Advancements in Gynecologic Cancer Trials

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Talk Objectives

- Discuss clinical advancements in the field of gynecologic oncology
  - **Ovarian Cancer**
    - PARP inhibition
    - De-escalation treatment for low-grade disease
  - **Endometrial Cancer**
    - Immunotherapy
    - HER2

The Decade of Gynecologic Cancer Advances

Published in final edited form as:
Lancet Oncol. 2013 February ; 14(2): 134–140. doi:10.1016/S1470-2045(12)70572-7.

A Phase Ii Trial Of Selumetinib (Azd6244) In Women With Recurrent Low-Grade Serous Carcinoma Of The Ovary Or Peritoneum: A Gynecologic Oncology Group Trial

John Farley, MD[1], William E. Brady, PhD[2], Vinod Vathipadiekal, PhD[3], Heather A. Lankes, PhD[2], Robert Coleman, MD[4], Mark A. Morgan, MD[5], Robert Mannel, MD[6], S. Diane Yamada, MD[7], David Mutch, MD[8], William H. Rodgers, MD[9], Michael Birrer, MD, PhD[3], and David M. Gershenson, MD[4]

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Published in final edited form as:
Cancer. 2014 February 1; 120(3): 344–351. doi:10.1002/cncr.28421.

Efficacy and Safety of Bevacizumab in Recurrent Sex Cord-Stromal Ovarian Tumors: Results of a Phase II Trial of the Gynecologic Oncology Group

Jubilee Brown, MD[1] [Associate Professor], William E. Brady, PhD[2] [Statistician], Julian Schink, MD[3] [Professor], Linda Van Le, MD[4] [Professor], Mario Leitao, MD[5] [Assistant Member], S. Diane Yamada, MD[6] [Professor], Koen de Geest, MD[7] [Clinical Professor], and David M. Gershenson, MD[8] [Professor]

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study

Martee L. Hensley, Danielle Enserro, Helen Hatcher, Petronella B. Ottevanger, Anders Krarup-Hansen, Jean-Yves Blay, Cyril Fisher, Katherine M. Moxley, Shashikant B. Lele, Jayanthi S. Lea, Krishnansu S. Tewari, Premal H. Thaker, Oliver Zivanovic, David M. O'Malley, Katina Robison, and David S. Miller

Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial

David M Gershenson, Austin Miller, William E Brady, James Paul, Karen Carty, William Rodgers, David Millan, Robert L Coleman, Kathleen N Moore, Susana Banerjee, Kate Connolly, Angeles Alvarez Secord, David M O'Malley, Oliver Dorigo, Stephanie Gaillard, Hani Gabra, Brian Slomovitz, Parviz Hanjani, John Farley, Michael Churchman, Ailith Ewing, Robert L Hollis, C Simon Herrington, Helen Q Huang, Lari Wenzel, Charlie Gourley

original reports

MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum

Bradley J. Monk, MD[1]; Rachel N. Grisham, MD[2]; Susana Banerjee, PhD[3]; Elsa Kalbacher, MD[4]; Mansoor Raza Mirza, MD[5]; Ignacio Romero, MD[6]; Peter Vuylsteke, MD[7,8]; Robert L. Coleman, MD[9]; Felix Hilpert, MD[10]; Amit M. Oza, MD[11]; Anneke Westermann, MD, PhD[12]; Martin K. Oehler, MD, PhD[13]; Sandro Pignata, MD, PhD[14]; Carol Aghajanian, MD[1]; Nicoletta Colombo, MD[15]; Esther Drill, DrPH[2]; David Cibula, MD, PhD[16]; Kathleen N. Moore, MD[17]; Janna Christy-Bittel, MSN[18]; Josep M. del Campo, MD[19]; Regina Berger, PhD[20]; Christian Marth, MD, PhD[21]; Jalid Sehouli, MD[22]; David M. O'Malley, MD[23]; Cristina Churruca, MD[24]; Adam P. Boyd, PhD[18]; Gunnar Kristensen, MD, PhD[25]; Andrew Clamp, MD, PhD[26]; Isabelle Ray-Coquard, MD, PhD[27]; and Ignace Vergote, MD, PhD[28]

Journal of Clinical Oncology > List of Issues > Volume 40, Issue 9 >
ORIGINAL REPORTS | Gynecologic Cancer

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

Matthew A. Powell, MD[1]; Virginia L. Filiaci, PhD[2]; Martee L. Hensley, MD[3]; Helen Q. Huang, MS[2]; Kathleen N. Moore, MD[4]; Krishnansu S. Tewari, MD[5]; Larry J. Copeland, MD[6]; Angeles A. Secord, MD[7]; David G. Mutch, MD[8]; Alessandro Santin, MD[9]; David P. Warshal, MD[10]; Nick M. Spirtos, MD[11]; Paul A. DiSilvestro, MD[12]; Olga B. Ioffe, MD[13]; and David S. Miller, MD[14]

Published in final edited form as:
Gynecol Oncol. 2018 July ; 150(1): 9–13. doi:10.1016/j.ygyno.2018.04.572.

Phase II Study of Single-Agent Cabozantinib in Patients with Recurrent Clear Cell Ovarian, Primary Peritoneal or Fallopian Tube Cancer (NRG-GY001)

Panagiotis A. Konstantinopoulos, MD, PhD[1], William E. Brady, PhD[2], John Farley, MD[3], Amy Armstrong, MD[4], Denise S. Uyar, MD[5], and David M. Gershenson, MD[6]

Clinical Trial > Gynecol Oncol. 2022 Jan;164(1):12-17. doi: 10.1016/j.ygyno.2021.10.087. Epub 2021 Nov 8.

Phase II study of enzalutamide in androgen receptor positive, recurrent, high- and low-grade serous ovarian cancer

Beryl L Manning-Geist [1], Sushmita B Gordhandas [1], Dilip D Giri [2], Alexia Iasonos [3], Qin Zhou [4], Jeffrey Girshman [5], Roisin E O'Cearbhaill [6], Dmitriy Zamarin [6], Stuart M Lichtman [6], Paul J Sabbatini [6], William P Tew [6], Karen Li [7], Autumn S McDonnell [8], Emeline M Aviki [9], Dennis S Chi [9], Carol A Aghajanian [6], Rachel N Grisham [10]

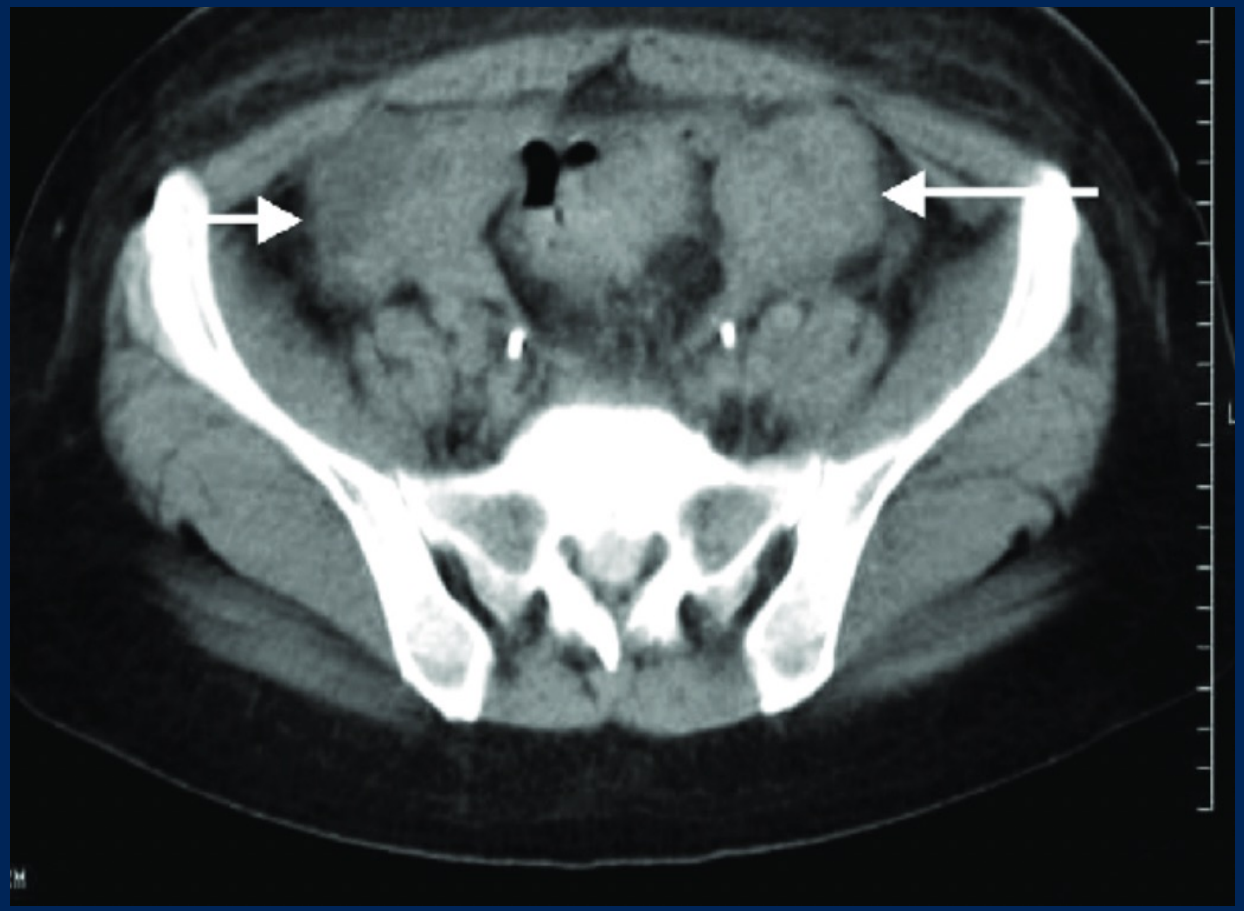
Published in final edited form as:
Clin Cancer Res. 2020 August 01; 26(15): 3928–3935. doi:10.1158/1078-0432.CCR-20-0953.

Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis

Amanda N. Fader[1], Dana M. Roque[2], Eric Siegel[3], Natalia Buza[4], Pei Hui[4], Osama Abdelghany[4], Setsuko Chambers[5], Angeles Alvarez Secord[6], Laura Havrilesky[6], David M. O'Malley[7], Floor J. Backes[7], Nicole Nevadunsky[8], Babak Edraki[9], Dirk Pikaart[10], William Lowery[11], Karim ElSahwi[12], Paul Celano[13], Stefania Bellone[4], Masoud Azodi[4], Babak Litkouhi[14], Elena Ratner[4], Dan-Arin Silasi[4], Peter E. Schwartz[4], Alessandro D Santin[4,*]

CASE #1

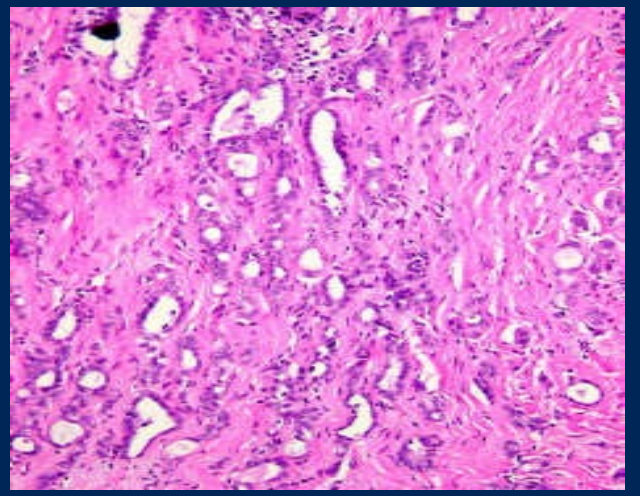
- A 31 year old presents with abdominal bloating and pain and early satiety. On CT scan has a bilateral, large cystic and solid ovarian masses and an omental cake. HER CA-125 is 360. What is the next best step?

