The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Management of Ovarian Cancer

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Creating a cancer-free world. *One person, one discovery at a time.*

Objectives

- Describe the current management of early and advanced ovarian cancer
- Review the most contemporary management updates in both surgical and medical management of ovarian cancer patients
- Understand the role of genetic testing and genetics referral amongst ovarian cancer patients

Disclosures

- UpToDate - Honorarium for authorship
- GOG Partners – Consultant
- Agenus – Advisory Board
- Incyte – Consultant
- Glaxo Smith Kline – Advisory Board

Ovarian Cancer

- **Epithelial Ovarian Cancer (90%)**
  - Less common Germ Cell, Sex-Cord Stromal
- **<u>Leading</u>** cause of death from GYN Cancer in US
  - For now
- 2020 estimates (US)
  - 21,750 new cases
  - 13,940 deaths
- 5 year survival is about 48%
- Incidence increases with age and is most prevalent in the sixth and seventh decades of life
- More then half present with distant disease
  - “Disease that whispers…”

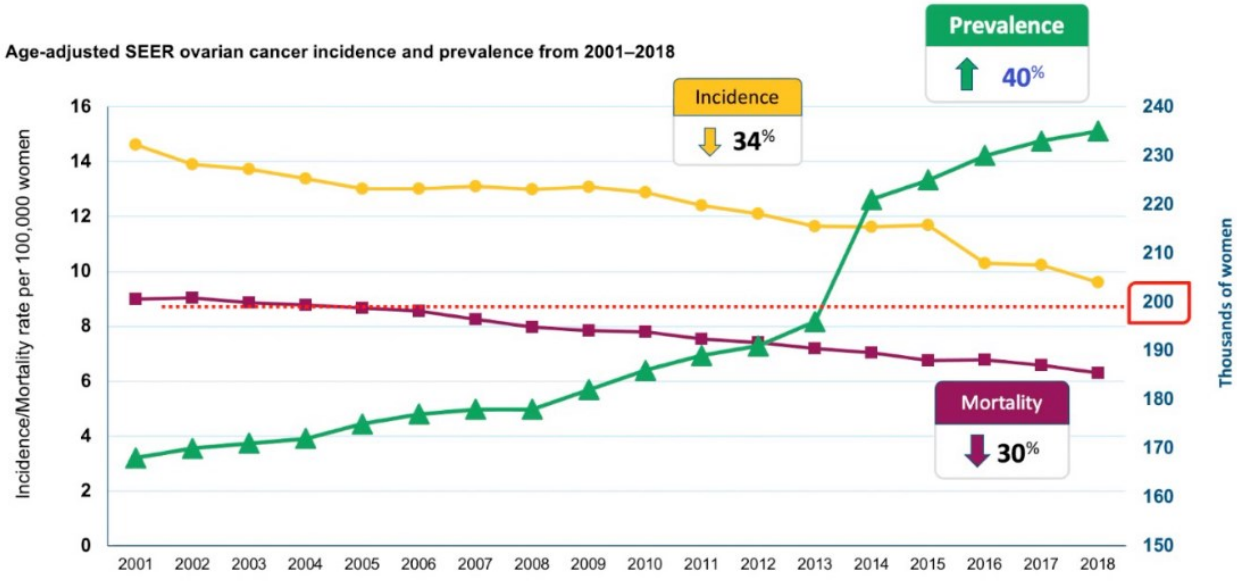


Figure 3. Leading Sites of New Cancer Cases and Deaths – 2020 Estimates

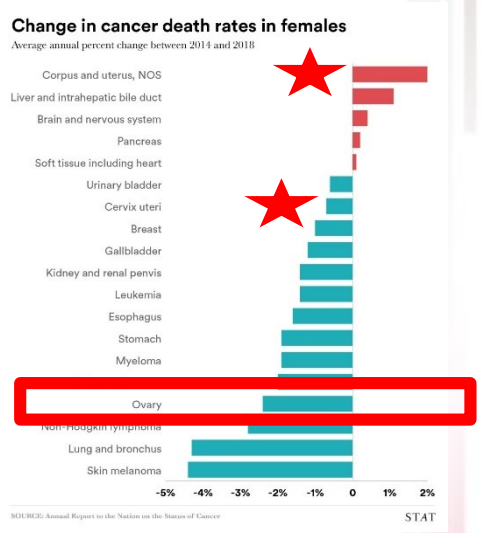
Estimated New Cases

Male			Female		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All sites	**893,660**		**All sites**	**912,930**	

Estimated Deaths

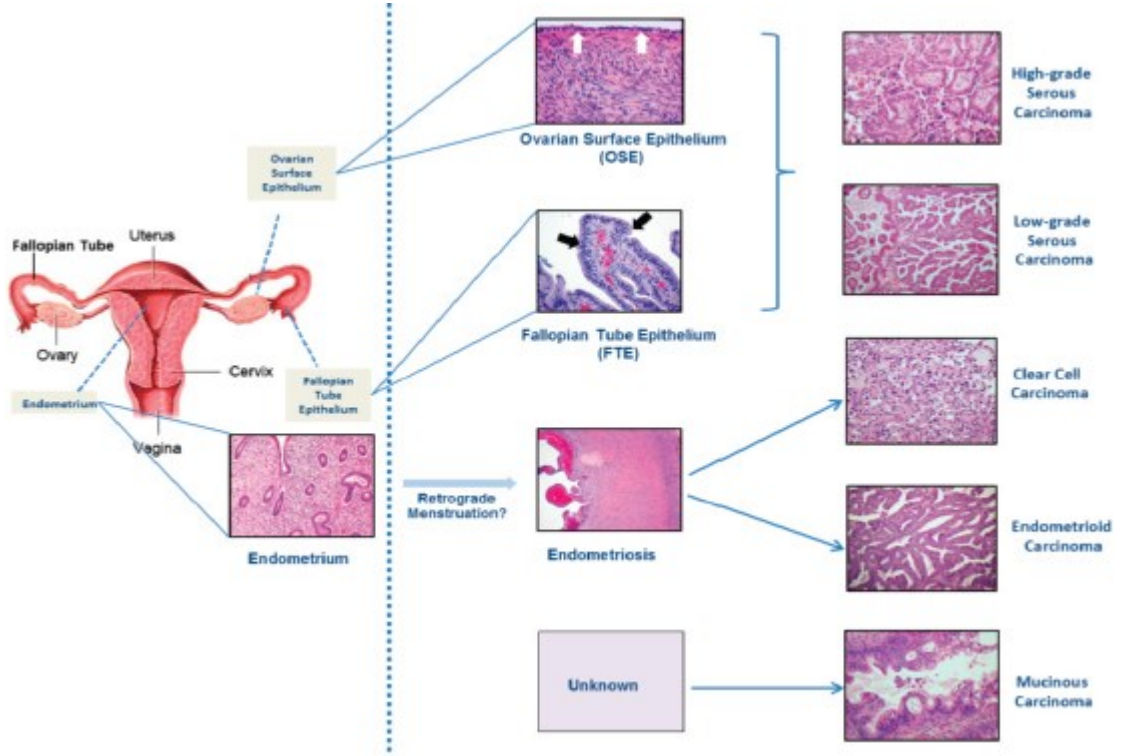
Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	**321,160**		**All sites**	**285,360**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.



Ovarian Cancer VS Fallopian Tube VS Peritoneum

- Epithelial subtypes
  - Serous (Low vs High Grade) – 80%
    - BRCA
    - Textbook OC
  - Endometrioid (FIGO Grades 1,2,3)
    - BRCA (higher grade)
    - Lynch Syndrome
    - Endometriosis
  - Clear cell
    - Endometriosis
    - Lynch Syndrome
  - Mucinous
    - Good prognosis early stage
    - Poor outcomes advanced stage
    - CEA, CA-19-9
    - Rule out GI primary
  - Borderline tumors/LMP/Atypical Proliferative
    - Surgically managed



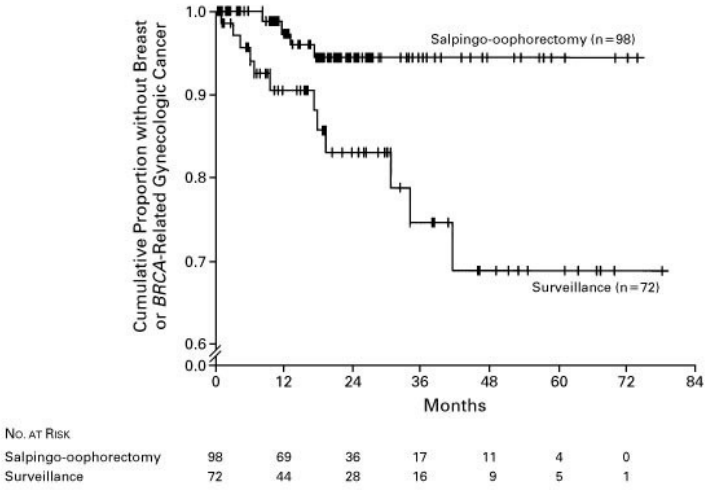
Ovarian Cancers: Evolving Paradigms in Research and Care (2016)

Epithelial Ovarian Cancers Need Genetics!

