent with serous primary
  - Paclitaxel/carboplatin x 3 cycles; switched to gemcitabine x 4 cycles due to reaction to carbo
- January 2014: Topotecan plus bevacizumab
- November 2015: PET/CT showed progression
- December 2015: Olaparib 400 mg BID
  - Dose reduced to 200 mg BID due to anemia
- Patient and sister are BRCA mutation-positive

Classes of Approved Systemic Treatments: PARP Era

Platinum Sensitive

Chemotherapy

Platinums, taxanes, gemcitabine, liposomal doxorubicin

Biologics

Bevacizumab

PARP Inhibitors

Olaparib, rucaparib, niraparib

Platinum Resistant

Chemotherapy

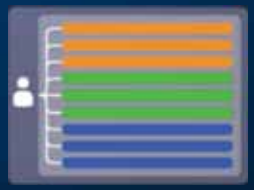
Taxanes, gemcitabine, liposomal doxorubicin, etoposide, topotecan

Biologics

Bevacizumab

PARP Inhibitors

Olaparib, rucaparib



PARP Inhibitors – FDA Approvals

Olaparib:

- December 2014: As monotherapy for advanced ovarian cancer after ≥3 prior lines of chemotherapy and with deleterious or suspected deleterious *germline BRCA-mutated* (as detected by an FDA-approved test)

Rucaparib:

- As monotherapy for advanced ovarian cancer after 2 or more chemotherapies and with a *specific gene mutation (deleterious BRCA)* as identified by an FDA-approved companion diagnostic test.

Niraparib:

- As maintenance treatment for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer that is in complete or partial response after platinum-based chemotherapy. *Approval is not dependent on presence of a specific genetic mutation*.

Olaparib in Germline BRCA1/2 Mutation-Positive Advanced Ovarian Cancer

- N = 137
- Deleterious or suspected deleterious germline BRCA mutation status verified retrospectively in 59/61 (97%) patients for whom blood samples were available, using the companion diagnostic BRACAnalysis CDx
- All patients had received 3 or more prior lines of chemotherapy
- All patients received olaparib 400 mg twice daily until disease progression or unacceptable toxicity
- Objective response rate: 34%
  - Complete/partial responses: 2%/32%
- Median DOR: 7.9 months

Olaparib package insert 01/2017.

Rucaparib in Germline and/or Somatic BRCA1/2 Mutation-Positive Advanced Ovarian Cancer

- N = 106 in 2 multicenter, single-arm, open-label clinical trials
- Tumor BRCA mutation status was verified retrospectively in 64/67 (96%) patients for whom a tumor tissue sample was available, using the companion diagnostic FoundationFocus CDx_{BRCA} test
- All patients had experienced disease progression after ≥2 prior lines of chemotherapy
- All patients received rucaparib 600 mg twice daily as monotherapy until progression or unacceptable toxicity
- Objective response rate: 54%
  - Complete/partial responses: 9%/45%
- Median DOR: 9.2 months

Rucaparib package insert 12/2016.

Niraparib in Patients with Recurrent Ovarian Cancer Who are in Complete or Partial Response to Platinum-Based Chemotherapy

- N = 553 – platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Eligible patients assigned to one of two cohorts based on the results of the BRACAnalysis CDx
  - gBRCAmut cohort: Deleterious or suspected deleterious germline BRCA mutations
  - Non-gBRCAmut cohort: Those without germline BRCA mutations
- All patients received ≥2 prior platinum-containing regimens and were in CR or PR to their most recent platinum-based regimen
- Patients received niraparib 300 mg orally daily or matched placebo
- Median PFS
  - gBRCAmut: 21.0 vs 5.5 months
  - Non-gBRCAmut: 9.3 vs 3.9 months

Niraparib package insert, 3/2017

ENGOT-OV16/NOVA

Accrual: N = 553

(N=203) gBRCA^{mut}
2:1

Eligibility

- Platinum-sensitive, recurrent ovarian cancer with high-grade serous histology
- Received and sensitive to at least 2 platinum-based regimens
- CR or PR and disease progression more than 6 months after last round of platinum-based chemo
- Germline BRCA mutant or mutation-negative* based on BRACAnalysis