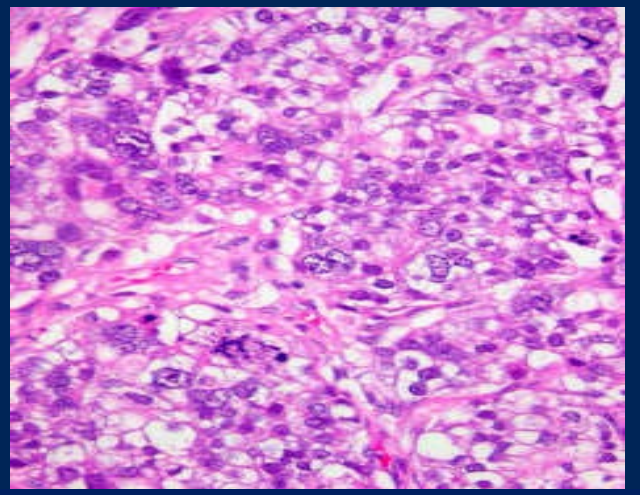


Two-Tiered Histologic Criteria

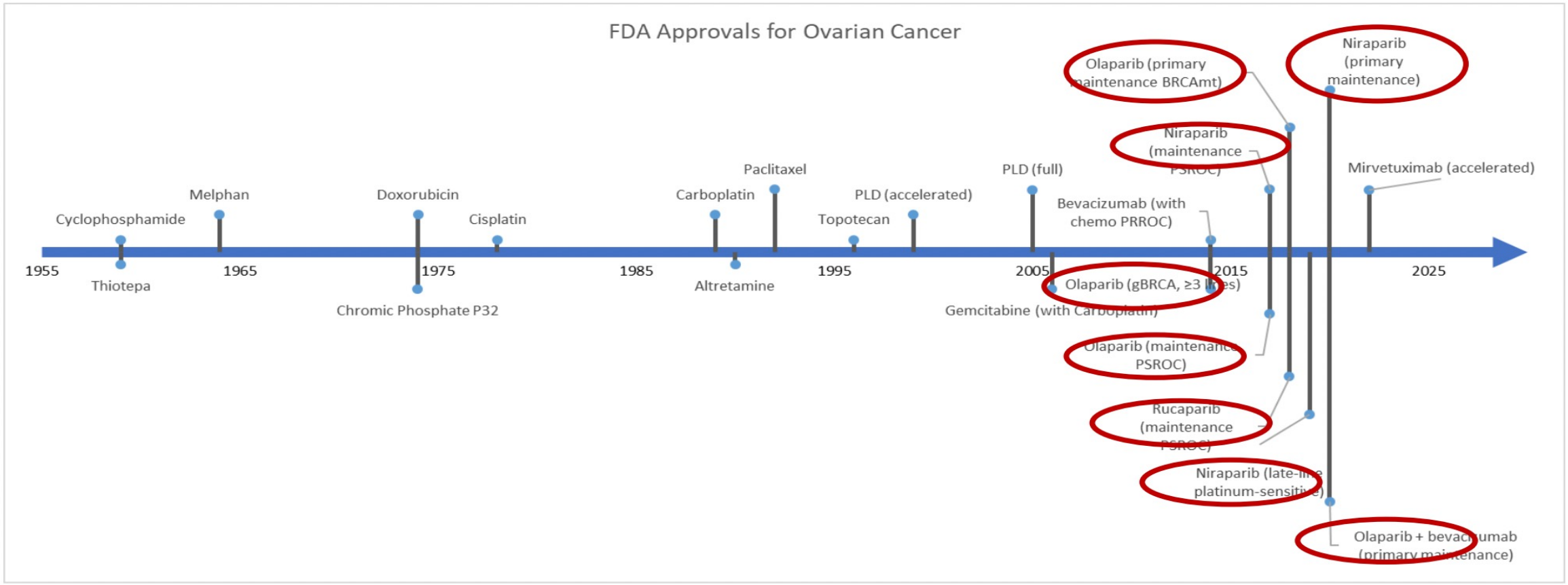
Variable	LGSC (Grade 1)	HGSC (Grade 2/3)
Nuclear atypia	Uniform round to oval with little variation	+++ Marked variation
Mitotic Index	<12 mitosis per 10 hpf	>12 mitoses per 10 hpf
Chromatin and variation in size of nucleus	Little	Marked (nuclear size ratio ≥3)
Mutation	KRAS ++ BRAF + ER/PR +++ PAX2 +	P53 +++
Precursor	Serous borderline tumor	Tubal intraepithelial neoplasia

Malpica et al, Am J Path, 2007; Kurman et al, Am J Path, 2007





70 Years of Advances in Ovarian Cancer



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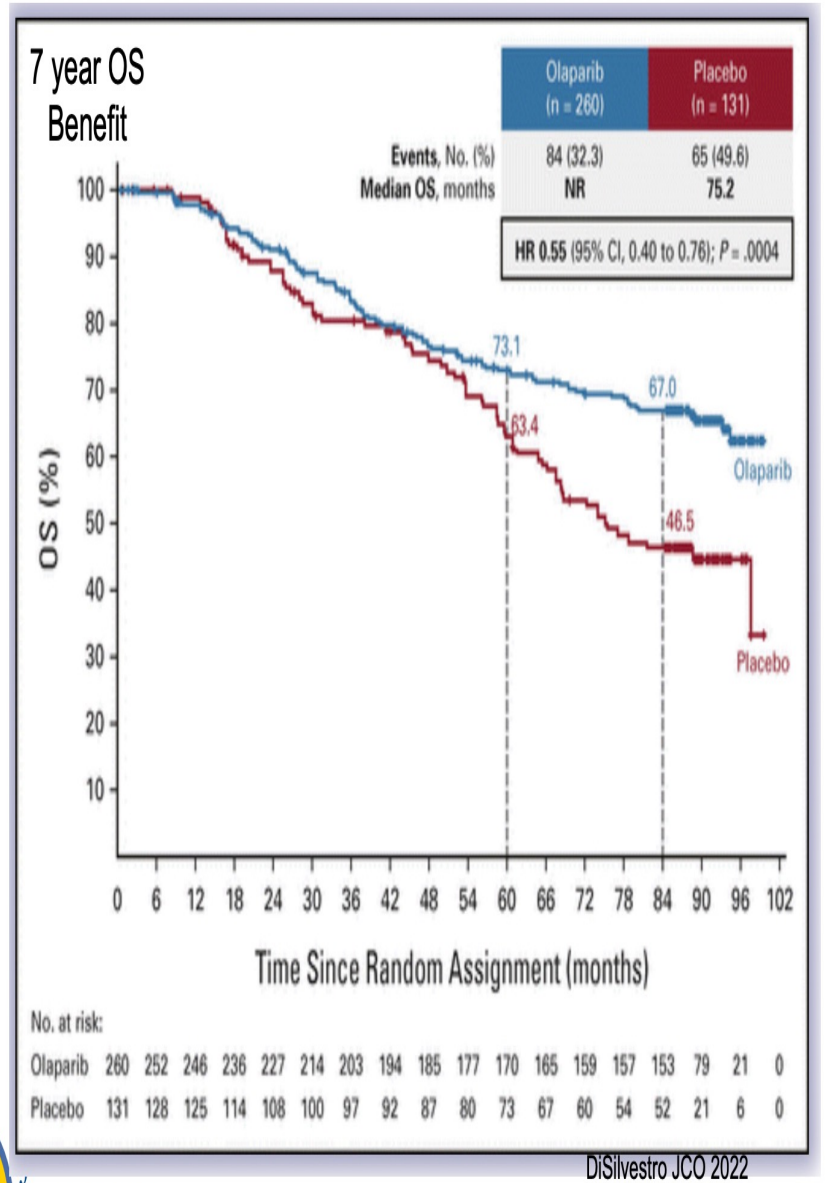
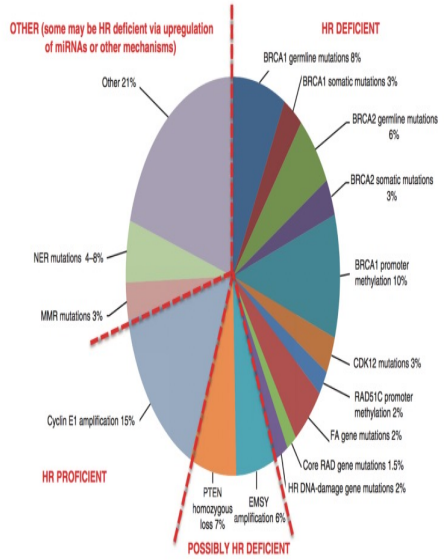
Paradigm Changing Benefit of PARP inhibitors



DiSilvestro JCO 2022



Konstantinopoulos Cancer Discovery 2015

PARP Inhibitors in Ovarian Cancer

FDA Approval

Dec 2022

Ovarian Cancer Clinical Setting

Population		Upfront maintenance	Plat Sens Rec (maintenance post chemo)	Plat Sens Rec (treatment)	Plat Res Rec (treatment)
BRCA mutated (*BRCAm or HRD)	III	SOLO-1 (olaparib)	SOLO-2 (olaparib)	SOLO-3 (olaparib vs chemo) ARIEL 4 (rucaparib v chemo)	~~olaparib~~ XXX
	II			~~Study 42 (olaparib¥)~~ XXX ~~ARIEL 2 (rucaparib#)~~ XXX ~~QUADRA (niraparib*¤)~~ XXX	~~QUADRA (niraparib*)~~
All Comers	III	PAOLA-1 (olaparib/bev*) VELIA (veliparib) PRIMA (niraparib) ATHENA-MONO (rucaparib)	~~Study 19 (olaparib)~~ NOVA (niraparib@) BRCA only ARIEL3 (rucaparib)	AVANOVA2 (niraparib+/-bev) GY-004 (olaparib vs other)	
	II	OVARIO (niraparib/bev)	MEDIOLA (olaparib/durva or olaparib/durva/bev)	LIGHT study (olaparib) ARIEL2/Study 10 (rucaparib) CLIO (olaparib vs. chemo)	

