

WORKING TO ERADICATE GYNECOLOGIC CANCERS

Clinical Trials: Where We Are and What You Need to Know

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WHAT ARE CLINICAL TRIALS?



- Clinical trials are research studies that investigate treatments and observe patient performance with new treatments. They play an important role in developing new treatment options for a variety of diseases, including gynecologic cancers. Before any treatment can be tested in humans, it must show positive results in the laboratory and/or in animal studies
- A clinical trial is one of the final stages of a long and careful gynecologic cancer research process. The research usually includes new drugs, new treatment combinations, or new medical devices or technologies



Phase I Trials

- Phase I is the first step in testing a new therapy in humans
- The goal of Phase I studies is to determine safety, the appropriate dose and how the treatment is processed inside the body
- In Phase I studies, a small group of patients, usually between 20 and 40 women, are tested with the new treatment.



Phase II Trials

- Phase II trials continue to test the safety of the drug, or a combination of drugs, and begin to evaluate how well the new drugs(s) work.
- Phase II trials usually focus on a particular type of cancer, such as ovarian cancer, and are designed to learn more about side effects of the drug(s)
- Phase II trials involve a larger number , usually between 25 and 100 women



Phase III Trials

- Phase III trials test how a new drug or a new surgical procedure, compares with the currently approved standard treatment.
- Phase III trials are randomized, meaning that women have an equal chance of being assigned to either the new therapy group or the approved treatment group
- Phase III trials often enroll large number of women (between 100 and 1,000 patients) and are used to determine if the new treatment is more effective than the standard of care.
- If the new therapy is found to be effective and meets safety requirements, an application will be submitted for FDA approval



Questions about clinical trials

- How do I know if I am eligible to be in a trial?
- Are there risks to participating in a clinical trial?
- If I enroll in a clinical trial, will I get a placebo rather than my regular treatment?
- Are the costs covered if I participate in a clinical trial?
 - **As of 1/1/14** newly issued or renewed health plans including on ACA exchange must cover costs associated with clinical trials
 - Medicaid *not* required to cover costs of clinical trials



Why should you participate in a clinical trial ?

- Access to new drugs and interventions before they are widely available; if the treatment is a success, you are among the first to benefit
- Health care provided by leading physicians in the field of gynecologic cancer research
- An opportunity to make a valuable contribution to gynecologic cancer research, helping other women diagnosed in the future



WHY ARE TRIALS IMPORTANT ?



- Clinical trials are a crucial step in finding new and promising ways to improve treatment for women diagnosed with a gynecologic cancer
- Most of the practice-changing advances in the treatment of ovarian cancer have come from clinical trials



Paclitaxel 175 mg/m² + Carboplatin AUC 7.5 GOG 158

Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

By Robert F. Ozols, Brian N. Bundy, Benjamin E. Greer, Jeffrey M. Fowler, Daniel Clarke-Pearson, Robert A. Burger, Robert S. Mannel, Koen DeGeest, Ellen M. Hartenbach, and Rebecca Baergen

Purpose: In randomized trials the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide in advanced-stage epithelial ovarian cancer. Although in nonrandomized trials, carboplatin and paclitaxel was a less toxic and highly active combination regimen, there remained concern regarding its efficacy in patients with small-volume, resected, stage III disease. Thus, we conducted a noninferiority trial of cisplatin and paclitaxel versus carboplatin and paclitaxel in this population.

Patients and Methods: Patients with advanced ovarian cancer and no residual mass greater than 1.0 cm after surgery were randomly assigned to receive cisplatin 75 mg/m² plus a 24-hour infusion of paclitaxel 135 mg/m² (arm I), or carboplatin area under the curve 7.5 intravenously plus paclitaxel 175 mg/m² over 3 hours (arm II).

Results: Seven hundred ninety-two eligible patients were enrolled onto the study. Prognostic factors were sim-

ilar in the two treatment groups. Gastrointestinal, renal, and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in arm I. Grade 2 or greater thrombocytopenia was more common in arm II. Neurologic toxicity was similar in both regimens. Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for arm I compared with 20.7 and 57.4 months, respectively, for arm II. The relative risk (RR) of progression for the carboplatin plus paclitaxel group was 0.88 (95% confidence interval [CI], 0.75 to 1.03) and the RR of death was 0.84 (95% CI, 0.70 to 1.02).

Conclusion: In patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior, when compared with cisplatin plus paclitaxel.

J Clin Oncol 21. © 2003 by American Society of Clinical Oncology.