R

Niraparib 300 mg

Placebo

R

Niraparib 300 mg

Placebo

(N=350) Non-gBRCA^{mut}
2:1

Primary endpoint: PFS in gBRCAmut and non-gBRCAmut cohorts (HRD-positive subset followed by overall)

https://gciggroup.com/system/files/2015_Oct_NSGO_ENGOT-OV16-NOVA-MIRZA.pdf

ENGOT-OV16/NOVA: Progression-Free Survival

	Niraparib (n = 138)	Placebo (n = 65)	Hazard ratio	*p*-value
Germline BRCA mutation – Median PFS	21.0 mo	5.5 mo	0.27	<0.001
No germline BRCA mutation with HRD positivity – Median PFS	12.9 mo	3.8 mo	0.38	<0.001
No germline BRCA mutation – Median PFS	9.3 mo	3.9 mo	0.45	<0.001

Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64.

SOLO2 Phase III Trial of Olaparib Monotherapy as Maintenance

Eligibility

- Platinum-sensitive, relapsed ovarian cancer with germline BRCA mutation
- Must be in response to most recent platinum-based chemotherapy after ≥2 lines of therapy

Maintenance olaparib 300 mg BID (n = 195)

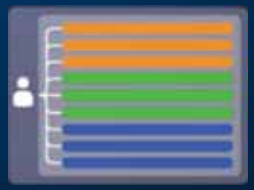
Placebo (n = 99)

Clinical endpoint	Olaparib (n = 196)	Placebo (n = 99)	HR (*p*-value)
Median PFS	19.1 mo	5.5 mo	0.30 (<0.0001)

Pujade-Lauraine E et al. *Proc SGO* 2017;Abstract LBA2.

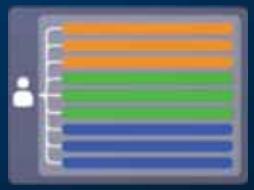
Strategies for Managing Nausea/Vomiting

- Prophylactic antiemetics
- Dose interruption
- Dose reduction
- Behavioral modification
  - Avoid sweet or spicy foods
  - Rest but do not lie flat for at least 2 hours after finishing a meal
  - 5 to 6 smaller meals, rather than 3 large meals, throughout the day



Strategies for Managing Anemia

- Rule out other causes
  - Iron deficiency
  - MDS/AML
  - Agents that increase blood levels of olaparib
    - CYP3A inhibitors (fluconazole, aprepitant, etc)
    - Grapefruit, Seville oranges
- Dose interruption
- Dose reduction
- Erythropoiesis-stimulating agents
- Blood transfusion



Examples of Ongoing Phase III Clinical Trials of PARP Inhibitors for Ovarian Cancer (OC)

PARP inhibitor	Ongoing trials
Veliparib (ABT-888)	Phase III: Study of combination veliparib as induction therapy followed by maintenance veliparib in newly diagnosed Stage III/IV OC
Rucaparib (CO-338 or AGO14699 or PF-01367338)	Phase III: As switch maintenance after platinum in relapsed high-grade serous OC (**ARIEL3**) Phase III: Rucaparib versus chemotherapy in relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (**ARIEL4**)
Niraparib (MK4827)	Phase III: Niraparib maintenance in advanced ovarian cancer after front-line platinum-based chemotherapy (**PRIMA**)
Olaparib	Phase III: As monotherapy compared to physician's choice of single-agent chemotherapy in platinum-sensitive, relapsed OC with germline BRCA1/2 mutation (**SOLO3**)

www.clinicaltrials.gov. Accessed May 2017.

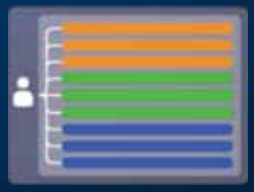
66-year-old woman with BRCA1 mutation and recurrent metastatic ovarian cancer (Ms Camp)

- April 2015: Neoadjuvant carboplatin AUC 6 with paclitaxel 175 mg/m^2 - severe hypersensitivity
- August 2015: Interval debulking surgery (TLH/BSO, omentectomy) and peritoneal biopsies
- September 2015: Adjuvant carboplatin AUC 6 with paclitaxel 175 mg/m^2
- May 2016: Admitted to hospital with gait instability; cerebellar and parietal metastases detected
- May 2016 - June 2016: Craniotomy and SRS
- September 2016: Liposomal doxorubicin
- February 2017: Rucaparib 600 mg x 1 cycle; LFTs elevated → Dose reduced to 500 mg