@Notice of Inferior OS from NOVA trial (5/2022)

XXX Withdrawal of FDA approval:

#Inferior OS in ARIEL 4, rucaparib withdrawal by Clovis (6/10/22)

¥SOLO3 Inferior OS, olaparib withdrawal by Astra Zeneca (8/26/22)

-AZ requiring reconsent for SOLO-3, Study 42 and LIGHT

¤QUADRA single arm w/o comparator, niraparib withdrawal by GSK: (9/6/22)

2nd line maintenance restricted to **BRCA Only** (11/2022)

XXX NCCN Change from Category 2A to Category 3

8/25/2022 ASCO Guidelines Update: PARPi monoRx should not routinely be offered

Adapted from Dr. Deborah Armstrong

MEDICINE

MDS/AML in Randomized Ovarian Cancer PARP Inhibitor Maintenance Trials

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Trial	Setting	Agent	PARPi Duration	MDS/AML Events by arm PARPi, n (%)	Comparator, n (%)
SOLO1[4]	1L maint	Olaparib	2 years	3/260 (1.5)	1/130 (0.8)
PRIMA[6]	1L maint	Niraparib	3 years	1/484 (<1)	0/244
PAOLA1[5]	1L maint	Olaparib	2 years	6/535 (1)	1/267 (0.4)
ATHENA MONO[9]	1L maint	Rucaparib	2 years	2/425 (0.5)	0/110
Study19[8]	PS maint	Olaparib	UDP, 18% >3yrs	2/136 (1.5)	1/129 (<1)
SOLO2[2]	PS maint	Olaparib	UDP, mean 29.1 mos	16/195 (8)	4/99 (4)
NOVA[3]	PS maint	Niraparib	UDP	13/367 (3.5)	3/179 (1.7)
g*BRCA*m				9/136 (6.6)	2/65 (3.1)
non-g*BRCA*m				4/231 (1.7)	1/114 (0.9)
ARIEL3[7]	PS maint	Rucaparib	UDP, median 8.3 mos	14/375 (3.8)	6/189 (3.2)
PARPi ≥24m[10]				9/79 (11.4%)	
non-g*BRCA*m				5/245 (2.0)	1/123 (0.8)
g*BRCA*m				9/130 (6.9)	3/63 (4.8)
PARPi ≥24 mos				7/46 (15.2)	

[2]Poveda A, et al. Lancet Oncol 2021, [3]Matulonis U. et al. SGO 2021, [4]DiSilvestro P, et al. J Clin Oncol 2022, [5]Ray-Coquard I et al. NEJM Dec 2019, [6]Gonzalez-Martin A et al. NEJM 2019, [7]Coleman RL et al. IGCS 2022, [8]Lederman J et al. Lancet 2016 17: 1579-89, [9]Monk B et al. J Clin Oncol 2022, [10]O'Malley et al. Gyn Onc 10/2022

1L maint – maintenance treatment after completion of first line chemotherapy treatment
PS maint – maintenance treatment after completion of second line or greater platinum sensitive chemotherapy treatment
UDP - until disease progression

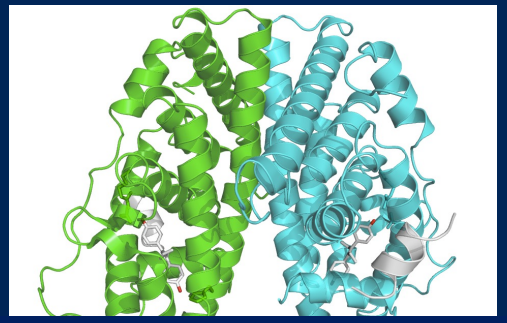
Courtesy of Dr. Deborah Armstrong

Key Considerations for PARP inhibitors

- Use them early in disease course – detrimental after exposure to multiple lines of chemotherapy
  - Must test for germline & somatic BRCA mutations AND HR deficiency at diagnosis/during initial chemotherapy
- Limit duration of exposure to PARP inhibitors – longer duration associated with increased risk of MDS/AML

Low-grade Serous Ovarian Carcinoma, Granulosa Cell, Low-Grade Endometrioid, Low-grade Endometrial Stromal Sarcoma Tumor Characteristics

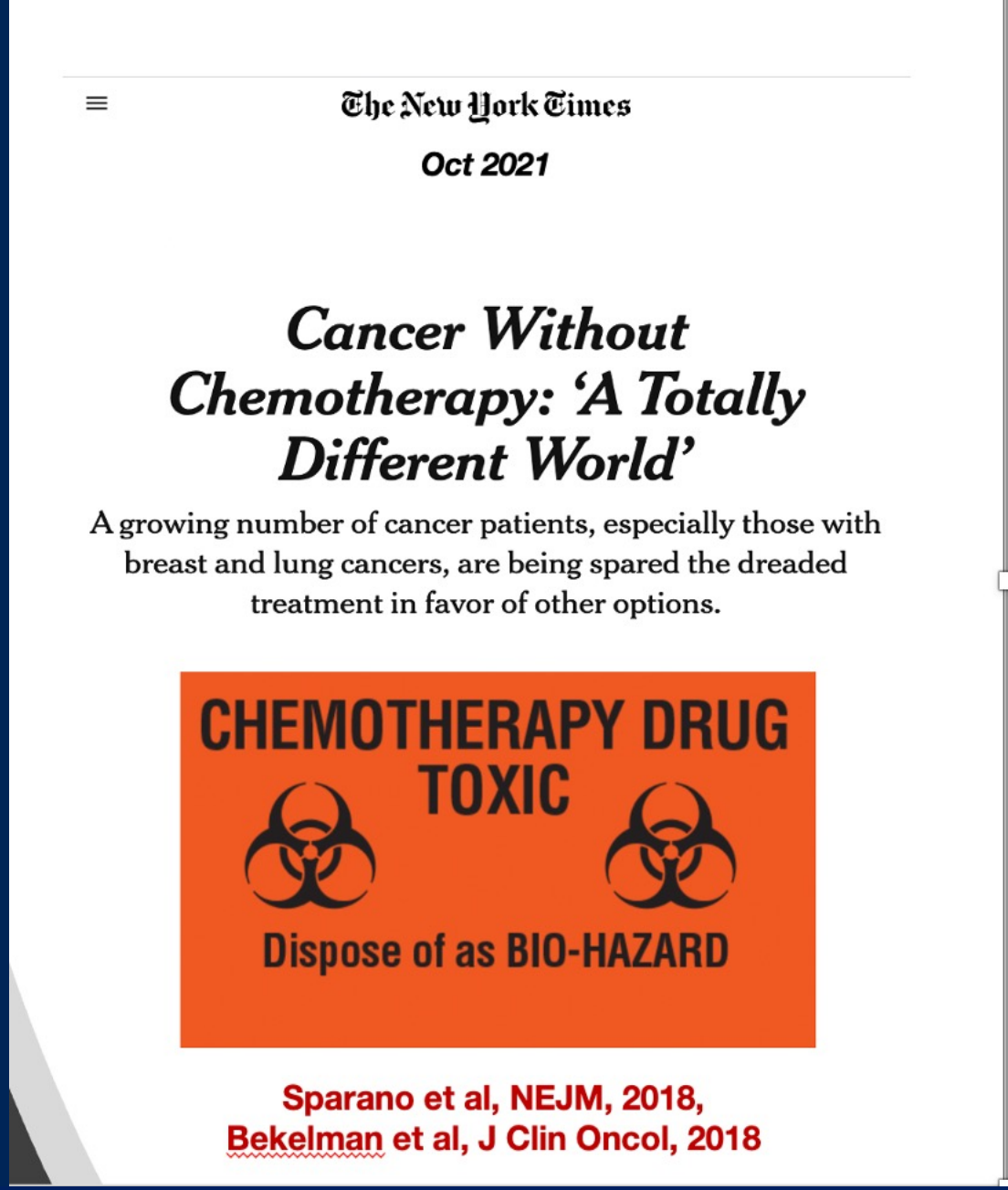
Relatively indolent growth pattern, low mitotic activity, and more likely to express estrogen (80-90%+) and progesterone receptors (55%) than other cancer subtypes



More Cancers Being Treated without Chemotherapy

- A growing number of cancers treated with targeted therapy and without chemotherapy
  - Breast
  - Prostate
  - Bladder
  - Lung
  - Ovarian
  - Melanoma
  - Non-Hodgkins Lymphoma

- Leveraging endocrine (and other targeted) therapies may be as—or more—effective than conventional cytotoxic treatments



Breast Cancer Treatment Landscape: The Last 25 Years

- NCI and NCCN Guidelines recommended chemotherapy for >80-90% of patients with breast cancer

- Understanding of molecular basis of the disease & development of targeted therapies and genomic scoring systems began a shift in treatment paradigms

- Sequential endocrine therapy regimens comprise the standard of care for hormone receptor-positive (HR+) advanced breast cancer

NCCN National Comprehensive Cancer Network®

NIH NATIONAL CANCER INSTITUTE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

Joseph A. Sparano, M.D., Robert J. Gray, Ph.D., Della F. Makower, M.D., Kathleen I. Pritchard, M.D., Kathy S. Albain, M.D., Daniel F. Hayes, M.D., Charles E. Geyer, Jr., M.D., Elizabeth C. Dees, M.D., Matthew P. Goetz, M.D., John A. Olson, Jr., M.D., Ph.D., Tracy Lively, Ph.D., Sunil S. Badve, M.B., B.S., M.D., et al.