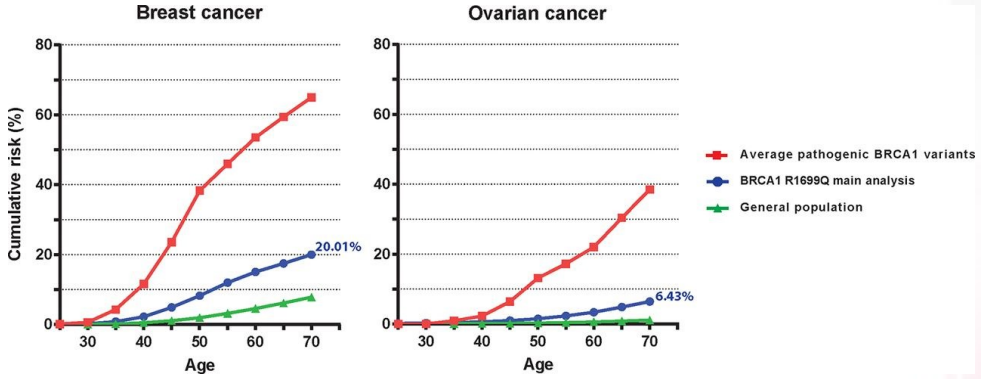
- ~20% of ovarian cancers have a hereditary component
  - BRCA 1 or 2 most common (~15%)
  - Lynch second most common cause of hereditary OC
  - Many other genes implicated (ATM, BRIP1, PALB2, RAD51 etc)

- Family history independent of gene mutation
  - First degree relative increases risk two-fold

- **Risk reducing surgery for high risk patients**
  - Reduced risk of breast, ovarian, fallopian and peritoneal cancers
  - Occult cancer can be identified is ~5%
  - Residual risk for developing primary peritoneal cancers (<4%)



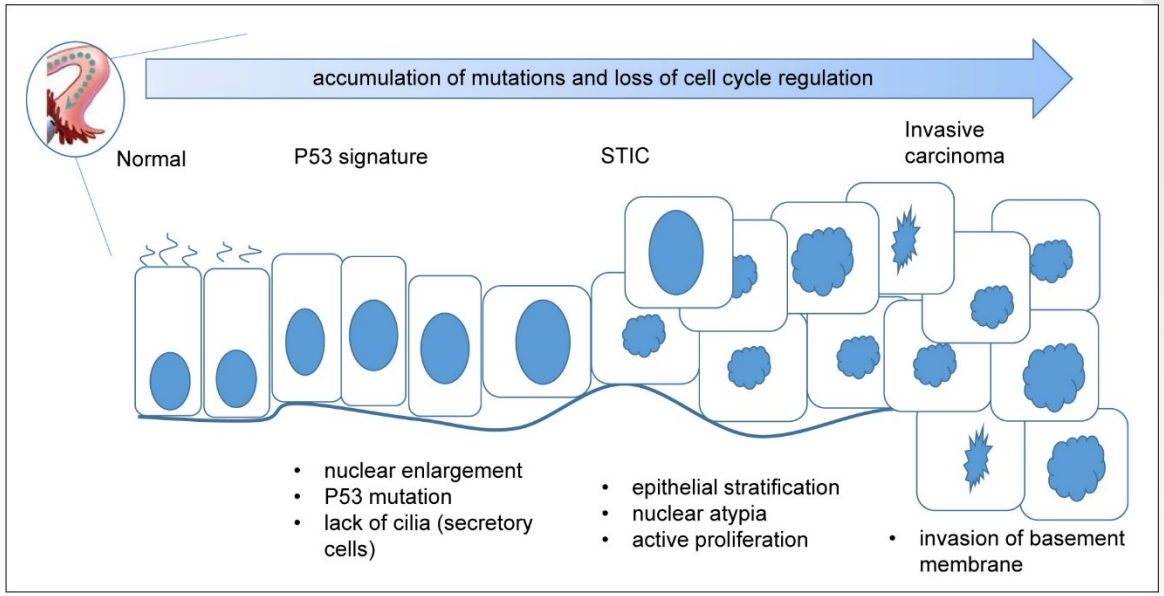
Kauff et al (2002) NEJM



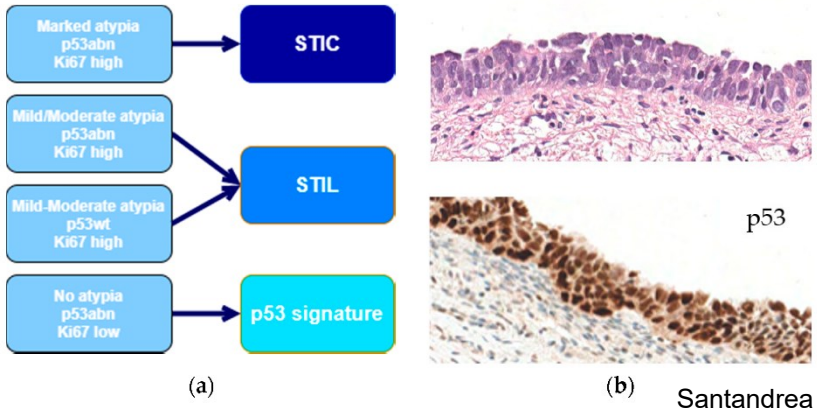
Moghadsi et al (2017) J Med Genetics

Serous Tubal Intraepithelial Carcinoma (STIC)

- Accepted that fallopian tube is origin of many ovarian cancers
  - STIC is precursor lesion
- Refer to GYN ONC for management
- Management **can** include
  - Observation alone +/- Ca-125
  - Removal of ovaries if not performed
  - Genetics referral (~10% risk of BRCA)
  - ???Surgical staging
  - ???Chemotherapy



Reade (2014) JOGC



Santandrea (2021) Diagnostics

No Screening for OC

- Symptoms are vague “Disease that whispers…”
  - Bloating, pelvic or abdominal pain, difficulty eating or early satiety, urinary symptoms (new and frequent)
- Screening with US +/- Ca-125 is **NOT** supported for the general population
  - Possible increase in earlier detection that ***does not*** lead to improvement in mortality
- USPSTF assessment of multiple trials concluded that in average risk women aged 45 years or older OC related mortality was not improved by screening
  - Positive predictive value was <50%
  - Harms of screening include false positives up to 44% which may cause stress and unnecessary surgery in up to 3.2% of women with complications in up to 15% of false positive surgeries
- UKCTOCS, PLCO screening trial, UC pilot trial

ARTICLES | VOLUME 397, ISSUE 10290, P2182-2193, JUNE 05, 2021

Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Prof Usha Menon, FRCOG • Aleksandra Gentry-Maharaj, PhD • Matthew Burnell, PhD • Naveena Singh, FRCPath • Andy Ryan, PhD • Chloe Karpinskyj, MSc • et al. Show all authors

THE LANCET

The reduction in stage III or IV disease incidence in the MMS group was not sufficient to translate into lives saved, illustrating the importance of specifying cancer mortality as the primary outcome in screening trials. Given that screening did not significantly reduce ovarian and tubal cancer deaths, general population screening cannot be recommended.

202 562 were included in the analysis

- 50 625 (25·0%) in the MMS group
- 50 623 (25·0%) in the USS group
- 01 314 (50·0%) in the no screening group
- 2055 women were diagnosed with tubal or ovarian cancer: 522 (1·0%) of 50 625 in the MMS group, 517 (1·0%) of 50 623 in the USS group, and 1016 (1·0%) of 101 314 in the no screening group
- Compared with no screening, there was a 47·2% (95% CI 19·7 to 81·1) increase in stage I and 24·5% (−41·8 to –2·0) decrease in stage IV disease incidence in the MMS group
- Overall the incidence of stage I or II disease was 39·2% (95% CI 16·1 to 66·9) higher in the MMS group than in the no screening group, whereas the incidence of stage III or IV disease was 10·2% (−21·3 to 2·4) lower
- 1206 women died of the disease: 296 (0·6%) of 50 625 in the MMS group, 291 (0·6%) of 50 623 in the USS group, and 619 (0·6%) of 101 314 in the no screening group
- No significant reduction in ovarian and tubal cancer deaths was observed in the MMS (p=0·58) or USS (p=0·36) groups compared with the no screening group.

Screening for Ovarian Cancer

- Ca-125 is **NOT** a screening test
- ROCA may improve earlier detection
  - Serial Ca-125 monitoring algorithms
- For women with high risk features (i.e. BRCA)
  - Risk-reducing surgery is ***preferred*** over screening
  - NCCN guidelines - ***Consider*** US and Ca-125 (both in younger women or those that do not pursue risk-reducing surgery

Other testing…

- Beyond Ca-125 (ROMA, OVA1 etc)
- OVA1 (example) is 5 markers (including Ca-125) in preoperative serum to assess the likelihood of malignancy in patients with an adnexal mass for which surgery is planned – AIM was to allow community providers determine referral to GYN ONC

Performance of ROMA with Initial Cancer Risk Assessment (ICRA)[3]

	ICRA	ROMA	ICRA + ROMA
Sensitivity	73.3%	82.6%	88.4%
Specificity	84.3%	75.5%	67.2%
PPV	51.6%	43.6%	38.2%
NPV	93.2%	95.0%	96.2%

ROMA provides equal sensitivity to other commercially available risk stratification tools while enhancing the specificity for assessing the risk level of malignancy.[3,4] This can aid in improved patient management within your practice.

ROMA is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. "ROMA should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of ROMA carries the risk of unnecessary testing, surgery, and/or delayed diagnosis."[3]

Ovarian Cancer Work up

- Imaging – US VS CT VS MRI
  - CT often will give all the information needed
- Usually reserve PET/MRI for indeterminant lesions
  - What question am I asking?
- Chest imaging (+/-)
- Tumor markers (*One size doesn't fit all*)
  - Ca125, HE4, inhibin, AFP, HCG, LDH, CEA, Ca 19-9
  - Ca125:CEA ratio (25)

Referral to GYN ONC?