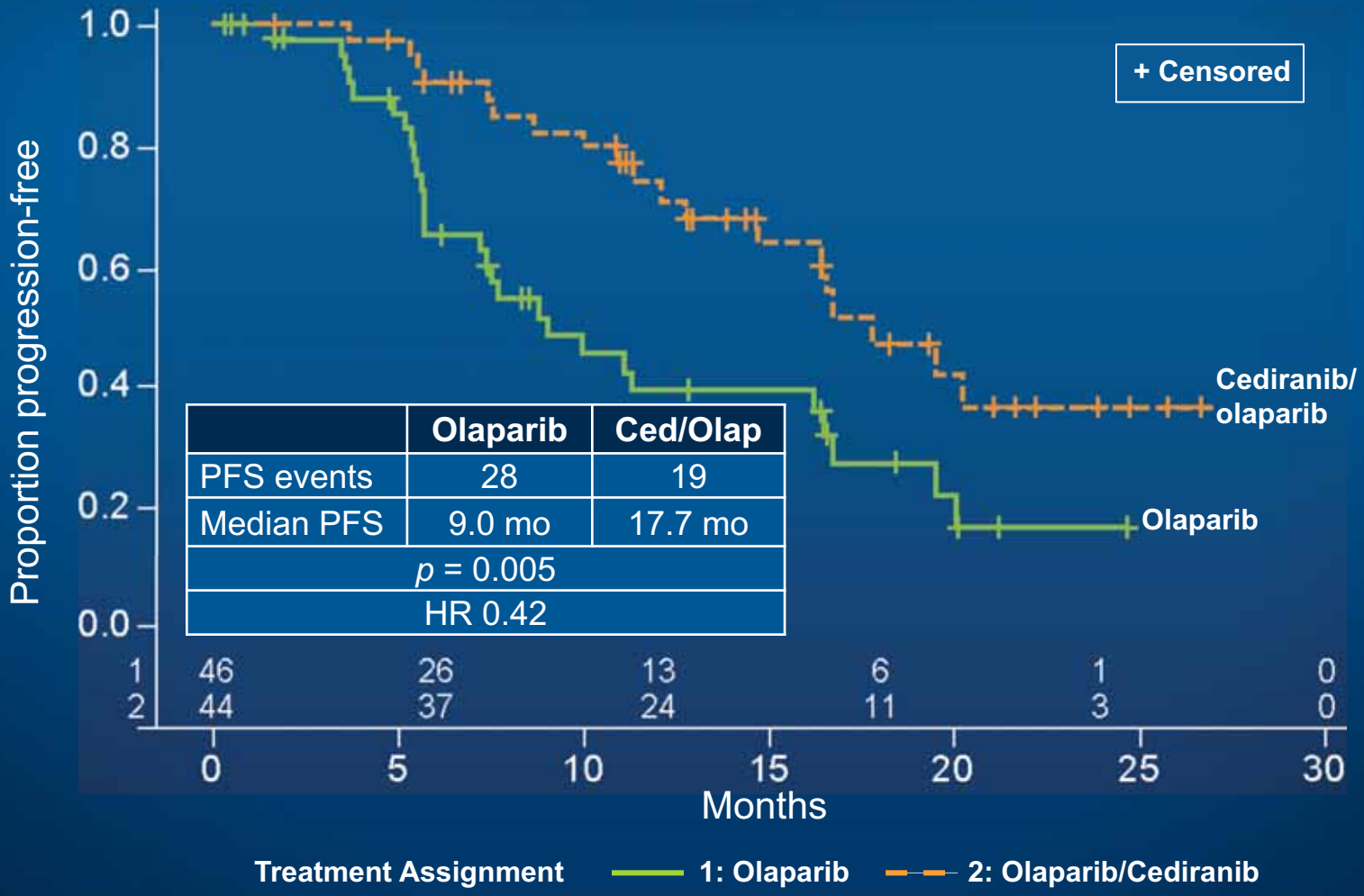
Module 4:
Future Directions and New Agents