Endocrine Therapies We Use in GYN Oncology

- Aromatase inhibitors:
  - Letrozole, Anastrozole, Exemestane
- Fulvestrant +/- CDK4/6 inhibiton
- Leuprorelin
- Progesterone agents
- SERDs/SERMs

Most Patients with LGSOC Do Not Benefit from Platinum/Taxane-Based Therapy

AGO mega-database: four RCTs of >5000 pts, women w/ LGSOC were less likely to respond to chemo than those w/ HGSC

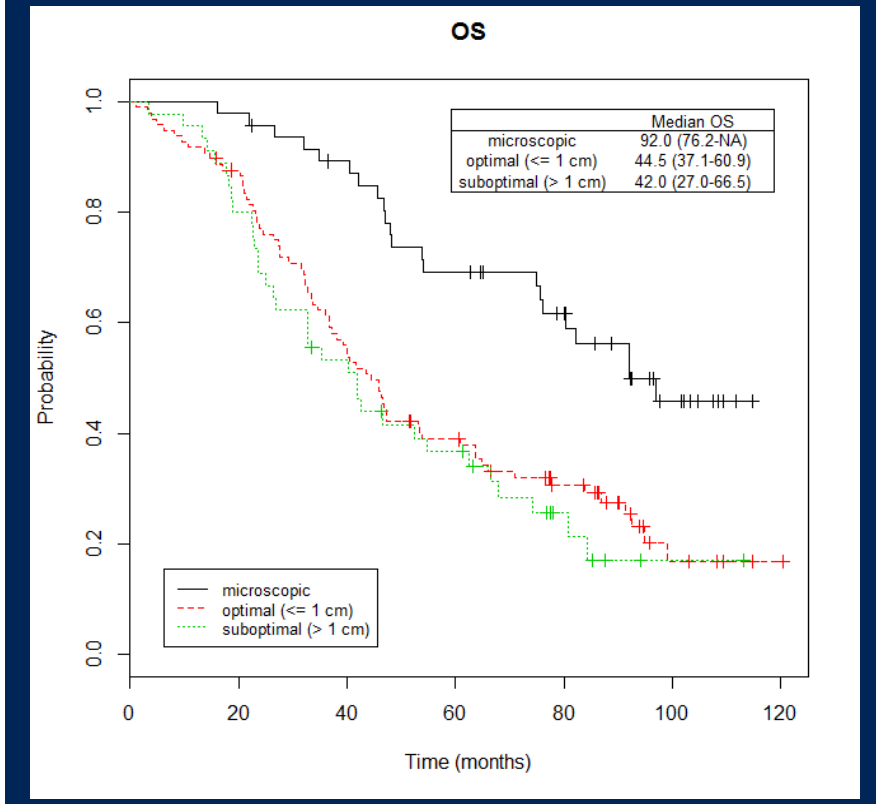
- 23.1% RR in LGSC suboptimal debulked cohort compared to 90.1% response rate in the HGSC control cohort (p<0.001)

NCDB study of 755 women with Stage IIIC-IV LGSOC

- Propensity score matched analysis
- Median OS not significantly different among 140 pts who received chemo after primary CRS (OS = 88 months) compared to 140 pts did not receive chemotherapy (OS = 95.9 months; *P*=0.7).

Grabowski et al, Gynecol Oncol 2016
Gockley et al, Obstet Gynecol, 2016

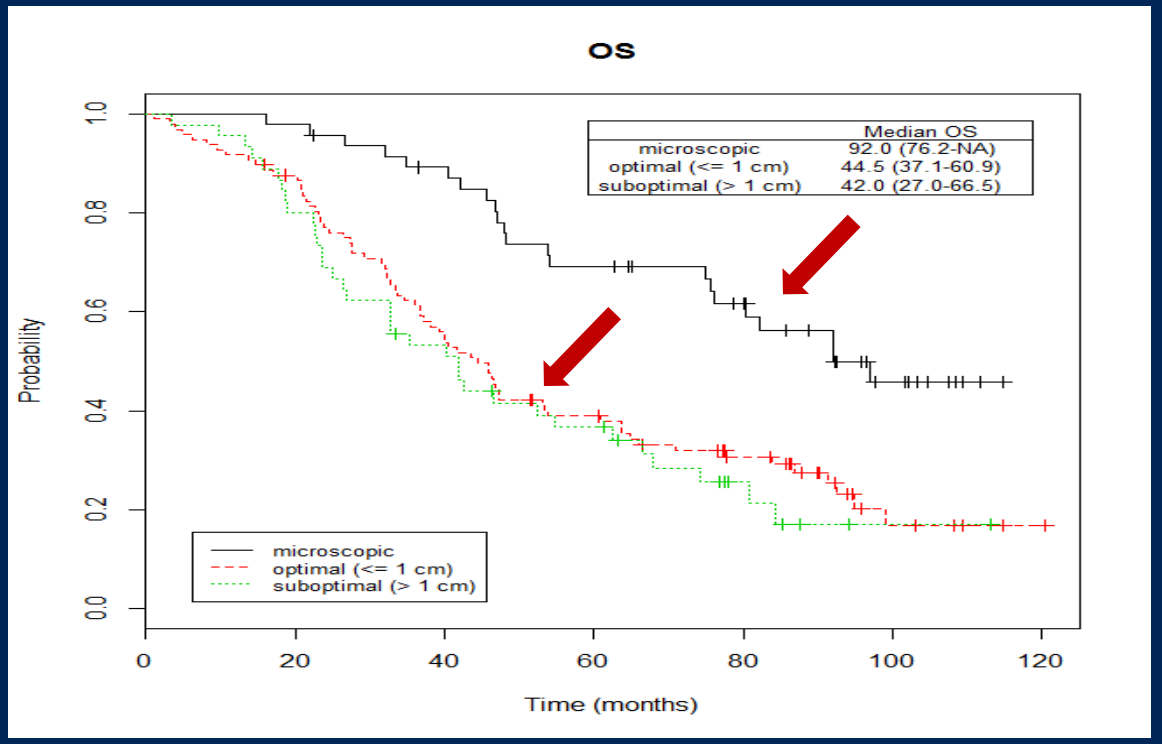
GOG 182



Fader et al, Obstet Gynecol, 2013

Ancillary Analysis of GOG 182

- **An ancillary analysis of women with stage III-IV epithelial ovarian cancer**
  - Treated with primary cytoreductive surgery
  - T/C compared with triplet or sequential doublet regimens
- **189 had Grade 1 serous disease (surrogate for LGSOC)**
- **On multivariate analysis, only residual disease status after primary**
- **debulking was significantly associated (p=.006) with survival (p=.006)**



Fader et al, *Obstet Gynecol*, 2013

Utilizing Hormonal Therapy to Treat Advanced LGSC

MD Anderson: 1° CRS→C/T +/- HMT (n=203)

- 70 received Hormonal therapy maintenance (HMT) after C/T
- **Median PFS carbo/paclitaxel/OBS vs. carbo/paclitaxel/HMT=26.4 vs. 64.9 mos (p<0.001)**
- Letrozole most common therapy

JHH: 1° CRS→hormonal monotherapy (n=27)

- Only 22% recurred after median follow-up of 41 months
- Median PFS and OS not reached but 2 year PFS 82.8% and OS 96.3%.

NRG ONCOLOGY™ Optimal treatment unknown

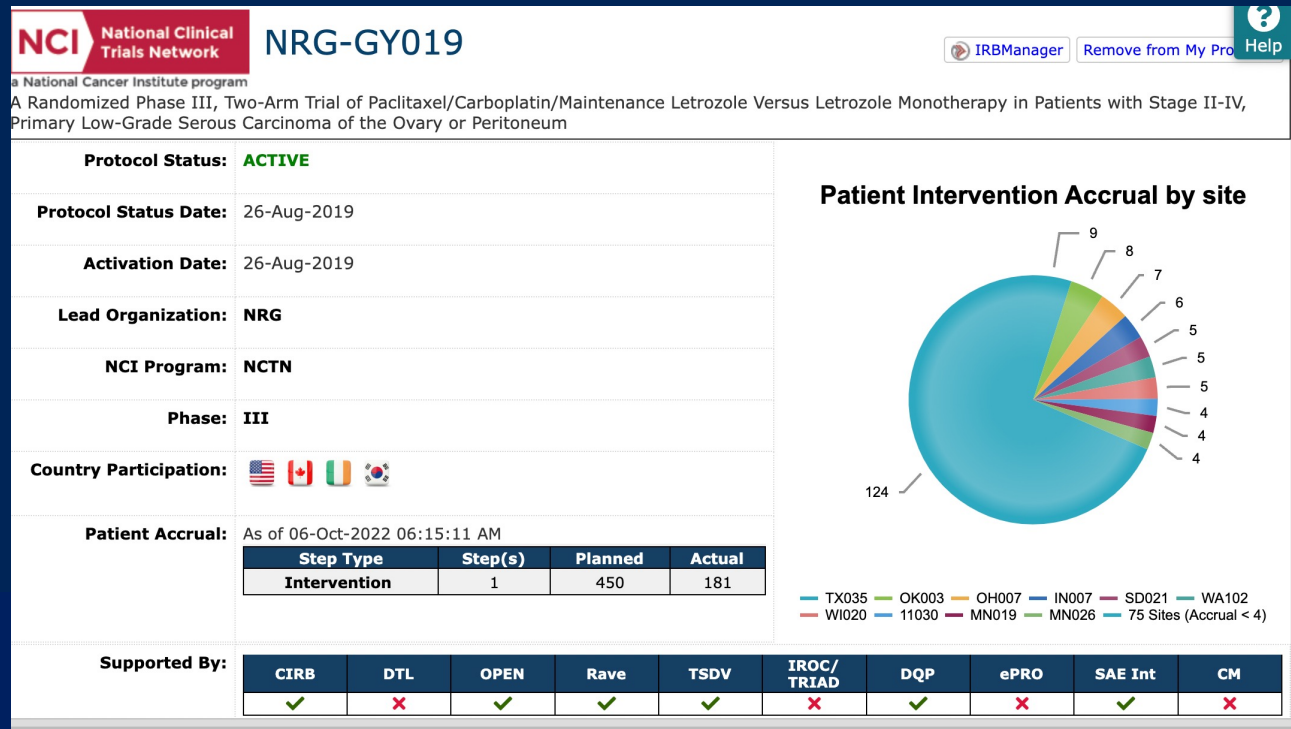
Gershenson et al, J Clin Oncol, 2016; Fader et al, Gynecol Oncol, 2016

NRG-GY019
A Randomized Phase III, Two-Arm Trial of Paclitaxel, Carboplatin, & Maintenance Letrozole Versus Letrozole Monotherapy in Patients with Stage II-IV, Primary Low-Grade Serous Carcinoma of the Ovary or Peritoneum