New *O*varian *E*laborate trial: **NOVEL** trial **JGOG 3016**

Ovarian Epithelial, Primary Peritoneal or
Fallopian Tube cancer
FIGO Stage II-IV



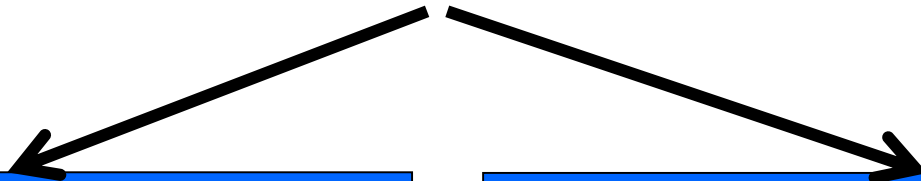
Randomization

Stratification;

Residual disease: $\leq 1\text{cm}$, $> 1\text{cm}$

FIGO Stage: II vs. III vs. IV

Histology: clear cell/mucinous vs serous/others



Conventional PC (c-PC)

Paclitaxel $180\text{mg}/\text{m}^2$, day 1

Carboplatin AUC 6, day 1

every 21 days for 6-9 cycles

Dose-dense weekly PC (dd-PC)

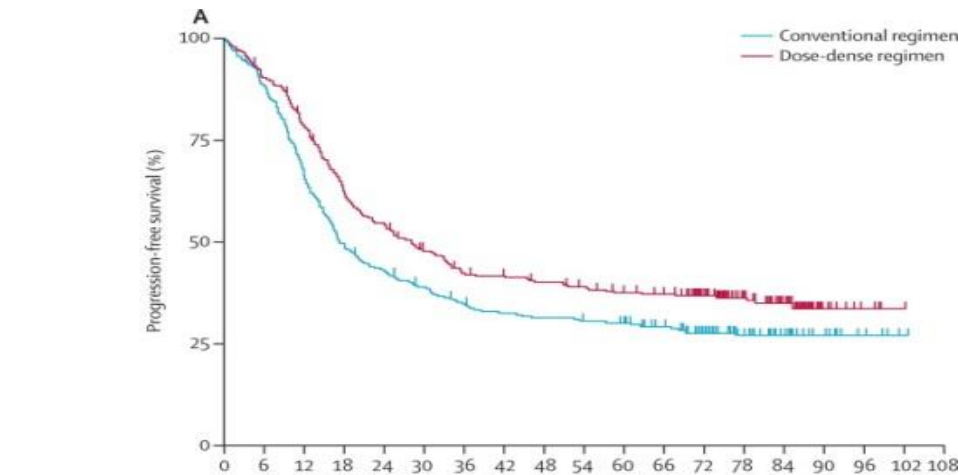
Paclitaxel $80\text{mg}/\text{m}^2$, days 1,8,15

Carboplatin AUC 6, day 1

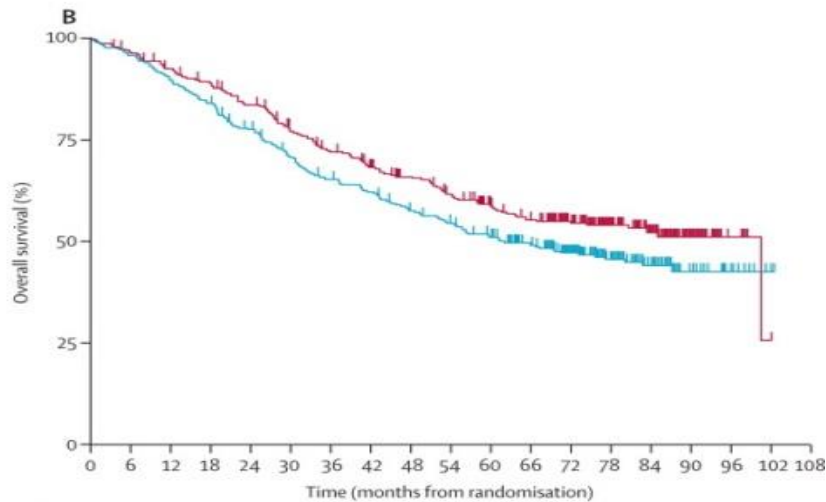
every 21 days for 6-9 cycles

New Ovarian ELaborate trial: NOVEL trial

JGOG 3016



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108
Conventional regimen	319	282	212	157	136	122	107	99	96	93	90	79	61	41	22	12	5	1	0
Dose-dense regimen	312	281	242	192	167	143	126	122	117	111	104	100	78	53	37	10	4	1	0