- Referral Guidelines from ACOG/SGO
  - Patients age, Ca-125 level, physical findings, imaging results, and family history (personal history)
- NCCN do not endorse guidelines for referral…
  - There case is that primary assessment and debulking by GYN Oncologist is associated with improved survival and that all patients with lesions suspected to be ovarian malignancies should be referred
- So who should be referred?
  - Ovarian Cancer (YES)
  - Adnexal masses (Not so simple)

Table 1. SGO and ACOG Referral Guidelines for a Newly Diagnosed Pelvic Mass

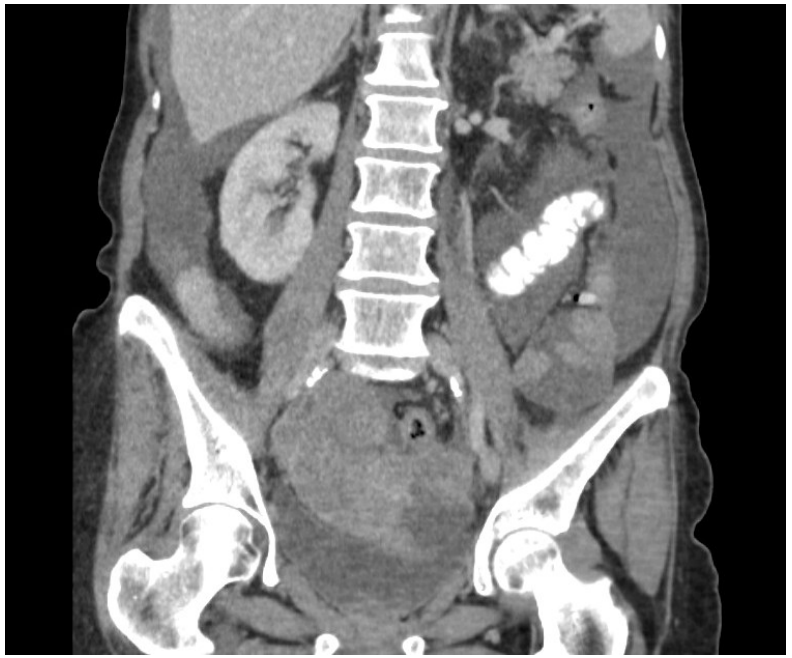
Age Group
Premenopausal (< 50 years old)
CA-125 > 200 U/mL
Ascites
Evidence of abdominal or distant metastasis (by exam or imaging study)
Family history of breast or ovarian cancer (in a first-degree relative)
Postmenopausal (> 50 years old)
CA-125 > 35 U/mL
Ascites
Nodular or fixed pelvic masses
Evidence of abdominal or distant metastasis
Family history of breast or ovarian cancer (in a first-degree relative)

Abbreviations: SGO, Society of Gynecologic Oncology; ACOG, American College of Obstetricians and Gynecologists.

Suspected Ovarian Cancer Patient

Questions:
Patient able to tolerate "big" surgery

Disease amenable to removal



Case 1:
Pelvic mass alone on imaging

- Surgery
- Frozen Section
- Diagnostic
- Therapeutic

Case 2:
Suspected Advanced Ovarian Cancer

- Suspicious imaging
- Surgery vs Biopsy

Primary Surgery

Neo-Adjuvant Chemotherapy

Surgery – Staging

- MIS VS OPEN
  - Staging can be performed MIS
  - Hysterectomy
  - BSO
  - Omentectomy
  - Peritoneal Biopsies
  - Pelvic and Aortic Lymphadenectomy
  - Pelvic Washings

- ~30% upstaging with apparent early stage disease

Staging is prognostic, may impact treatment and complete staging has been associated with improved outcomes

Stage	Relative 5-Year Survival Rate
I	90%
IA	94%
IB	92%
IC	85%

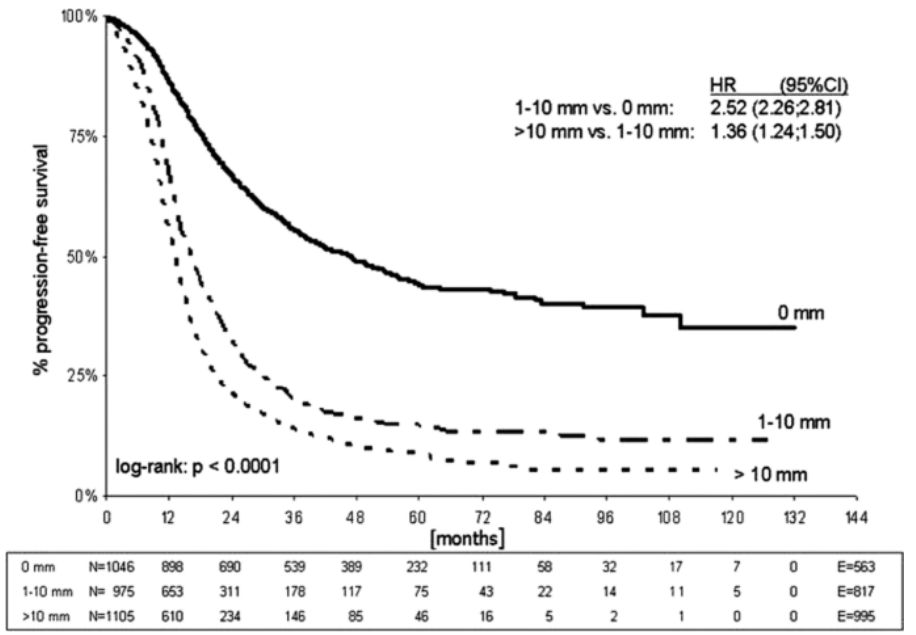
Stage	Relative 5-Year Survival Rate
II	70%
IIA	78%
IIB	73%
IIC	57%

Stage	Relative 5-Year Survival Rate
III	39%
IIIA	59%
IIIB	52%
IIIC	39%

Stage	Relative 5-Year Survival Rate
IV	17%

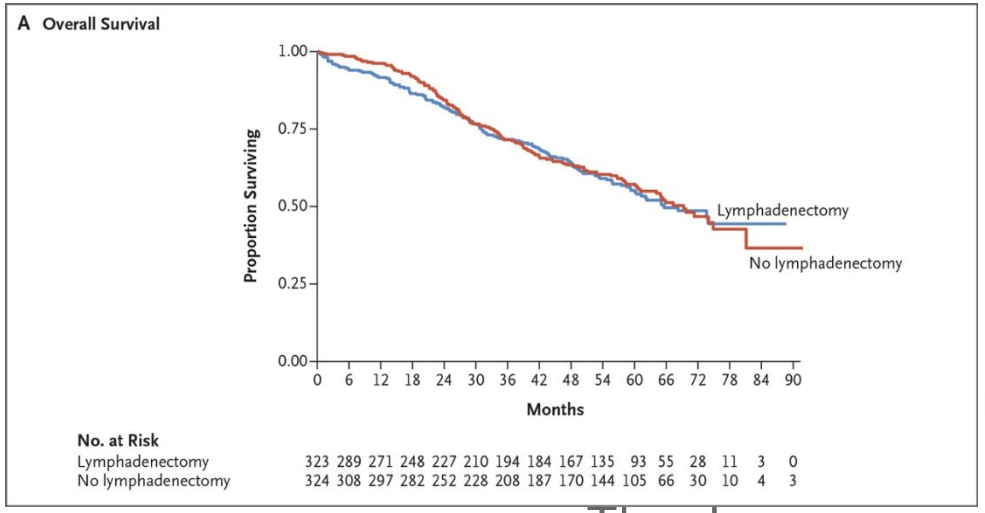
Surgery –Debulking

- MIS VS OPEN
  - Debulking usually best accomplished with laparotomy
    - Laparoscopic assessment for “debulkability”
  - Reports of MIS for debulking in select cases



du Bois A et al (2009) Cancer

- Debulking **GOALs**
  - **<u>OPTIMAL/COMPLETE</u>** VS SUB-OPTIMAL
  - Lymphadenectomy +/-



Harter (2019) NEJM

Neo-Adjuvant Chemotherapy

- NACT
  - Patient Factors VS Disease Factors
  - Advanced age, frailty, poor performance status, co-morbidities
  - Disease unlikely to be optimally cytoreduced
- EORTC55971, SCORPION, JCOG0602
- Long Story Short…
  - NACT is on the rise
  - Oncologic outcomes *likely* not different
  - Surgical complexity is lower
  - Diagnostic imprecision, non-response and not getting to surgery remain problematic