International Trial

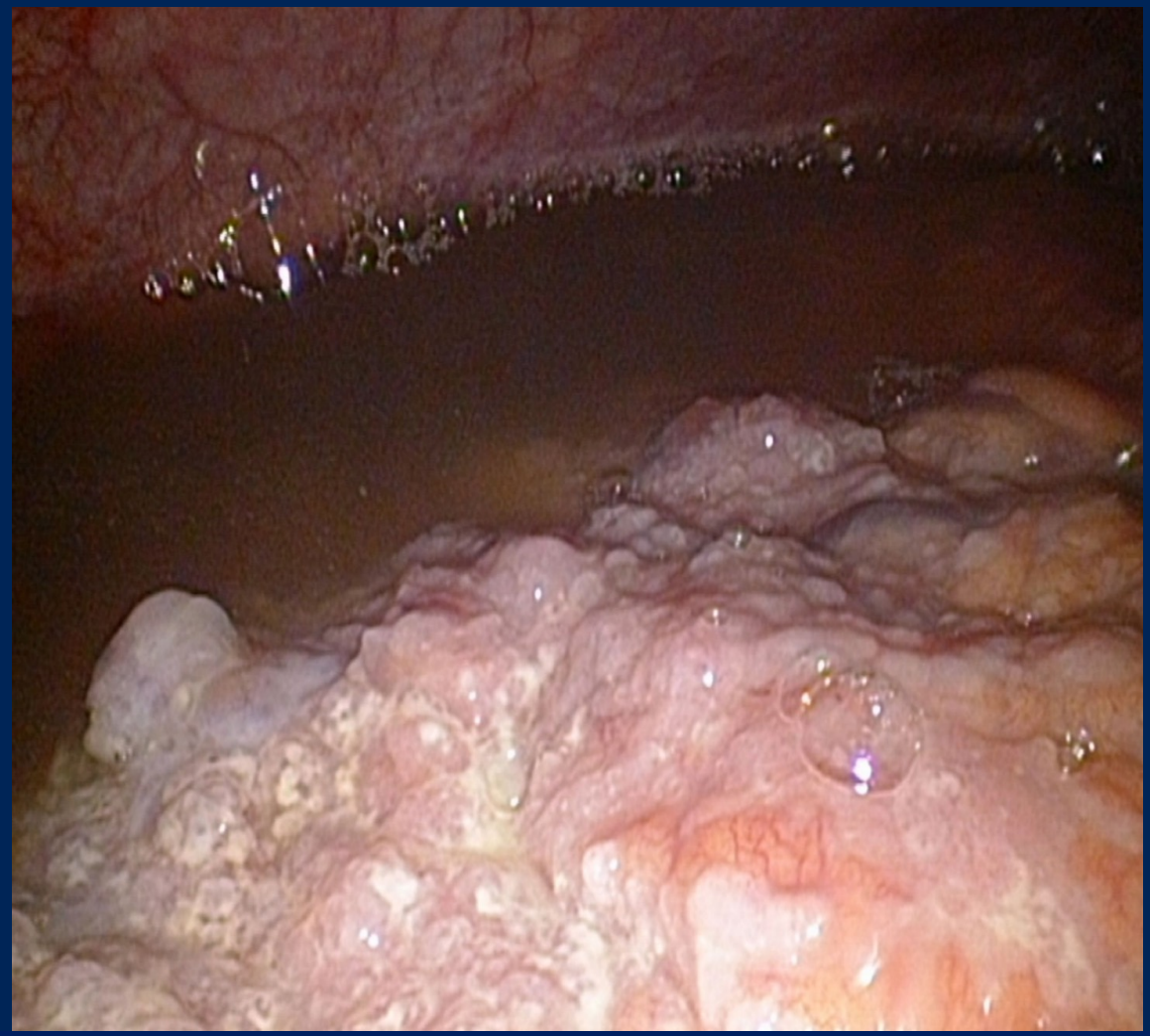
- Moving beyond the “Add on" clinical trial design model (i.e., building upon a chemo backbone)
- 65% of patients enrolled to date

NRG-019:
One of the first adjuvant trials in advanced ovarian cancer that does not contain a platinum/taxane treatment arms



Case #2

A 55-year old woman presents with carcinomatosis and lung metastases and on percutaneous biopsy is diagnosed with low-grade serous ovarian carcinoma? What is the next best step in treatment?

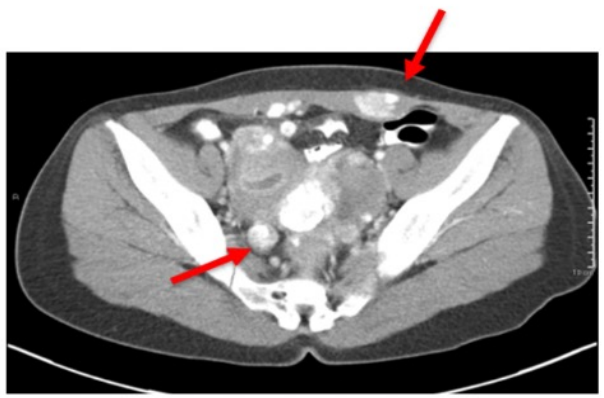


Is Carboplatin/Paclitaxel really the best we can do?

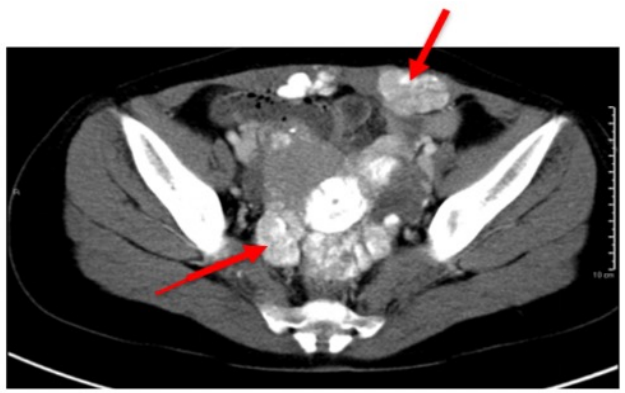
- **Response rates to neoadjuvantly-administered carboplatin/paclitaxel are ultra-suboptimal**

Clinical/Molecular Features	Low Grade Serous (LGS)	High Grade Serous (HGS)
Response Rate to Neoadjuvant Chemotherapy	4-23%	80-90%

Table acknowledgment: Rachel Grisham, MD



Pre-chemo



Progression and SBO after 2 cycles of chemotherapy

Gershenson et al, Gynecol Oncol, 2008
Cobb et al, Gynecol Oncol 2020
Scott et al, Gynecol Oncol 2020

Background

- LGSOC has similarities to hormone receptor positive breast cancer

- Based on the activity of anti-estrogen + CDK4/6 inhibitor combination therapy in HR+ breast cancer (e.g., the Monarch 2 and 3 trials, PFS benefit to combo therapy), this pilot phase II study was performed.

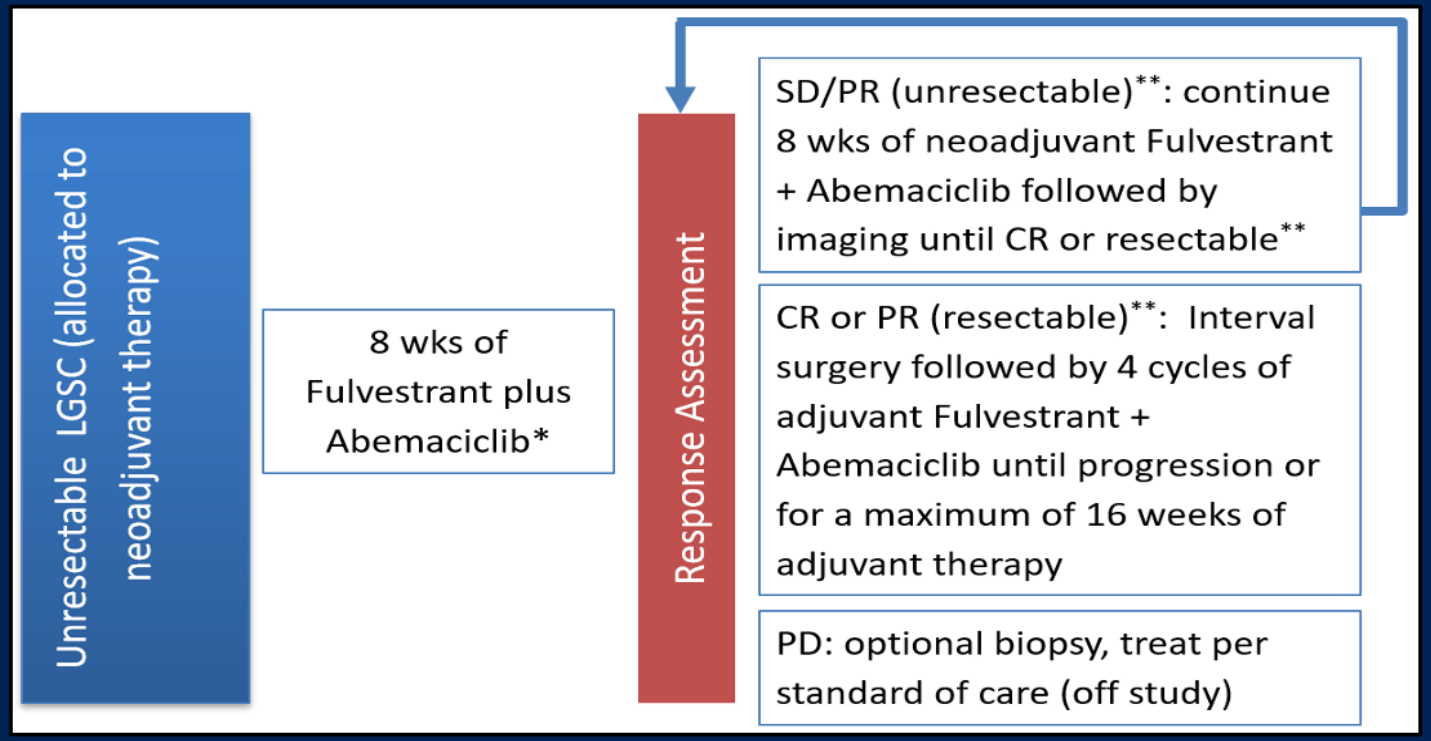
Sledge et al, J Clin Oncol, 2017
Stephens, Nature, 2019

Methods

Abstract ID: 5522

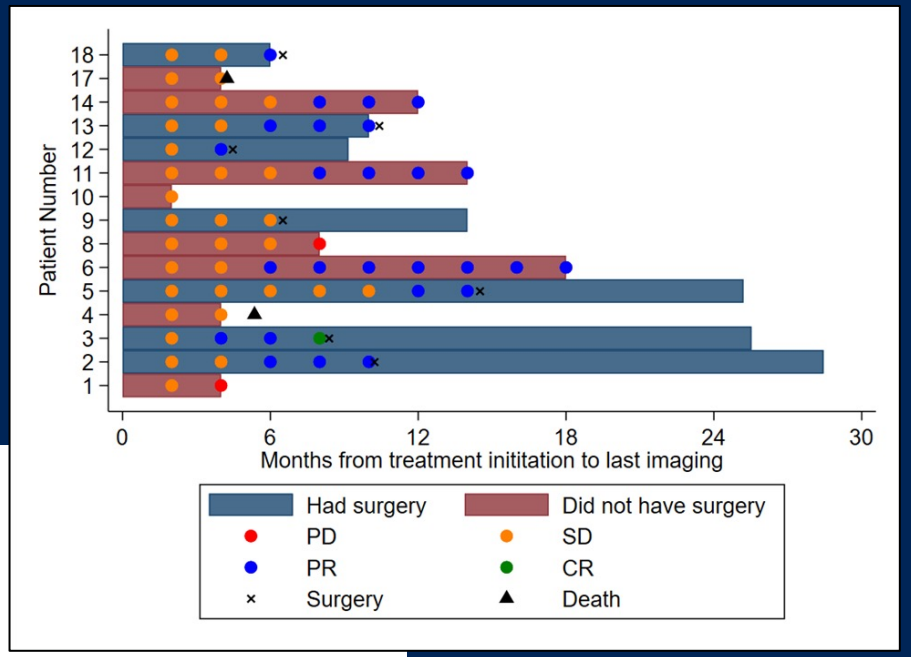
A Pilot Phase II Study of Neoadjuvant Fulvestrant plus Abemaciclib in Women with Advanced Low Grade Serous Carcinoma