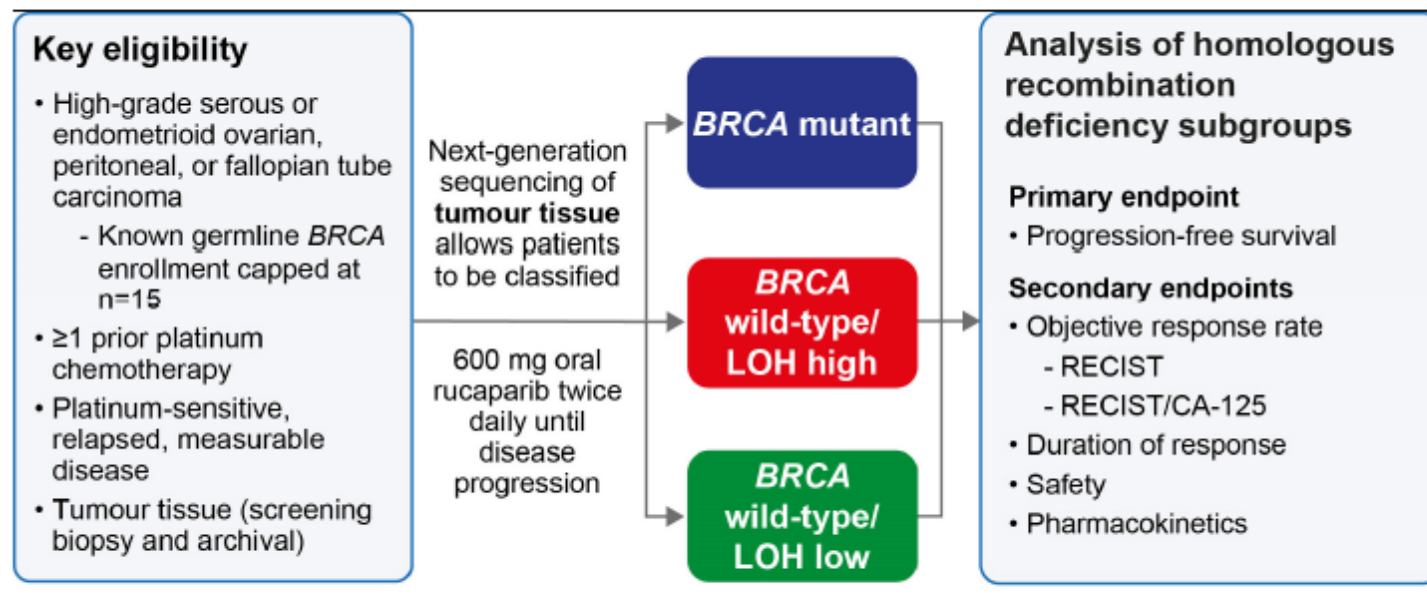


Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108
Conventional regimen	319	305	285	266	241	217	199	189	172	161	148	132	108	76	44	21	10	1	0
Dose-dense regimen	312	300	286	272	255	230	213	198	186	171	155	143	118	80	53	21	6	1	0

	dd-PC	PC
PFS (mos)	28.2	17.5
HR 0.76, 95% CI 0.62-0.91; p=0.0037		
OS (mos)	100.5	62.2
HR 0.79, 95% CI 0.63-0.99; p=0.039		