Future Directions and New Agents

- Novel anti-angiogenic strategies in OC, including tyrosine kinase inhibitors (eg, cediranib, nintedanib) and the peptibody trebananib
- Mechanism of action, early data and side effects and toxicities associated with mirvetuximab soravtansine
- Available safety and efficacy data with anti-PD-1/PD-L1 antibodies in OC
- Other novel agents and strategies under investigation



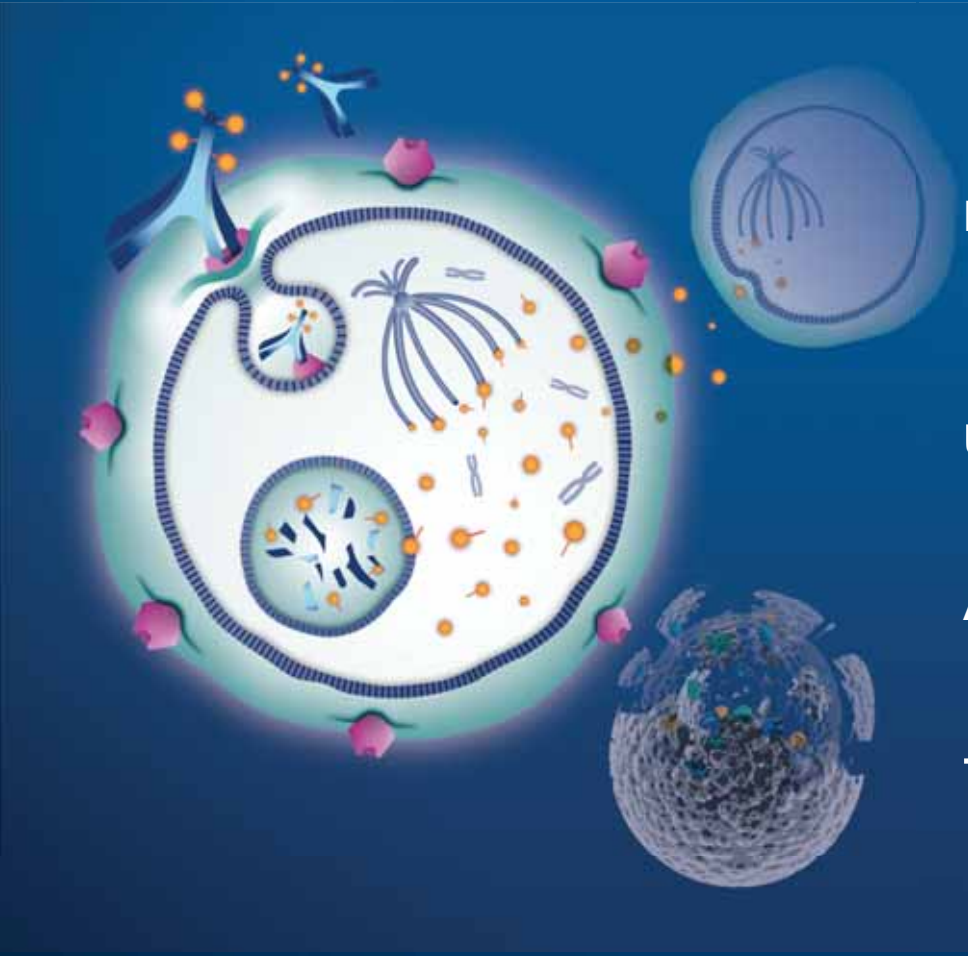
Primary Outcome: Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone



	Olaparib	Ced/Olap
PFS events	28	19
Median PFS	9.0 mo	17.7 mo
p = 0.005		
HR 0.42		

Liu J et al. *Proc ASCO* 2014;Abstract LBA5500.