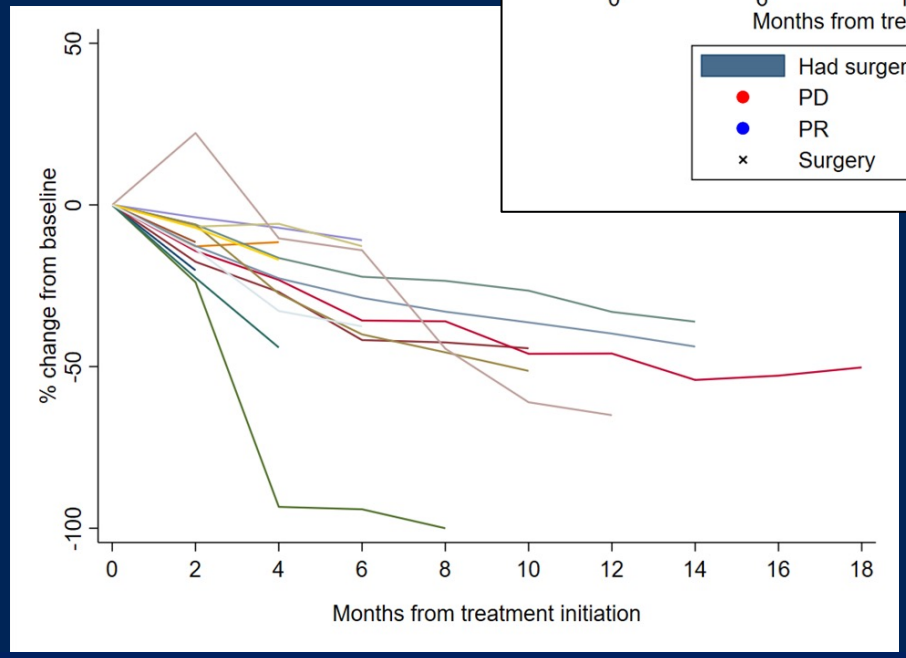
- Eligibility – women with unresectable, untreated stage III or IV LGSOC of the ovary, fallopian tube, or peritoneum



- Primary endpoint: clinical benefit rate
- Patients received fulvestrant (500mg IM on day 1 and 15 of the first 28-day cycle, followed by day 1 of subsequent cycles) and abemaciclib 150mg orally BID
- Following Interval CRS and completion of adjuvant treatment, patients transitioned to maintenance letrozole

Results





Best overall response N=15:

Partial response – 9/15 (60%)

** One with radiologic PR but with pathologic CR at ICS*

Stable disease – 6/15 (40%)

BOR Clinical Benefit Rate – 100%

Interval cytoreductive surgery:

Underwent surgical resection to date – 7/15 (47%)

Achieved complete gross resection – 5/7 (71%)

Achieved optimal cytoreduction – 7/7 (100%)

Most patients who achieved a PR did so between 4-8 months.

*Adverse events (grade 3 or 4) possibly related to abemaciclib occurred in 2 patients (13.3%) and included acute kidney injury (6.7%) and neutropenia (6.7%).

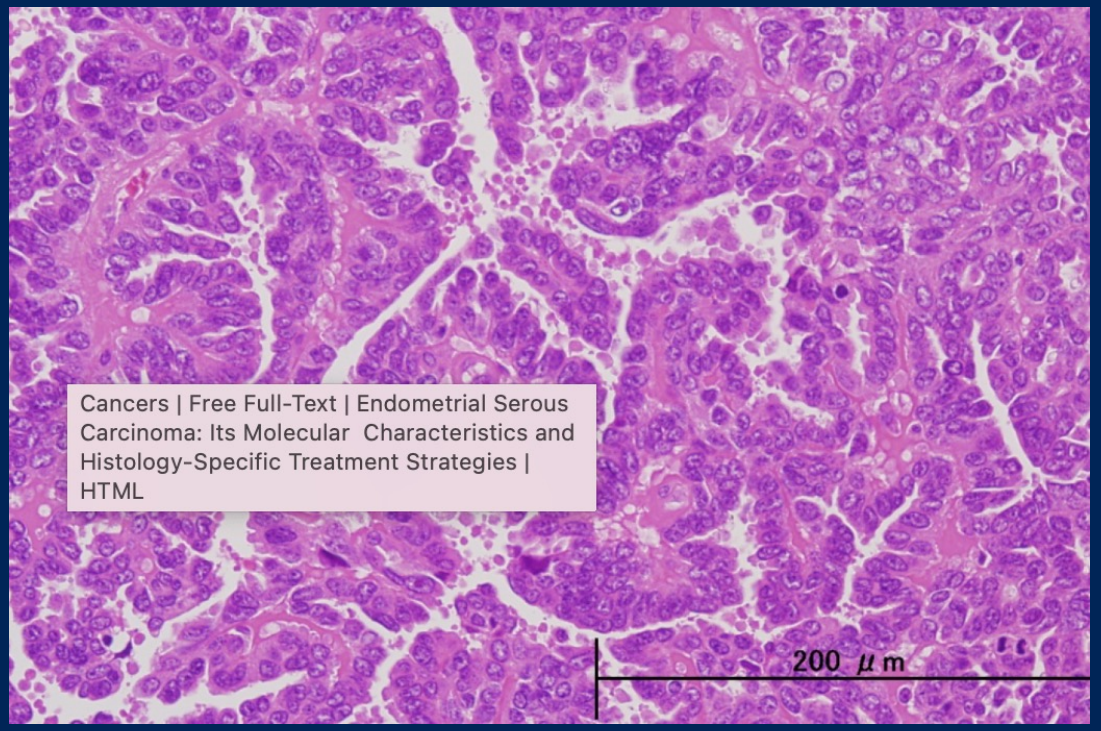
Results are Very Exciting…

- The first neoadjuvant treatment trial in advanced ovarian cancer to omit cytotoxic chemotherapy with promising results

- Small, physician selected, incompletely assessed patient cohort, unprecedented response rates in neoadjuvantly-treated population
  - 60% ORR and 100% CBR!
  - Expansion cohort data eagerly anticipated

Case #3

- A 64-year-old woman presents to her gynecologist with postmenopausal bleeding. Endometrial biopsy demonstrates a high-grade carcinoma of the endometrium with serous features. CT scan shows 2 enlarged pelvic lymph nodes but no other metastatic disease. What should the next best step in management be?



Endometrial Cancer Trends: Rare Tumors Matter

- **Incidence of many cancers (i.e., solid tumors) has plateaued or decreased in last two decades[1]**
- **Endometrial cancer (EC) incidence has increased annually, and mortality has more than doubled, from 1978-2013**
- **Rare tumor histologies account for 40-50% of deaths!**
- **Carbo/paclitaxel was SOC—GOG 209 (Miller, JCO 2012)**
- There is a high unmet need for effective therapies to treat advanced/recurrent EC.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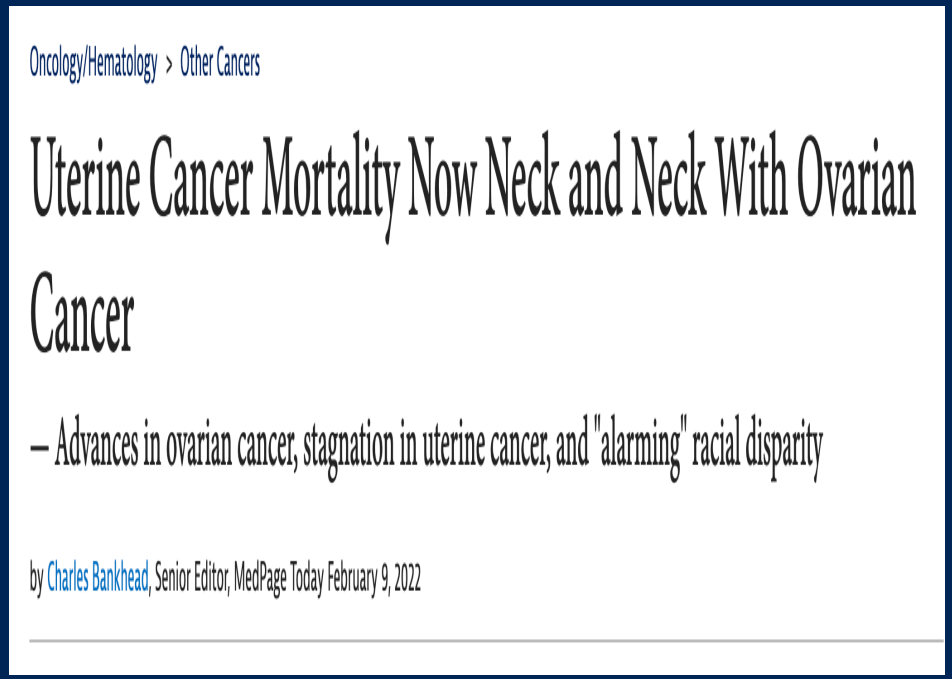

Oncology/Hematology › Other Cancers

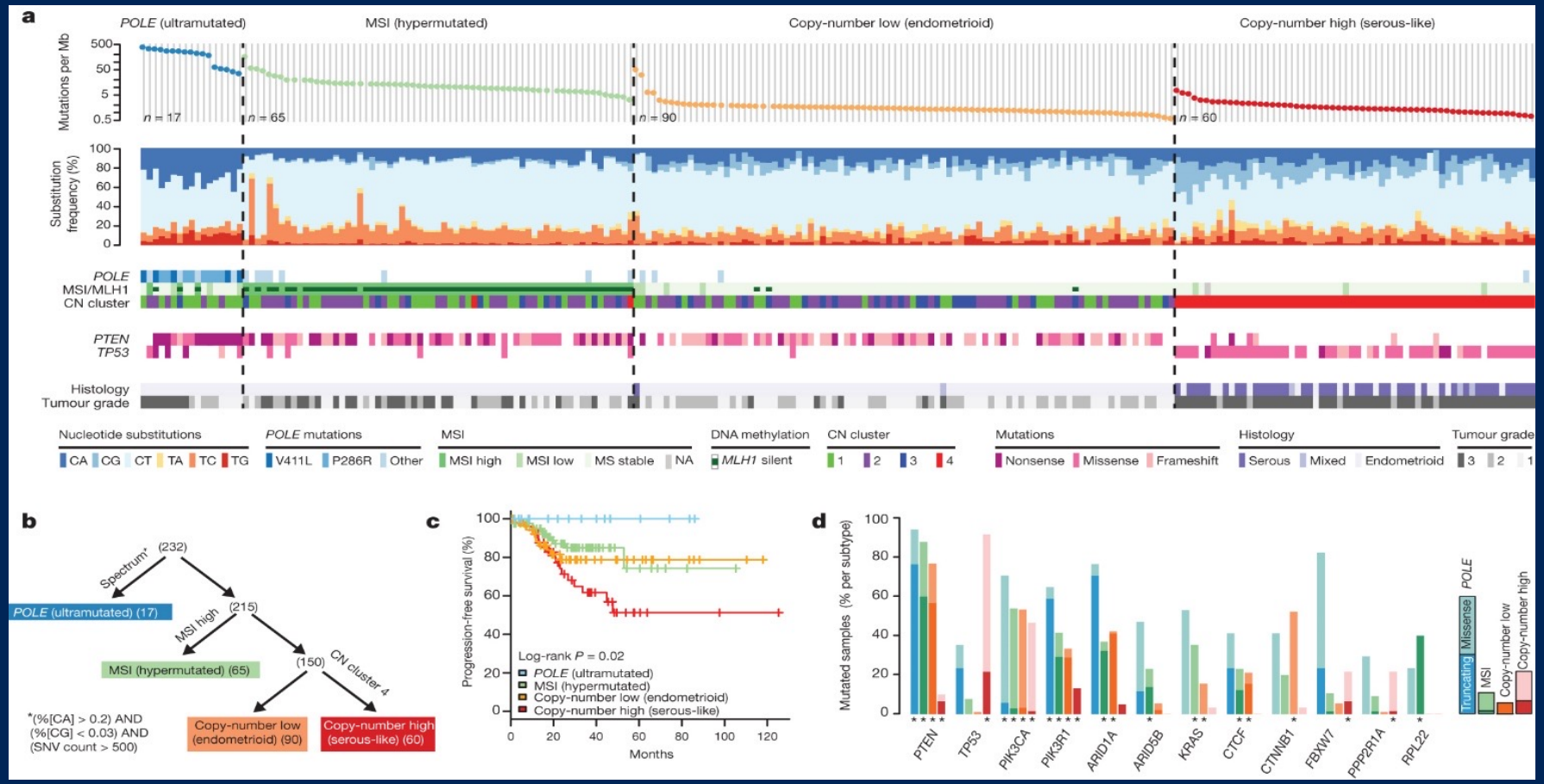
Uterine Cancer Mortality Now Neck and Neck With Ovarian Cancer