Rucaparib in Platinum Sensitive Relapsed OC: ARIEL 2, Part 1

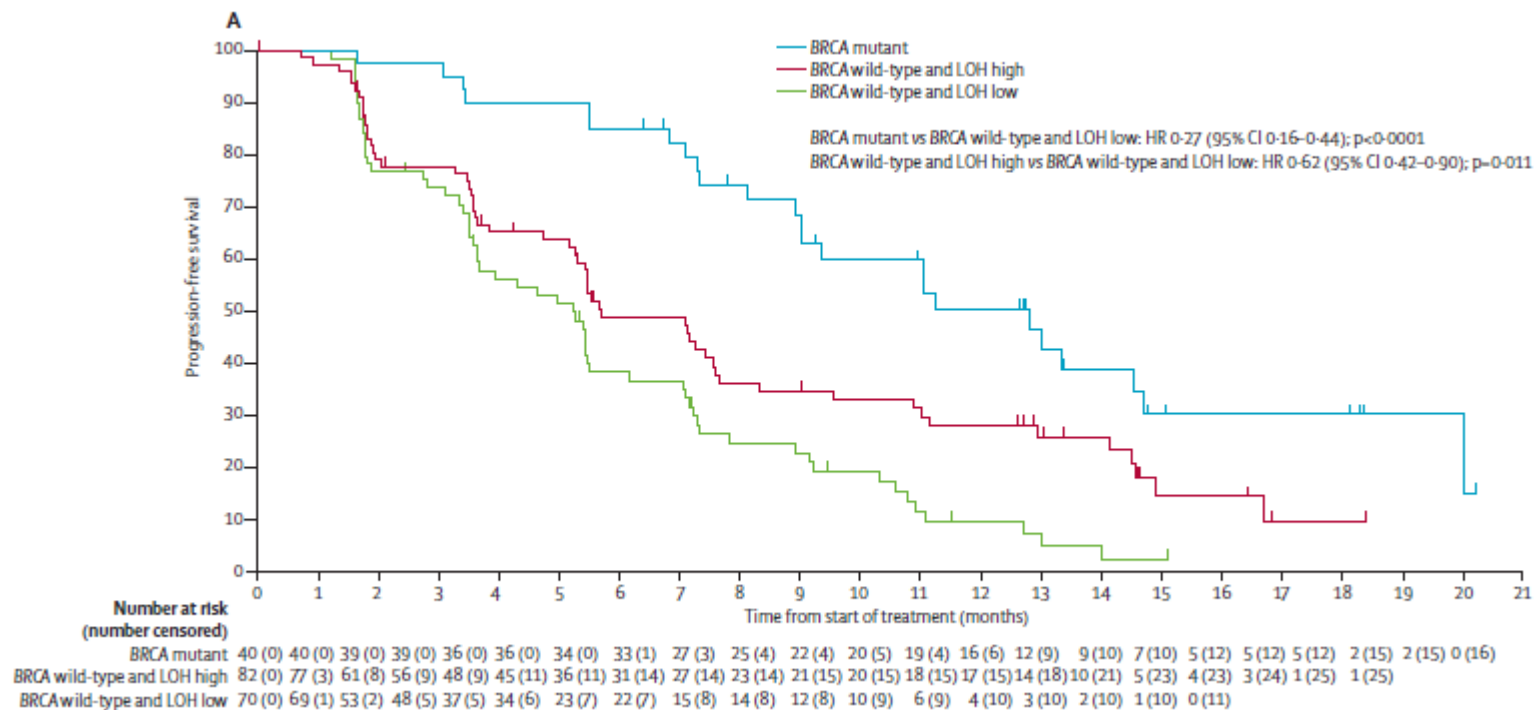
Figure S1: Study scheme



CA-125=cancer antigen 125. LOH=loss of heterozygosity. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

Rucaparib in Platinum Sensitive Relapsed OC: ARIEL 2, Part 1

PFS stratified by homologous recombination deficiency subgroup



+ additional data (Ariel 2, Part 2 and Study 10) led to FDA approval 12/19/2016 with FoundationCDxBRCA: 2 priors, + FFPE biomarker

SOLO2/ENGOT-Ov21: Phase III trial of olaparib tablet maintenance treatment in patients with PSR SOC and a gBRCAm

Patients:

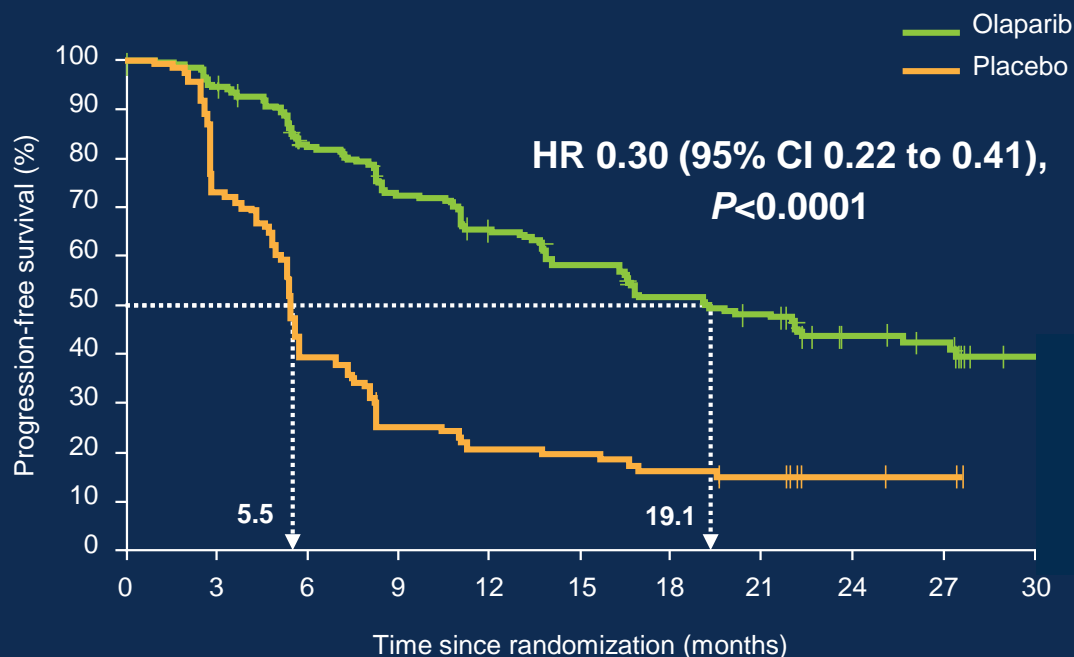
- PSR SOC and gBRCA1/2m
- ≥ 2 prior lines of platinum therapy
- CR or PR to most recent therapy