Mirvetuximab Soravtansine (IMGN853) Mechanism of Action



AN INTEGRATED SYSTEM

Linker

- Cleavable linker stable in the blood stream
- Bystander killing of neighboring cancer cells

Ultra-potent anticancer agent

- DM4 — a potent tubulin-targeting agent

Antibody (Ab)

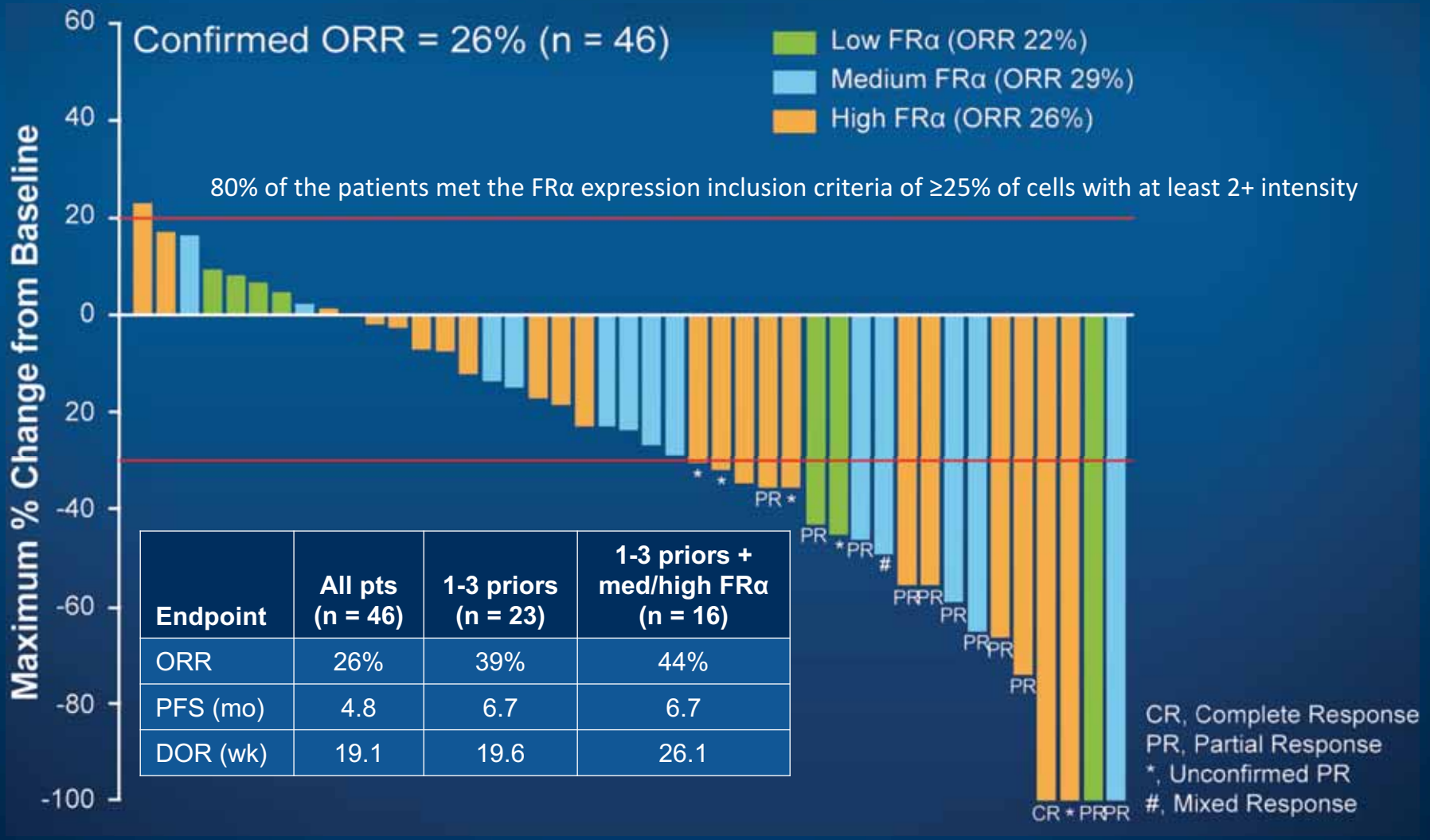
- A folate receptor α (FRα)-binding antibody

Target

- Highly expressed in ovarian and other cancers

Martin LP et al. AACR/EORTC/NCI 2015;Poster C47.