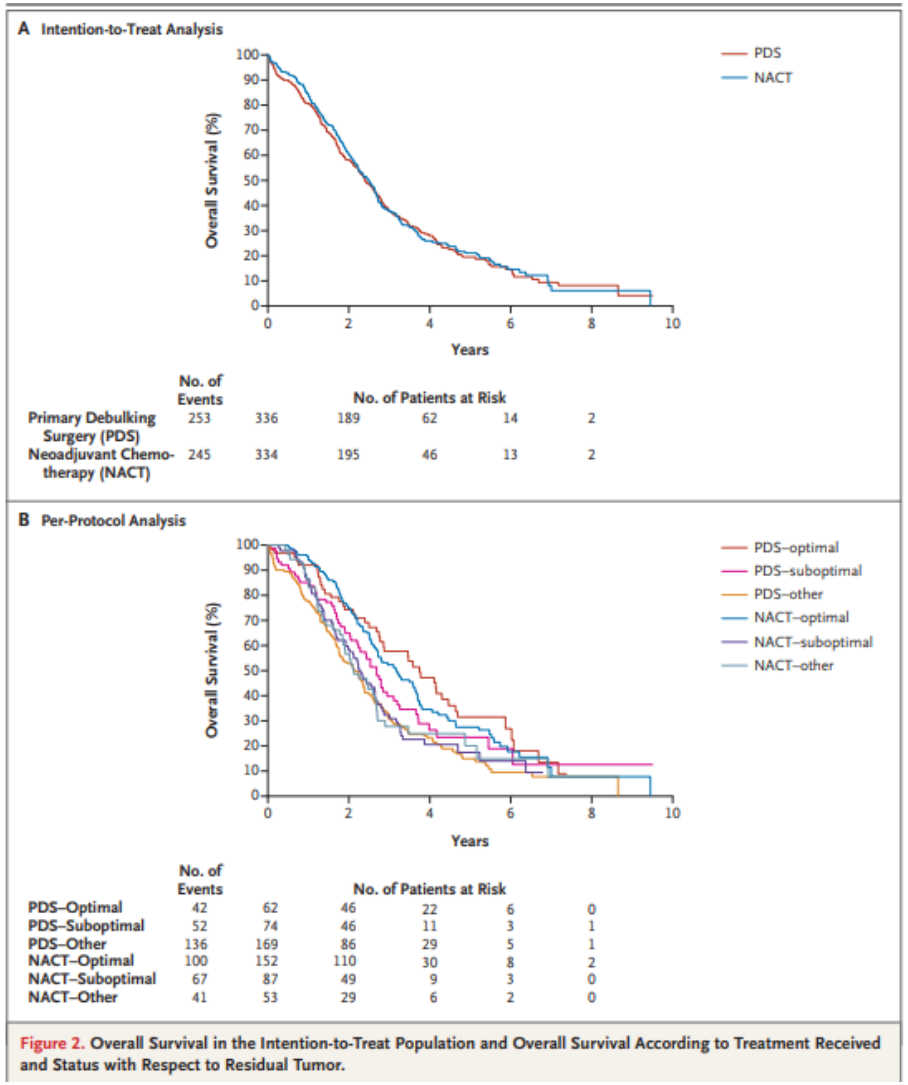


Figure 2. Overall Survival in the Intention-to-Treat Population and Overall Survival According to Treatment Received and Status with Respect to Residual Tumor.

Vergot (2010) NEJM

Intraperitoneal (IP) Chemotherapy

2006

Clinical Advisory: NCI Issues Clinical Announcement for Preferred Method of Treatment for Advanced Ovarian Cancer

NCI Issues Clinical Announcement for Preferred Method of Treatment for Advanced Ovarian Cancer

The National Cancer Institute (NCI), part of the National Institutes of Health, today issued an announcement encouraging treatment with anticancer drugs via two methods, after surgery, for women with advanced ovarian cancer. The combined methods, which deliver drugs into a vein and directly into the abdomen, extend overall survival for women with advanced ovarian cancer by about a year.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D. for the Gynecologic Oncology Group*

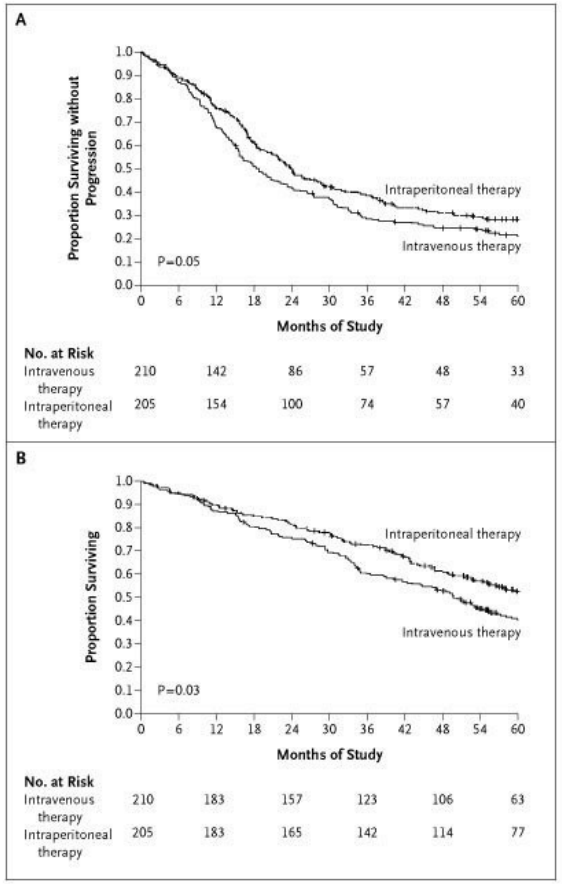
Improved Overall Survival: The median duration of overall survival in the intravenous-therapy and intraperitoneal-therapy groups was 49.7 and 65.6 months, respectively (P=0.03 by the log-rank test). Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to six weeks after treatment but not one year after treatment.

- **Only 42% of IP patients completed the 6 cycles of treatment**

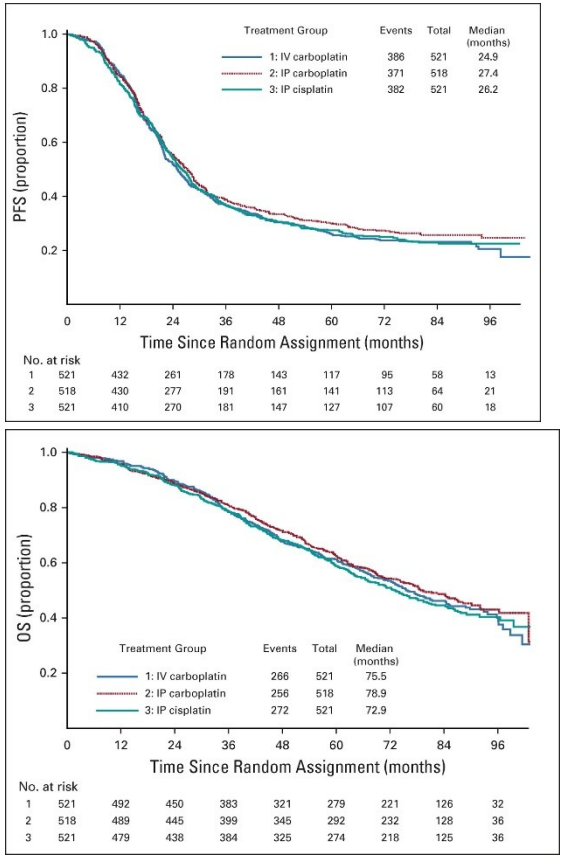
IP Chemo Has Fallen out of Favor

- Different Regimens
  - GOG172 (24 hour Taxol, higher dose cisplatin)
  - Bevacizumab in GOG252
- IP is more toxic
  - Catheter complications
  - Neuropathy, GI etc

GOG172 Armstrong (NEJM)



GOG252 Walker (JCO)



HIPEC

- HIPEC has been proposed at the time of IDS
- Still an area of research/debate

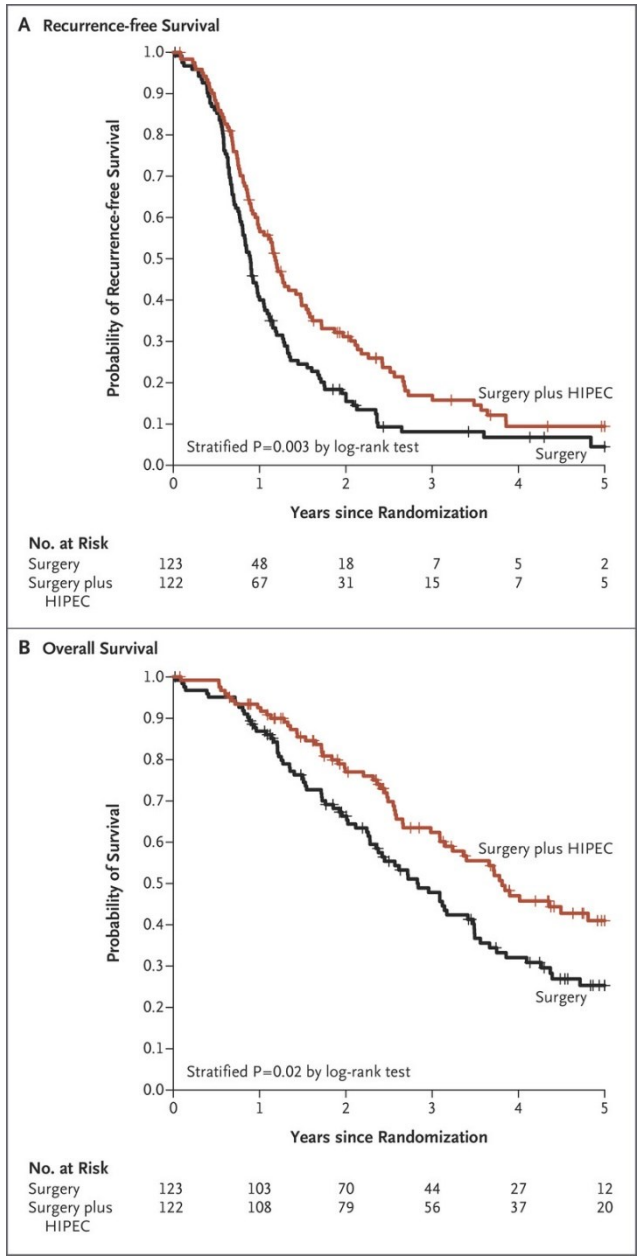
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

Willemien J. van Driel, M.D., Ph.D., Simone N. Koole, M.D., Karolina Sikorska, Ph.D., Jules H. Schagen van Leeuwen, M.D., Ph.D., Henk W.R. Schreuder, M.D., Ph.D., Ralph H.M. Hermans, M.D., Ph.D., Ignace H.J.T. de Hingh, M.D., Ph.D., Jacobus van der Velden, M.D., Ph.D., Henriëtte J. Arts, M.D., Ph.D., Leon F.A.G. Massuger, M.D., Ph.D., Arend G.J. Aalbers, M.D., Victor J. Verwaal, M.D., Ph.D., et al.