Randomized
2:1

Olaparib
300 mg bid
n=196

Placebo
n=99

Primary endpoint:
Investigator-assessed PFS



No. at risk

Olaparib
Placebo

196	182	156	134	118	104	89	82	32	29	3
99	70	37	22	18	17	14	12	7	6	0

bid, twice daily; CI, confidence interval; CR, complete response; gBRCAm, germline BRCA mutation; HR, hazard ratio; PFS, progression-free survival; PR, partial response

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

Ovarian Cancer Therapies

FDA Approved

1978 Cisplatin
1990 Altretamine
1991 Carboplatin
1992 Paclitaxel
1996 Topotecan
2000 Pegylated liposomal doxorubicin (PLD)
2006 Gemcitabine + Carboplatin
2014 Bevacizumab – platinum resistant
(+weekly paclitaxel, PLD or topotecan)
2014 Olaparib (Accelerated) – Study 42
2016 Bevacizumab – platinum sensitive
(+paclitaxel/carboplatin;
gemcitabine/carboplatin)
2016 Rucaparib (Accelerated) – ARIEL2

NCCN 1 or 2A

- Capecitabine
- Cyclophosphamide
- Docetaxel
- Doxorubicin
- Etoposide (oral)
- Ifosfamide
- Irinotecan
- Melphalan
- Oxaliplatin
- Paclitaxel, albumin bound (nab-paclitaxel)
- Pemetrexed
- Vinorelbine

WHERE ARE WE WITH CLINICAL TRIALS? *IN CRISIS!*



The Crisis in Gyn Cancer Clinical Trials

- Randomized clinical trials have significantly improved survival for women with gynecologic cancers, including cervical, ovarian, endometrial, and vulvar cancers
- The gynecologic cancer community has a 50yr history of developing trials, many by the Gynecologic Oncology Group (GOG) in partnership with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI CTEP).



The Crisis in Gyn Cancer Clinical Trials

- The successful completion of these trials has resulted in peer-reviewed publications that have advanced care for women with gynecologic cancer
- Two examples of these trials, both of which resulted in NCI-issued clinical alerts¹ are:
 - The addition of chemotherapy to radiation in the treatment of patients with cervical cancer: *40-50% improvement in survival*
 - The adoption of intraperitoneal chemotherapy in advanced ovarian cancer: *Improvement in survival from 50 months to 65 months*



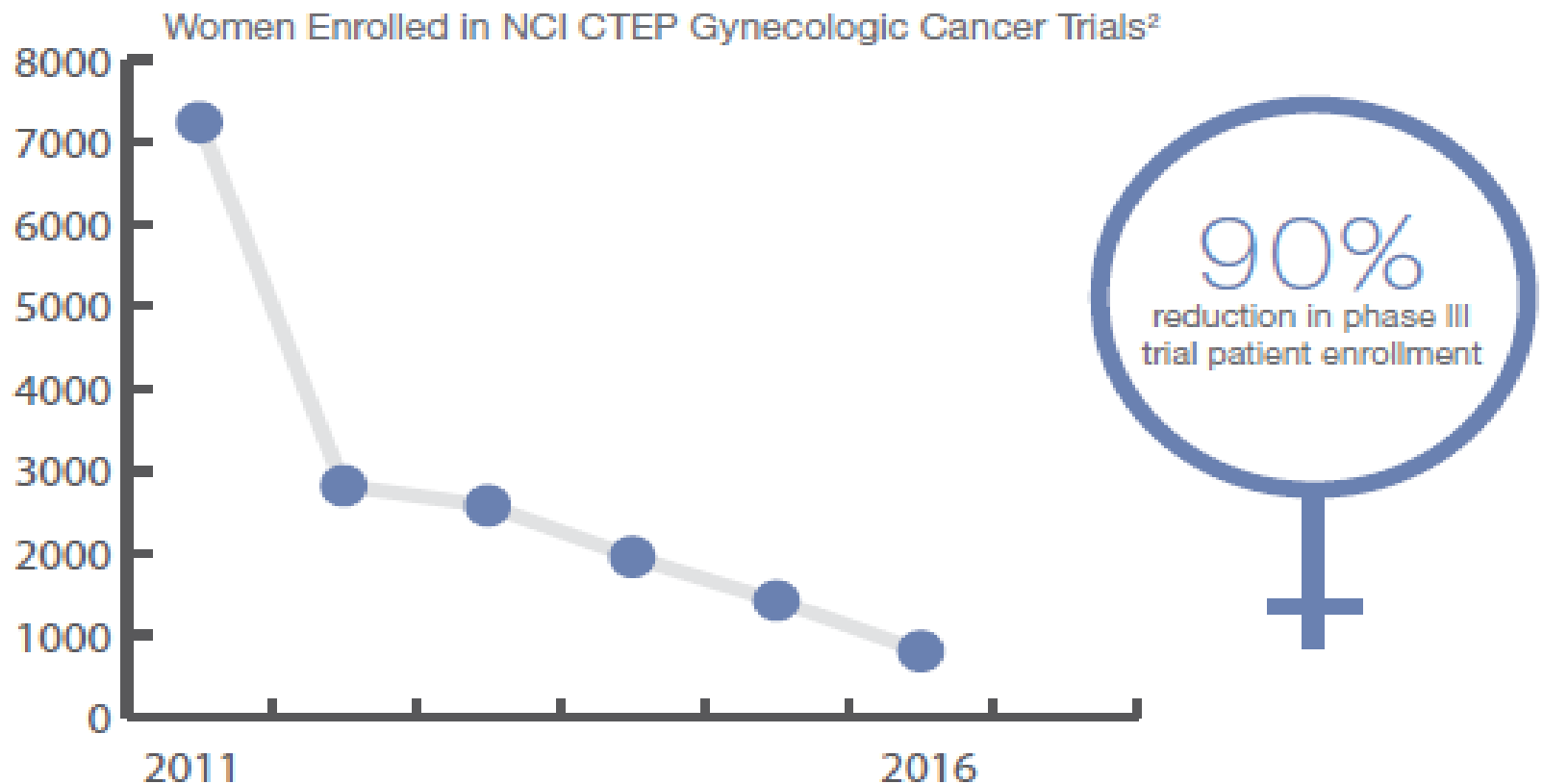
The Crisis in Gyn Cancer Clinical Trials