– Advances in ovarian cancer, stagnation in uterine cancer, and "alarming" racial disparity

by Charles Bankhead, Senior Editor, MedPage Today February 9, 2022

[1] Lortet-Tieutent J et al, *JNCI*, 2017

TCGA Mutation Spectra for Endometrial Carcinoma



Levine et al, Nature, 2013

Immune Checkpoint Inhibitor Therapy in Endometrial Cancer

Pembrolizumab (KN-158): Robust Antitumor Activity in Patients With MSI-H Advanced EC

Variable	MSI-H EC n = 79	EC (biomarker unselected) n = 107
ORR % (95% CI)	**48** (37-60)	**11.2** (5.9-18.8)
Complete response	11 (14)	0
Partial response	27 (34)	12 (11.2)
Stable disease	14 (18)	26 (24.3)
Progressive disease	23 (29)	56 (52.3)
Not evaluable	1 (1)	2 (1.9)
Not assessed	3 (4)	11 (10.3)

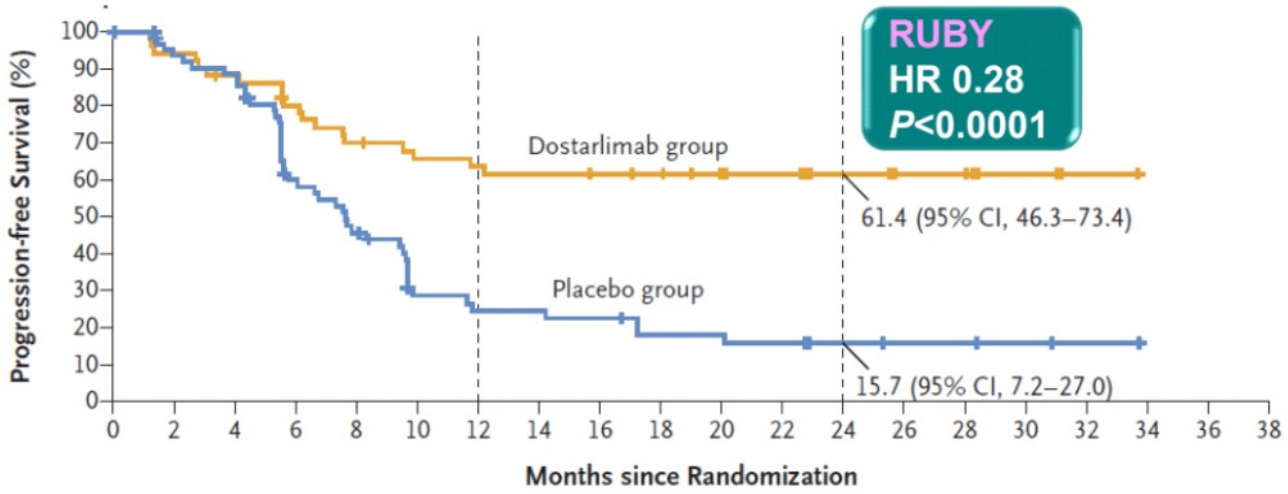
Marabelle, J Clin Oncol 2020

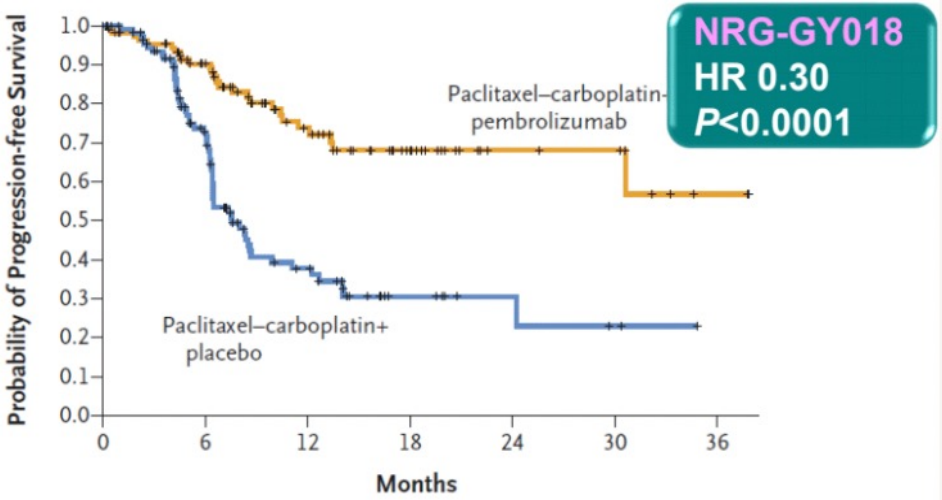
Dostarlimab (GARNET Cohorts A1 & A2): Clinical Benefit in dMMR and MMRp EC Patients

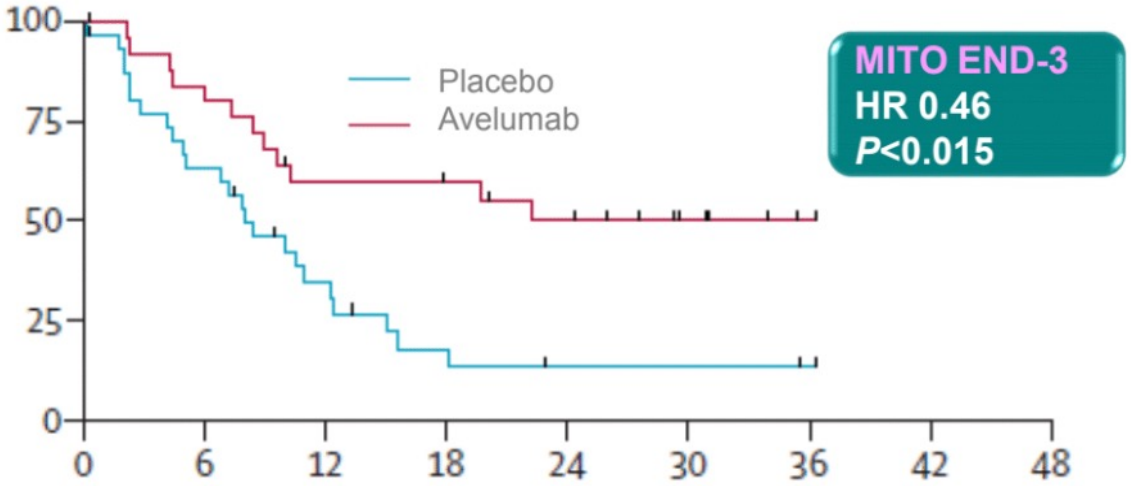
Variable	dMMR EC n = 103	MMRp EC n = 142
ORR % (95% CI)	**46** (34.9-54.8)	**19** (8.3-20.1)
Complete response	11 (10.7)	3 (2.1)
Partial response	35 (34.0)	16 (11.3)
Stable disease	13 (12.6)	31 (21.8)
Progressive disease	39 (37.9)	77 (54.2)
Not evaluable	3 (2.9)	0
Not done	2 (1.9)	15 (10.6)