Mirvetuximab Soravtansine Monotherapy in Platinum-Resistant EOC



Endpoint	All pts (n = 46)	1-3 priors (n = 23)	1-3 priors + med/high FRα (n = 16)
ORR	26%	39%	44%
PFS (mo)	4.8	6.7	6.7
DOR (wk)	19.1	19.6	26.1

Moore KN et al. *Proc ASCO* 2016;Abstract 5567.

Efficacy of Nivolumab in Platinum-Resistant Ovarian Cancer

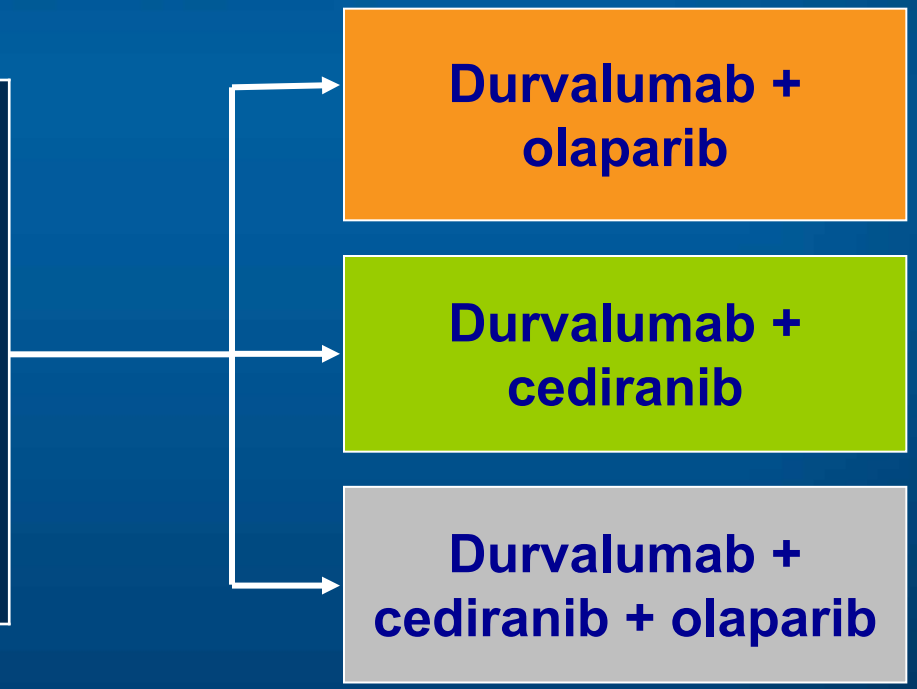
PD-1 inhibitor	No. pts	ORR	DCR	Median PFS	Median OS
Nivolumab 1 & 3 mg/kg	20	3/20 (15%)	9/20 (45%)	3.5 mo	20.0 mo

Grade 3/4 AE rate: 8/20 (40%)

Hamanishi J et al. *J Clin Oncol* 2015;33(34):4015-22.

Phase I/II Study of Durvalumab (MEDI4736) with Olaparib and/or Cediranib

- Advanced or recurrent solid tumors (ovarian, triple-negative breast, lung, prostate, colorectal)
- No prior checkpoint inhibitor therapy
- (N = 338)



Primary endpoints:

- Phase I: Recommended Phase II dose, safety in all patients
- Phase II: Overall response rate for patients with recurrent OC

www.clinicaltrials.gov; NCT02484404

Ongoing Phase III Trials of of Anti-PD-1/PD-L1 Checkpoint Inhibitors in Ovarian Cancer

- ATALANTE: Atezolizumab + platinum-containing chemo + bev in late relapse
- NCI-2016-01081: PLD/atezolizumab ± bevacizumab vs PLD/bevacizumab in platinum resistant, relapsed
- JAVELIN Ovarian 200: Avelumab, PLD or the combination in platinum relapsed
- IMagyn050: Carbo/paclitaxel/bev ± atezolizumab in newly diagnosed Stage III-IV
- JAVELIN Ovarian 100: Chemo ± avelumab maintenance, chemo + avelumab followed by avelumab maintenance

www.clinicaltrials.gov. Accessed May 2017.

Reminder

Please turn in your CNE course evaluation for credit as you exit the activity.

Thank you for joining us.