- Clinical trials advance the field of gynecologic cancer prevention & treatment affording women with gyn cancer improved outcomes, better quality of life and better survival.

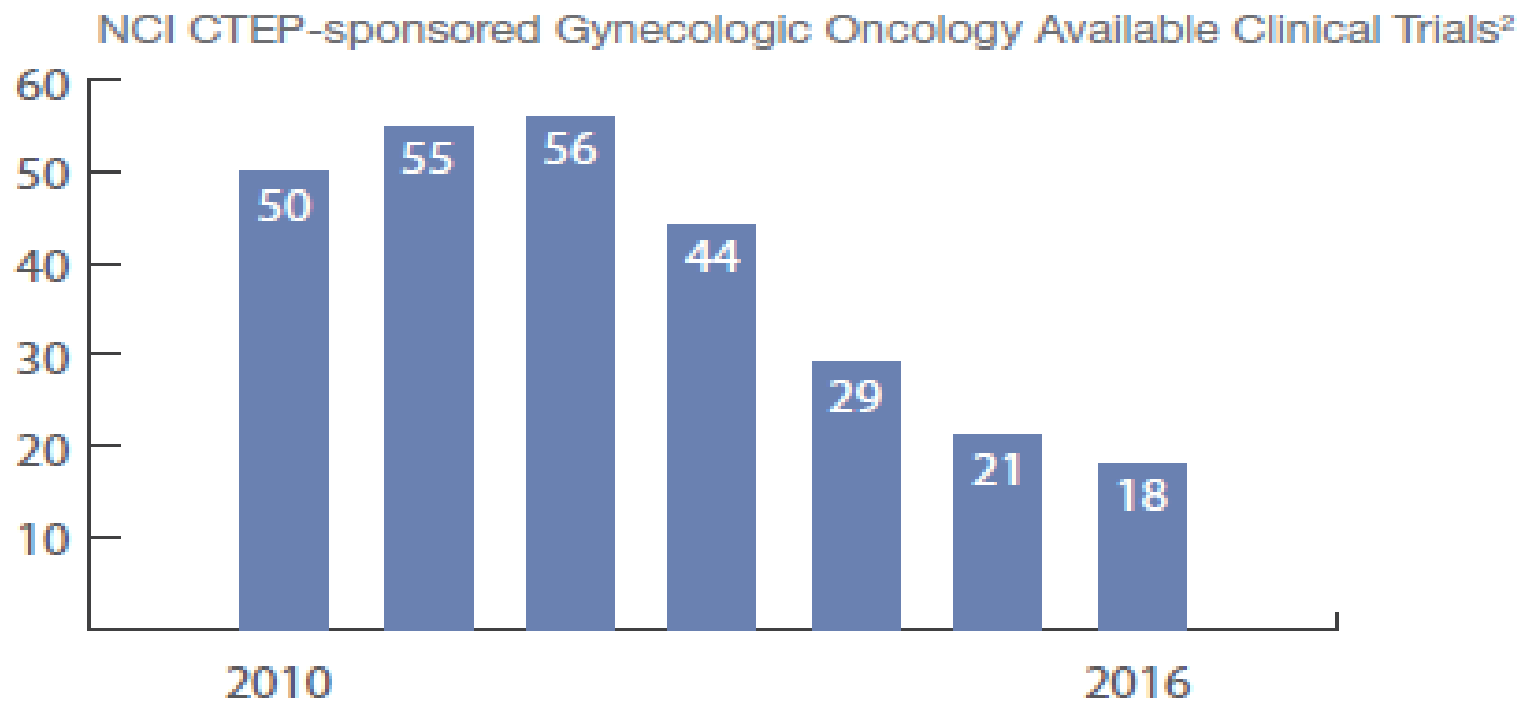
However, in 2017, a robust clinical trials platform to achieve these goals is in crisis!