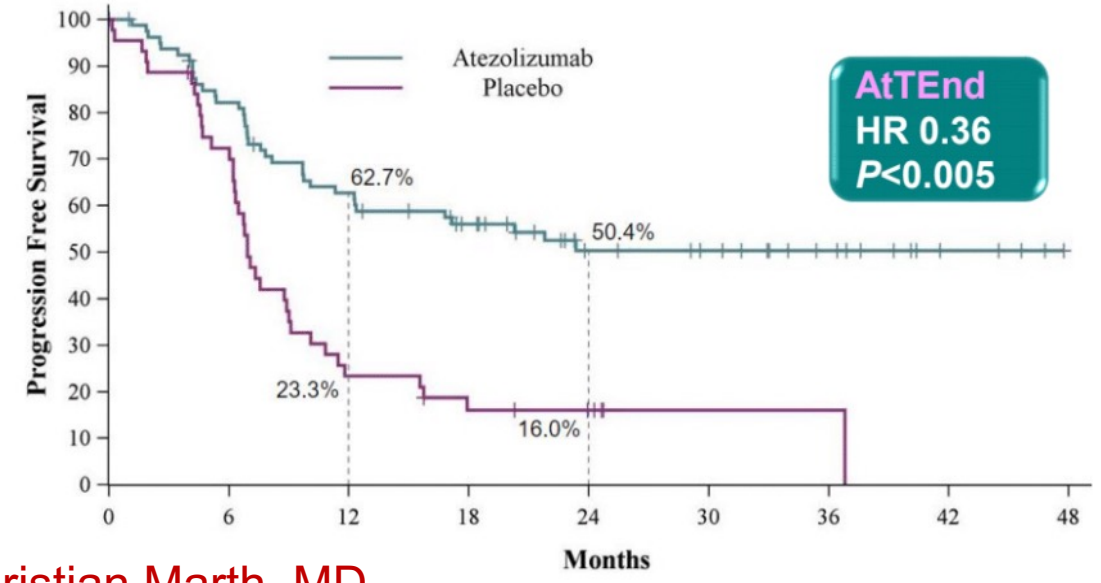
Courtesy of Dr. Rebecca Arend

Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in **dMMR** Tumors









Courtesy of Christian Marth, MD

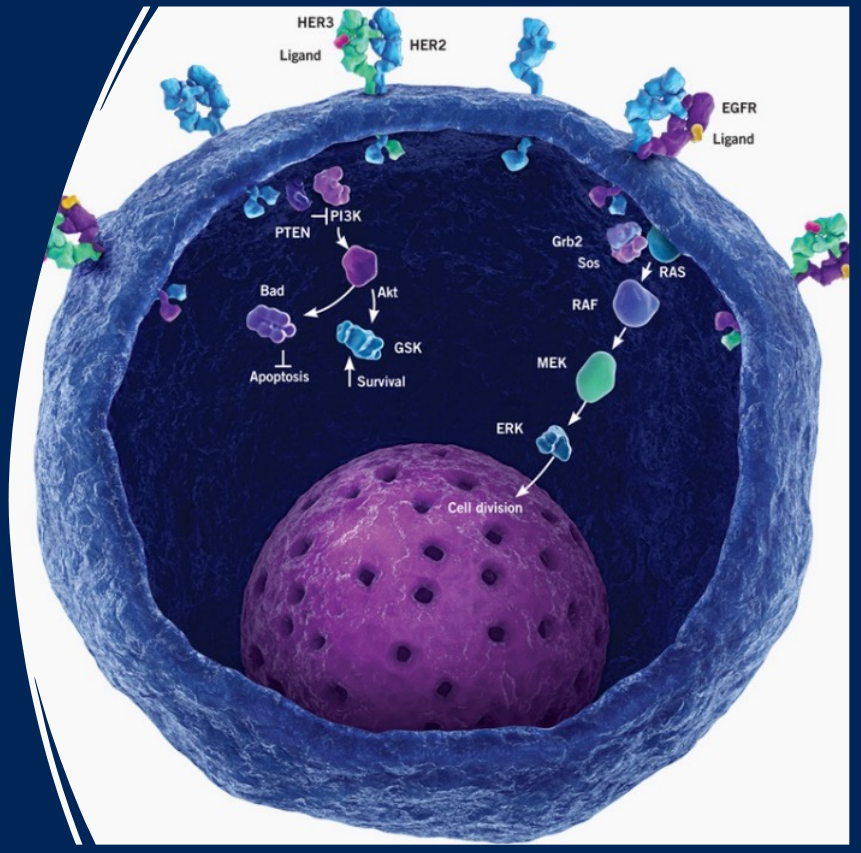
Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Sandro Pignata et al. The Lancet Oncology 2023, Nicoletta Colombo et al. ESMO 2023

Treatment Based Upon Molecular Make Up: HER2

- *Her2/neu* overexpression by IHC demonstrated in 14-60% of USC. Estimates vary widely due to lack of standardized algorithms for interpretation and scoring of Her2 immunostains in endometrial cancer

- Dysregulation of *Her2/neu oncogene* reported in 27% of USC in Whole Exome Sequencing (WES) studies performed by TCGA network (Levine DA , Nature 2013)

- HER2/neu functions as preferred partner for heterodimerisation with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and responsible for regulating cell growth and differentiation



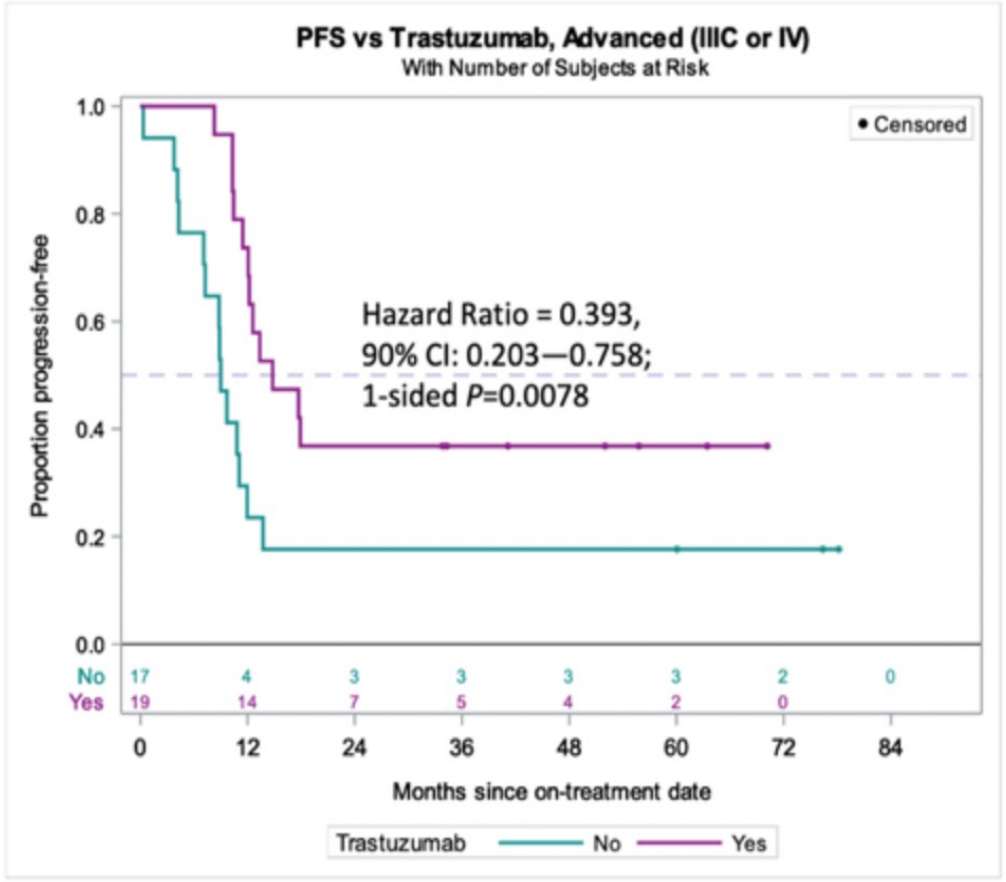
Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress Her2/neu (NCT01367002)

Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura 4 Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

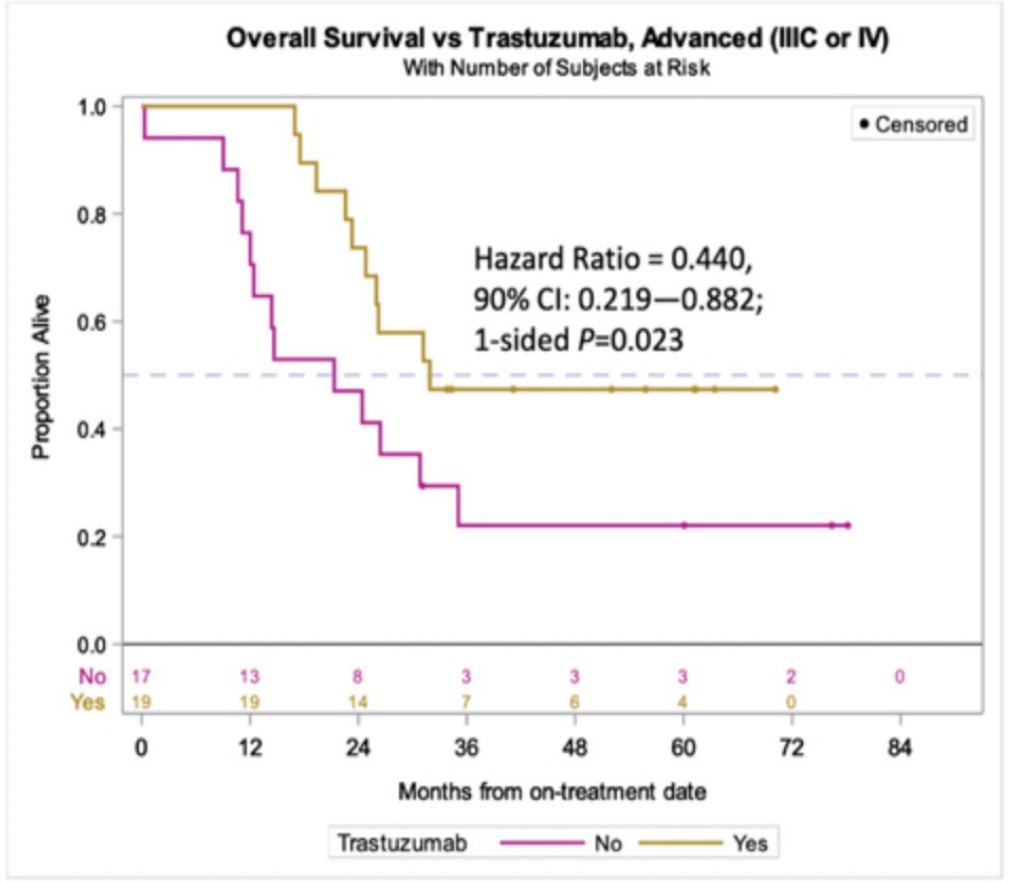
Yale University School of Medicine, New Haven, CT; John Hopkins School of Medicine, Baltimore, MD; University of Arkansas for Medical Sciences, Little Rock, AR; University of Arizona, Tucson, AZ; Duke University School of Medicine, Durham, NC; The Ohio State University School of Medicine, Columbus, OH; Montefiore Medical Center, Bronx, NY John Muir Medical Center, Brentwood, CA Penrose Cancer Center-St. Francis, Colorado Springs, CO, Walter Reed Medical Center, Bethesda, MD

Fader et al, J Clin Oncol, 2018

Improvement in PFS and OS for Advanced-Stage Disease with addition of Trastuzumab



Fader AN, JCO, 2018



Fader AN, Clin Cancer Res, 2020

NRG GY-026

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
TransIx PI: Alessandro Santin

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Safety Lead-In (n=45)

Arm 1: Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2: Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Arm 3: Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Strata:

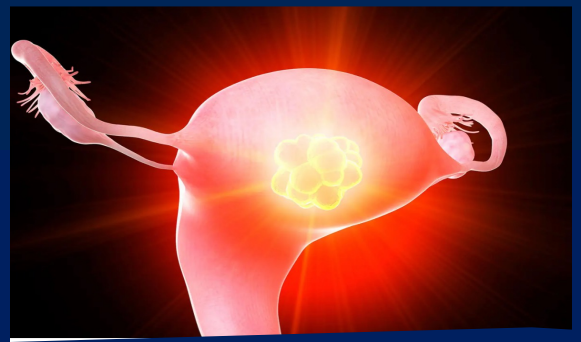
- Stage (I-II vs III-IV)
- Measurable vs. non-measurable dz
- Histology (serous vs carcinosarcoma)

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/ prohibitive toxicity)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

Summary

- A *one-size-fits-all* strategy does not work for advanced ovarian or uterine cancer treatments
- Precision-based medicine and identification of *actionable molecular targets* is one of the best way to personalize and improve treatment options for women with GYN malignancies
- Major advances have occurred in rare tumor science for gynecologic cancers with more trials than ever and several changes in standards of care in the last decade
- Endocrine therapy effective for low grade, hormone-positive tumors
- Targeted strategies with anti-HER2 and anti-angiogenesis and immunotherapy treatments helpful in management of highest risk endometrial cancer subtypes



Thank you!

- Dr. Santos
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- afader1@jhmi.edu