The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P=0.76)



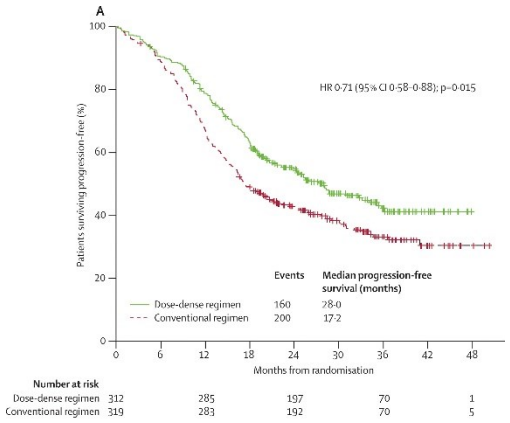
Dose Dense Chemotherapy

JGOG3016

THE LANCET
Volume 374, Issue 9698, 17–23 October 2009, Pages 1331-1338

Articles

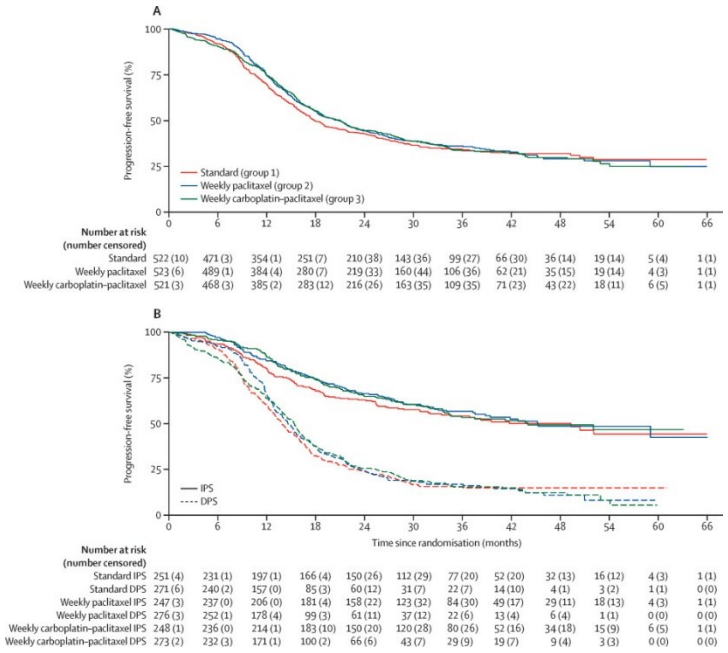
Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial



THE LANCET

ARTICLES | VOLUME 394, ISSUE 10214, P2084-2095, DECEMBER 07, 2019

Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial

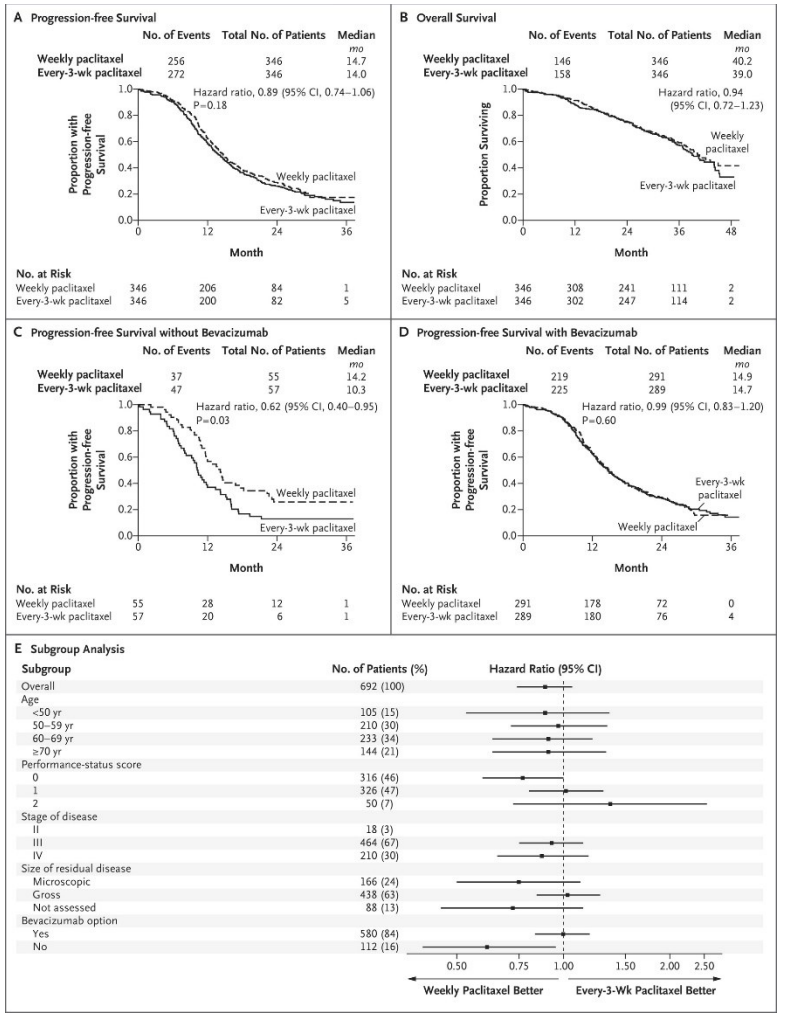


ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer

John K. Chan, M.D., Mark F. Brady, Ph.D., Richard T. Penson, M.D., Helen Huang, M.S., Michael J. Birrer, M.D., Ph.D., Joan L. Walker, M.D., Paul A. DiSilvestro, M.D., Stephen C. Rubin, M.D., Lainie P. Martin, M.D., Susan A. Davidson, M.D., Warner K. Huh, M.D., David M. O'Malley, M.D., et al.



Initial management conclusions:

- Primary surgery – staging or debulking followed by chemotherapy
  - Carboplatin/Paclitaxel every 3 weeks
  - Can consider IP chemo
- Neo-adjuvant chemotherapy – then IDS
  - Carboplatin/Paclitaxel every 3 weeks before and after
  - Can consider HIPEC at time of IDS

- ~6 cycles of chemotherapy
- If advanced stage (III/IV) and response… **maintenance**

Maintenance?

~85%

OF WOMEN WITH ADVANCED OVARIAN CANCER WILL SEE IT RETURN IN THEIR LIFETIME.[2]

WHY MAINTENANCE THERAPY

WITH ADVANCED OVARIAN CANCER, RECURRENCE IS COMMON

More than 22,000 women are diagnosed with ovarian cancer each year[1] — a disease that affects approximately 222,000 women in the US.[3] Sadly, ovarian cancer signs and symptoms are hard to recognize, so women are often diagnosed at later stages with advanced disease.[4,5] For these women, nearly 85% will see the cancer return in their lifetime[2] —known as recurrence — which produces additional anxiety, worry and uncertainty.[6]

Previously, observation or "watching and waiting," was the only option for women with advanced ovarian cancer between treatments. Fortunately, women have more choices to help delay a recurrence, whether or not they have the *BRCA* mutation.[7]

olaparib
tablets 150 mg

Maintenance therapy may make a difference

After chemotherapy, some doctors may choose to monitor you closely with tests and scans or prescribe maintenance therapy.

Maintenance therapy may help keep your advanced ovarian cancer from growing or returning after you have had a partial or complete response to a previous platinum-based chemotherapy.

Without maintenance therapy, advanced ovarian cancer may return in

about 7 out of 10 women within 3 years.*

*After surgery and their first line of chemotherapy.

Ovarian Cancer Molecular Testing

- Germline testing (ALL epithelial ovarian cancers)
  - Multi-gene panel testing
  - BRCA 1/2
  - Other homologous recombination genes (RAD51C/D)

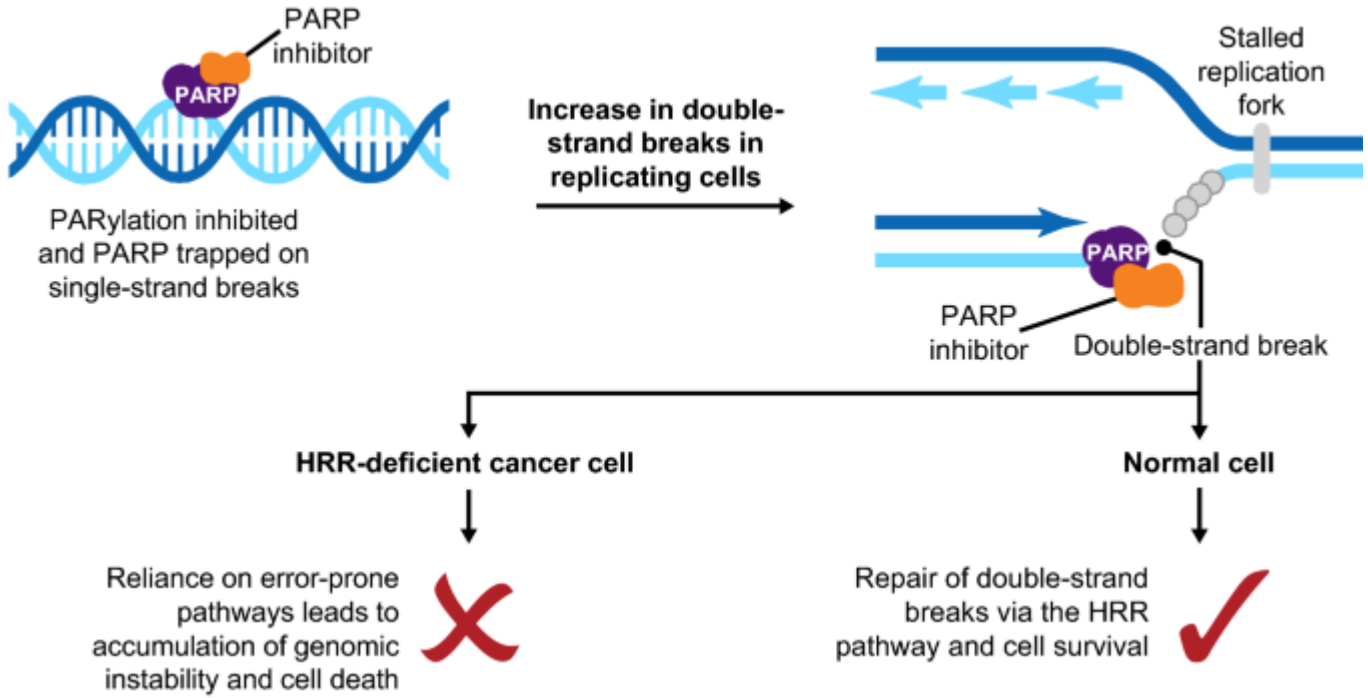
- Somatic (tumor) testing
  - Many include testing for homologous recombination deficiency (HRD)
  - Does **NOT** replace GERMLINE testing