THE CURRENT STATE: A SEVERE DECLINE IN NUMBER OF WOMEN WITH GYN CANCER ENROLLED IN TRIALS



THE CURRENT STATE: A SEVERE DECLINE IN AVAILABILITY OF CLINICAL TRIALS FOR WOMEN WITH GYNECOLOGIC CANCER



²Gynecologic Oncology Group, www.gog.org



ANALYSIS: WHY HAS THIS OCCURRED?

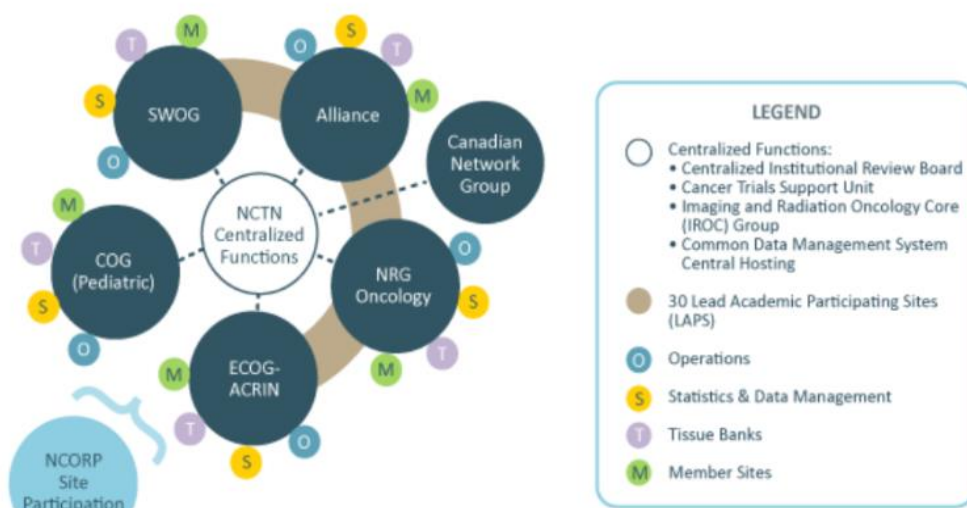
- National Institutes of Health Budget Reduction and Stagnation
 - 1998 NIH \$14 billion
 - 2016 NIH \$31 billion
 - ***FY2018* \$24 billion***

18.3% Reduction



ANALYSIS: WHY HAS THIS OCCURRED?

- Restructuring of NCI-sponsored cooperative groups, with formation of NRG Oncology in 2012.
- Previously, the GOG and the Gynecologic Cancer Steering Committee (GCSC) were independent entities, focused only on developing trials in gynecologic cancers.



ANALYSIS: WHY HAS THIS OCCURRED?

- There is shifting emphasis to smaller biomarker-driven studies, with concomitant reduction of clinical trials

Current Commentary

Underrepresentation of Women in Clinical Trials

Why Gynecologic Oncologists Are Worried

Marcela G. del Carmen, MD, MPH, and Laurel W. Rice, MD

In gynecologic oncology, significant advances with improved patient outcomes have clearly and thankfully resulted from randomized clinical trials. The recent restructuring of cooperative groups and decreased funding for phase III clinical trials have unintentionally resulted in a 90% reduction of available trials and accrual in gynecologic oncology. This Commentary reviews the history of the underrepresentation of women in clinical trials, highlighting the challenges that threaten the viability of gynecologic oncology clinical research, resulting in a decreased likelihood of improving the survival of women with gynecologic cancer. We suggest an opportunity for partnering with the U.S. government and the private sector to enhance research funding opportunities while increasing advocacy efforts to reinvigorate our clinical trials platform.

(Obstet Gynecol 2015;0:1–4)

DOI: 10.1097/AOG.0000000000000695

Level 1 evidence, randomized clinical trials are the gold standard by which we care for and advise our patients. The Gynecologic Oncology Group (GOG), which was established in 1965, has been the bedrock on which research in our field has been conducted. Data generated from several randomized clinical trials executed through the GOG have resulted in improved patient survival. Examples of these advances include

the addition of chemotherapy to radiation in the treatment of patients with cervical cancer and the adoption of intraperitoneal chemotherapy in ovarian cancer, both of which have resulted in two National Cancer Institute (NCI) clinical alerts.^{1–6} With the recent changes in the NCI's clinical trials infrastructure, combined with commentary from Dr. Francis Collins and more (see below), there is mounting evidence regarding the disproportionately low allocation of resources for enrolling women in clinical trials in general and in gynecologic oncology trials specifically.