- BRCA Mutations (HR Gene Mutations) and HRD status are important biomarkers for ovarian cancer

BRCA and HRD in Ovarian Cancer

- BRCA and HRD have become critically important biomarkers in management of OC
- BRCA and HRD predict response to PARP inhibitors

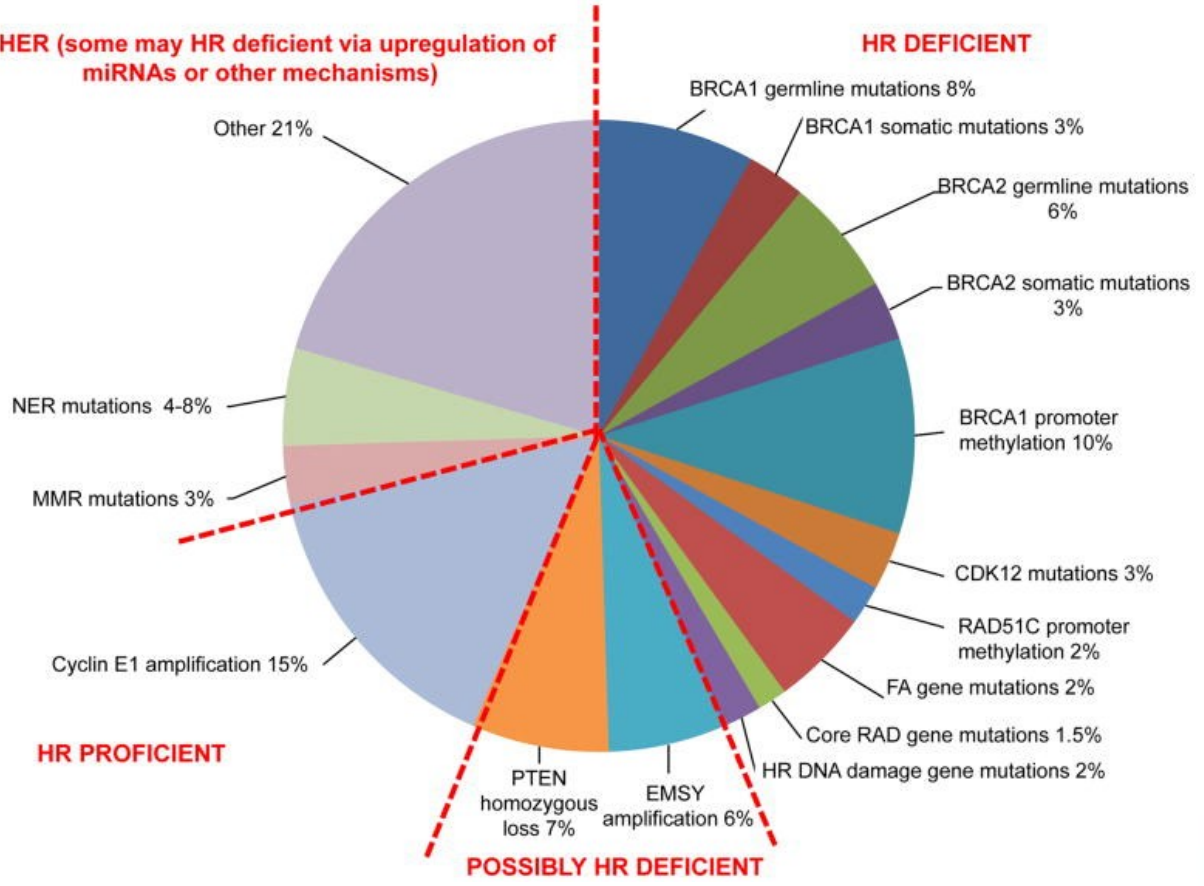
Synthetic Lethality



Ovarian Cancer Molecular Testing

- ~15% BRCA germline
- ~50% somatic HRD
- ~3% MMR mutations
  - Immunotherapy

Still a lot to figure out



Konstantinopoulos (2015) Cancer Discovery

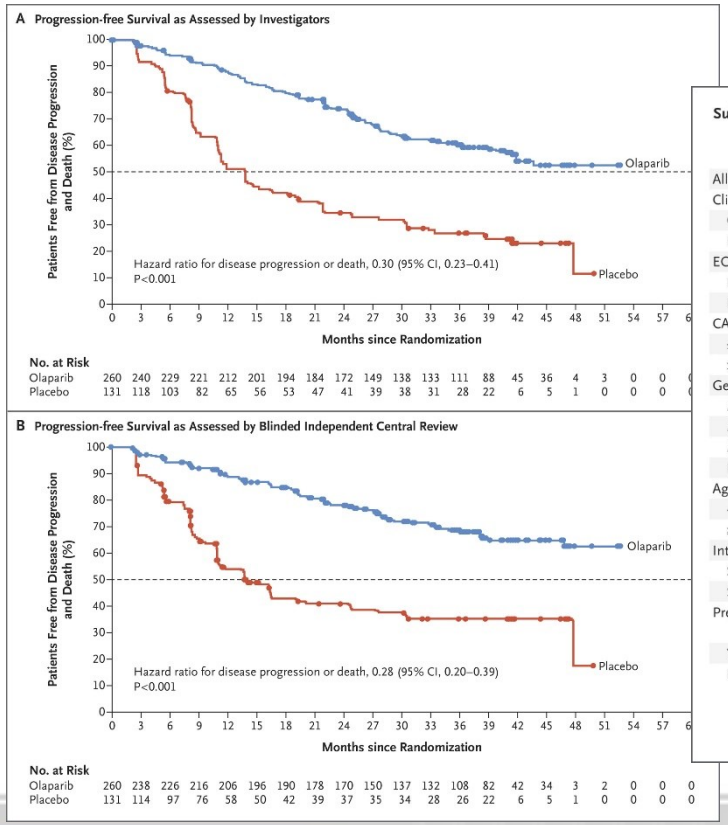
The NEW ENGLAND JOURNAL of MEDICINE

2018

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Kathleen Moore, M.D., Nicoletta Colombo, M.D., Giovanni Scambia, M.D., Byoung-Gie Kim, M.D., Ph.D., Ana Oaknin, M.D., Ph.D., Michael Friedlander, M.D., Alla Lisyanskaya, M.D., Anne Floquet, M.D., Alexandra Leary, M.D., Gabe S. Sonke, M.D., Ph.D., Charlie Gourley, M.D., Ph.D., Susana Banerjee, M.D., Ph.D., et al.



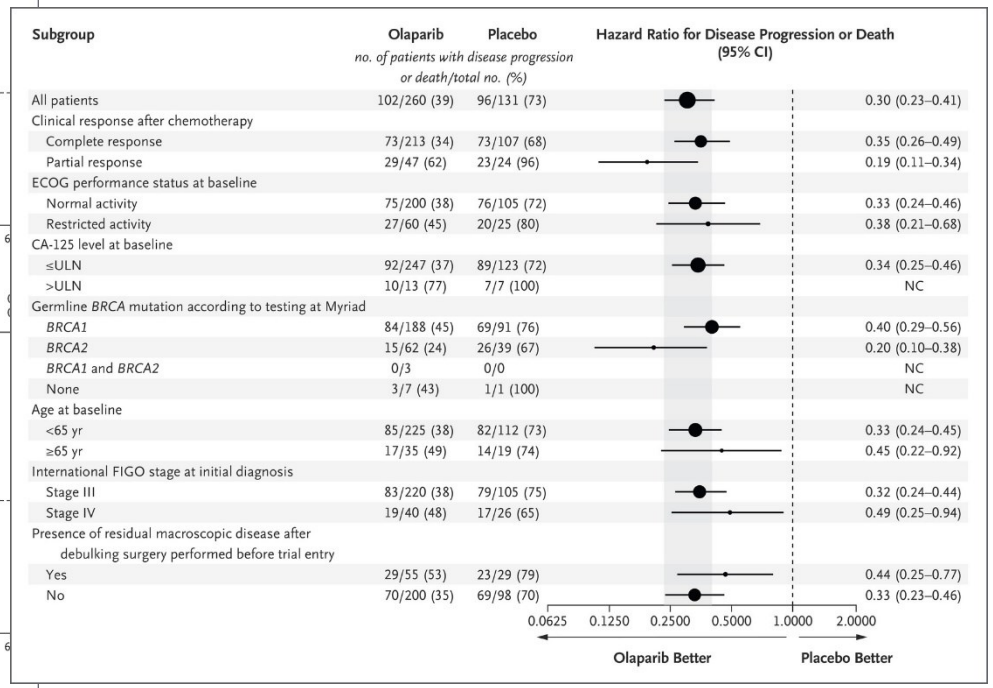


Table 2. Summary of Adverse Events.*

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

* Shown are data on adverse events that occurred in at least 15% of the patients in either trial group (except where noted) during the trial intervention or up to 30 days after discontinuation of the intervention. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA denotes not available.

† The data include patients with anemia, a decreased hemoglobin level, a decreased hematocrit, a decreased red-cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.

‡ The data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, a decreased neutrophil count, idiopathic neutropenia, granulocytopenia, a decreased granulocyte count, or agranulocytosis.

§ Thrombocytopenia occurred in less than 15% of the patients in each trial group, but the data are provided to complete the profile of hematologic toxic effects. The data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

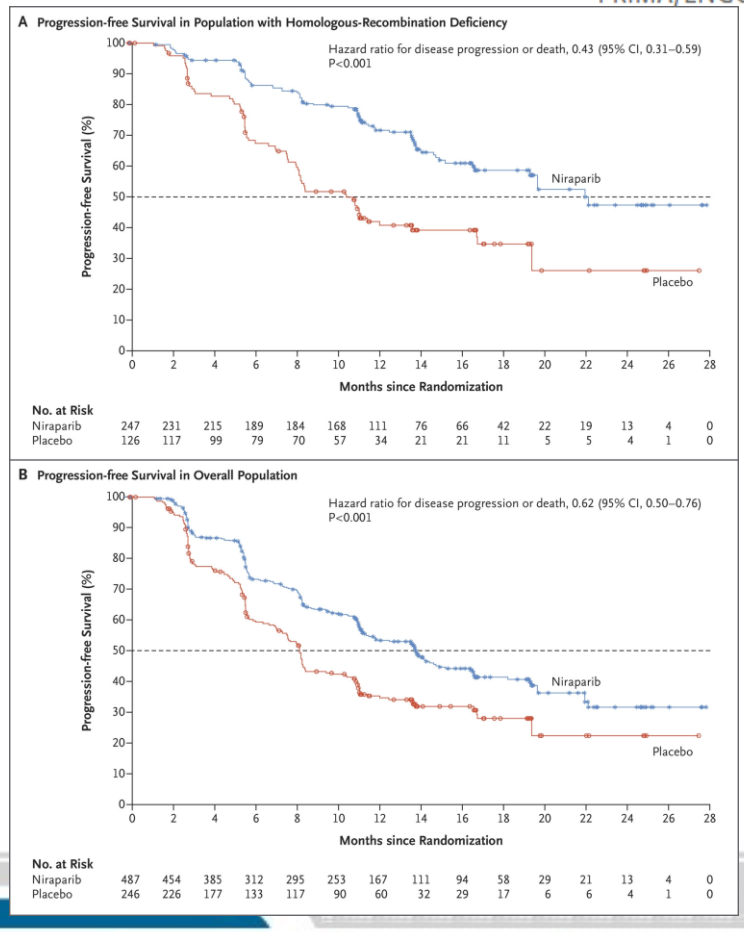
The NEW ENGLAND JOURNAL of MEDICINE

2018

ORIGINAL ARTICLE

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Antonio González-Martín, M.D., Ph.D., Bhavana Pothuri, M.D., Ignace Vergote, M.D., Ph.D., René DePont Christensen, Ph.D., Whitney Graybill, M.D., Mansoor R. Mirza, M.D., Colleen McCormick, M.D., M.P.H., Domenica Lorusso, M.D., Ph.D., Paul Hoskins, M.D., Gilles Freyer, M.D., Klaus Baumann, M.D., Kris Jardon, M.D., et al., for the PRIMA/ENGOT-OV26/GOG-3012 Investigators*



Subgroup	Niraparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	232/487 (47.6)	155/246 (63.0)	0.62 (0.50–0.76)
Age			
<65 yr	136/297 (45.8)	86/147 (58.5)	0.61 (0.47–0.81)
≥65 yr	96/190 (50.5)	69/99 (69.7)	0.53 (0.38–0.74)
ECOG score			
0	146/337 (43.3)	107/174 (61.5)	0.60 (0.46–0.77)
1	86/150 (57.3)	48/72 (66.7)	0.69 (0.48–1.00)
Stage of disease at initial diagnosis			
III	143/318 (45.0)	103/158 (65.2)	0.54 (0.42–0.70)
IV	89/169 (52.7)	52/88 (59.1)	0.79 (0.55–1.12)
Neoadjuvant chemotherapy			
Yes	151/322 (46.9)	107/167 (64.1)	0.59 (0.46–0.76)
No	81/165 (49.1)	48/79 (60.8)	0.66 (0.46–0.94)
Best response to platinum therapy			
Complete response	146/337 (43.3)	100/172 (58.1)	0.60 (0.46–0.77)
Partial response	86/150 (57.3)	55/74 (74.3)	0.60 (0.43–0.85)
Geographic region			
North America	104/218 (47.7)	82/115 (71.3)	0.50 (0.37–0.68)
[illegible]	[illegible]	[illegible]	[illegible]
Homologous-recombination status			
BRCA mutation	49/152 (32.2)	40/71 (56.3)	0.40 (0.27–0.62)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)	0.50 (0.31–0.83)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)	0.68 (0.49–0.94)
Not determined	40/71 (56.3)	26/40 (65.0)	0.85 (0.51–1.43)

Table 2. Adverse Events.

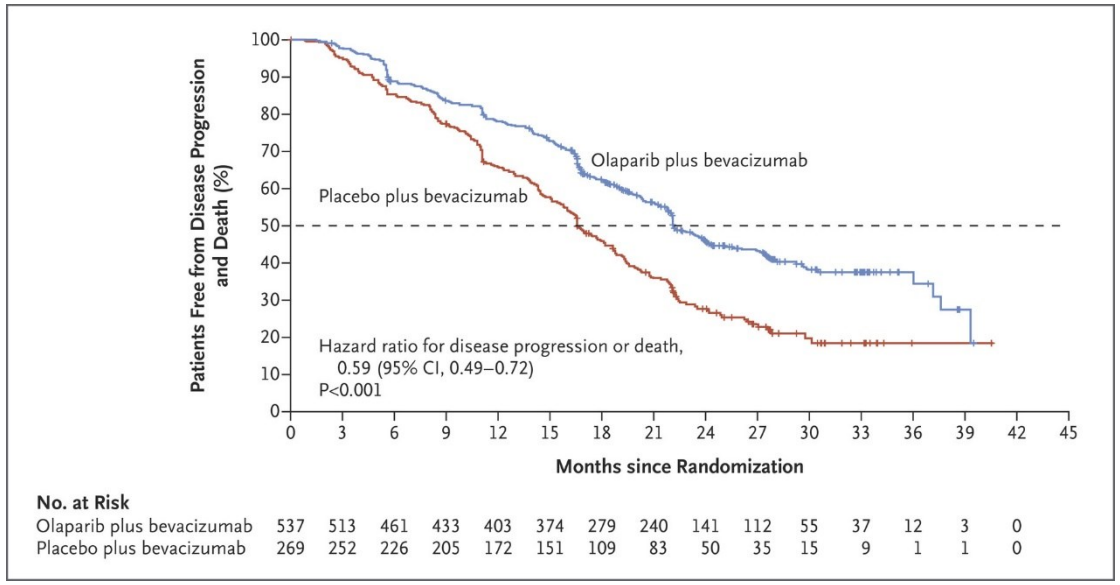
Adverse Events	Niraparib (N=484)	Placebo (N=244)
	no. of patients (%)	
Overall population		
Adverse event		
Any	478 (98.8)	224 (91.8)
Grade ≥3	341 (70.5)	46 (18.9)
Treatment-related adverse event*		
Any	466 (96.3)	168 (68.9)
Grade ≥3	316 (65.3)	16 (6.6)
Serious adverse event		
Any	156 (32.2)	32 (13.1)
Treatment-related	118 (24.4)	6 (2.5)
Leading to treatment discontinuation	58 (12.0)	6 (2.5)
Leading to dose reduction	343 (70.9)	20 (8.2)
Leading to dose interruption	385 (79.5)	44 (18.0)
Leading to death	2 (0.4)	1 (0.4)
[illegible]		
Anemia		
Any grade	307 (63.4)	43 (17.6)
Grade ≥3	150 (31.0)	4 (1.6)
Nausea		
Any grade	278 (57.4)	67 (27.5)
Grade ≥3	6 (1.2)	2 (0.8)
Thrombocytopenia		
Any grade	222 (45.9)	9 (3.7)
Grade ≥3	139 (28.7)	1 (0.4)
Constipation		
Any grade	189 (39.0)	46 (18.9)
Grade ≥3	1 (0.2)	0
Fatigue		
Any grade	168 (34.7)	72 (29.5)
Grade ≥3	9 (1.9)	1 (0.4)
Platelet count decreased		
Any grade	133 (27.5)	3 (1.2)
Grade ≥3	63 (13.0)	0
Neutropenia		
Any grade	128 (26.4)	16 (6.6)
Grade ≥3	62 (12.8)	3 (1.2)
Headache		
Any grade	126 (26.0)	36 (14.8)
Grade ≥3	2 (0.4)	0
Insomnia		
Any grade	119 (24.6)	35 (14.3)
Grade ≥3	4 (0.8)	1 (0.4)
Vomiting		
Any grade	108 (22.3)	29 (11.9)
Grade ≥3	4 (0.8)	2 (0.8)
Abdominal pain		
Any grade	106 (21.9)	75 (30.7)
Grade ≥3	7 (1.4)	1 (0.4)