Historically, clinical trials were carried out in men only. The argument for doing so included the rationale that male-only studies were simpler and less expensive to conduct.⁷ Investigators were also reticent to include women of childbearing age, given the potential risk of harming a fetus.⁷ As a result, women were excluded from many vitally important clinical trials.⁷ In the Harvard Physicians' Health Study, evaluating the effects of aspirin on cardiovascular disease and published in 1989, 22,071 male and 0 female physicians were enrolled.⁸ In the Multiple Risk Factor Intervention Trial—evaluating the relationship between blood pressure, cholesterol, tobacco use, and coronary artery disease (and published in 1982)—12,866 men and 0 women were enrolled.⁹ The Baltimore Longitudinal Study of Aging, conducted from 1958 to 1975 and published in 1986, included men only.¹⁰ Most notably (and most



GOING FORWARD: HOW CAN WE ADDRESS THIS CRISIS?

- Immediately increase funding for the National Cancer Institute for clinical trials
- Annual Summit for Clinical Trials in Gynecologic Cancer. Establish annual summit with members to include CTEP, SGO, Advocacy groups and other stakeholders



GOING FORWARD: HOW CAN WE ADDRESS THIS CRISIS?

- Establish a Clinical Trialist Career Development Program with NCI and CTEP, and develop grants for mentored research to increase investment in young investigators that represent the future in gynecologic cancer trial research.
- Make gynecologic cancers a priority in any NIH-supported biomarker development programs.



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- Make gynecologic cancers a priority in any NIH-supported biomarker development programs.



Training the Next Generation of Scientists in Clinical Trials

- **SGO/NCI Training Workshop 3/10/2017**
 - Workshop for young scientists that will feature sessions by NCI staff and SGO leaders.



The Public/Private Partnership Working Group

- **Summit 3/11/2017**
 - Strategize around available resources – private foundation, public, industry.
 - Leveraged ***together*** to increase clinical trials for patients with gynecologic cancer.
 - Develop the foundation for future efforts/opportunities.

Training the Next Generation of Scientists in Clinical Trial Design Working Group

- Establish the Young Scientists Clinical Trials Design Network.
- Follow-up Meeting/Training Session in Fall 2017.
 - NCI is committed to the training and retaining of young scientists in our field.
- The SGO's Foundation for Women's Cancer leverages its highly successful Research Grants and Awards Program to offer a named junior faculty research grant.

SGO Legislative/Congressional Ambassadors Continue to Expand (both number and spheres of influence)

- Education of Congressional Offices on Clinical Trials Crisis
 - 150+ SGO members are in contact with their Member of Congress' offices, stressing the importance of increased support to the NCI.
- Education of Patients and Advocates
 - Expand and integrate our network, create formal coalition structure.
 - Use new technology, such as Voter Voice, that will improve efficiencies and streamline processes for patients to communicate with Congress.

Patient Advocacy Working Group

- Expand and more effectively engage/integrate our Patient Advocacy Groups – local, state and national to work together.
 - Outreach to NCI, providing support.
 - Outreach to other organizations with influence.
 - Build a more effective interface with Ambassadors.

#Trials4GynCancer**NOW**



**Women with #gyncancer deserve progress.
Fund trials now @realDonaldTrump
#Trials4GynCancerNow @SGO_org**

FY 2018 DoD Ovarian Cancer Research Funding

- Thank you OCRFA for a great partnership!!!
- FY 2018 DoD Ovarian Cancer Research Funding (seeking \$20 million)
 - 2018 Funding – Excellent Member of Congress Request Letters
 - Best House Letter Ever – 121 Members of Congress signed in support on the program.
 - Senate Democrat Dear Colleague Letter with 19 signers, included two Freshman Senators
 - Grassroots to Members of the House Appropriations Committee asking them to contact Committee Leadership in support.



FY 2018 DoD Ovarian Cancer Research Funding

– Next Steps

- Grassroots Advocacy to all Members of the House of Representatives for Defense Appropriations Vote.
 - Expect possible House vote in July
- Outreach to Senate Appropriations Offices to Support the \$20 million for FY 2018
- Be Prepared for Amendments to the Senate Consideration of the National Defense Authorization Act.
 - Senator McCain was offered the last week in July for considered by the Senate, could be delayed due to HCR vote.
- Start to Lay the Groundwork for an increased request in FY 2019.
 - Fundable grants about 50% more than \$20 million