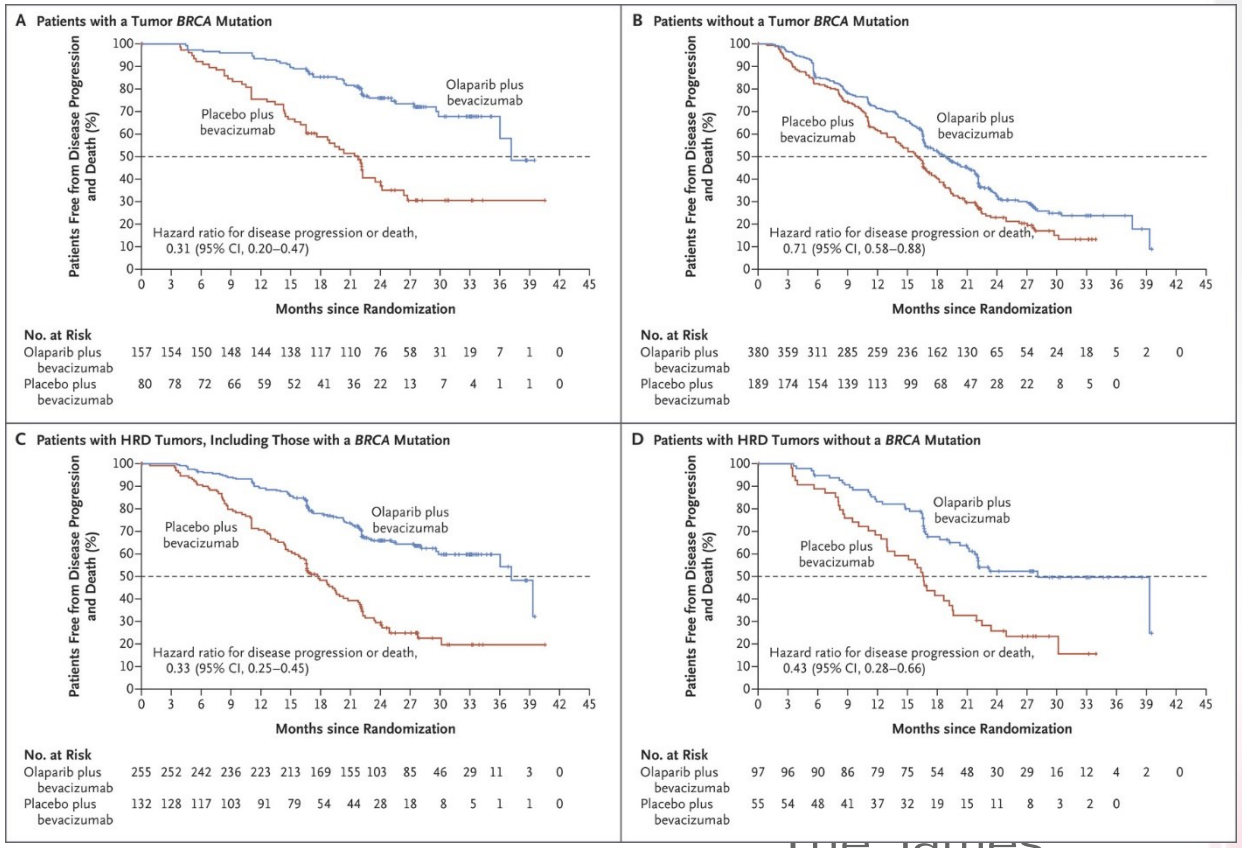
The NEW ENGLAND JOURNAL of MEDICINE 2019

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

Isabelle Ray-Coquard, M.D., Ph.D., Patricia Pautier, M.D., Sandro Pignata, M.D., Ph.D., David Pérol, M.D., Antonio González-Martín, M.D., Ph.D., Regina Berger, Ph.D., Keiichi Fujiwara, M.D., Ph.D., Ignace Vergote, M.D., Ph.D., Nicoletta Colombo, M.D., Johanna Mäenpää, M.D., Ph.D., Frédéric Selle, M.D., Jalid Sehouli, M.D., et al., for the PAOLA-1 Investigators*

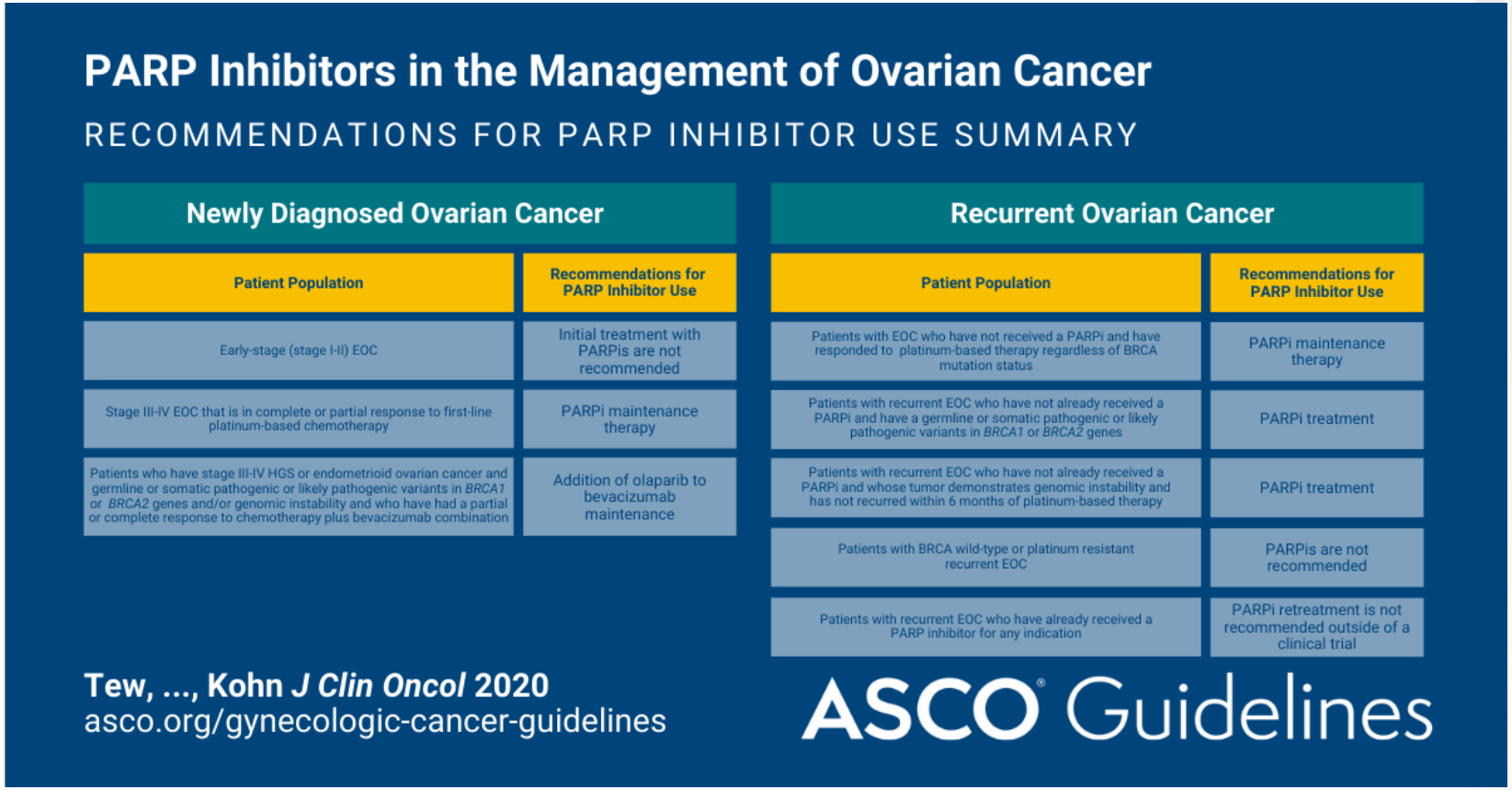




Non-HRD/Unknown HR =0.92 (95% CI 0.72-1.17)
This combination only approved for HRD+

PARP Inhibitor in Upfront Setting

- If response to platinum based chemotherapy
- PARP as maintenance
  - Veliparib was given concurrent with chemo (VELIA)
- Opportunities for treatment in recurrent setting



PARP Inhibitors in the Management of Ovarian Cancer

RECOMMENDATIONS FOR PARP INHIBITOR USE SUMMARY

Newly Diagnosed Ovarian Cancer

Patient Population	Recommendations for PARP Inhibitor Use
Early-stage (stage I-II) EOC	Initial treatment with PARPis are not recommended
Stage III-IV EOC that is in complete or partial response to first-line platinum-based chemotherapy	PARPi maintenance therapy
Patients who have stage III-IV HGS or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes and/or genomic instability and who have had a partial or complete response to chemotherapy plus bevacizumab combination	Addition of olaparib to bevacizumab maintenance

Recurrent Ovarian Cancer

Patient Population	Recommendations for PARP Inhibitor Use
Patients with EOC who have not received a PARPi and have responded to platinum-based therapy regardless of BRCA mutation status	PARPi maintenance therapy
Patients with recurrent EOC who have not already received a PARPi and have a germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes	PARPi treatment
Patients with recurrent EOC who have not already received a PARPi and whose tumor demonstrates genomic instability and has not recurred within 6 months of platinum-based therapy	PARPi treatment
Patients with BRCA wild-type or platinum resistant recurrent EOC	PARPis are not recommended
Patients with recurrent EOC who have already received a PARP inhibitor for any indication	PARPi retreatment is not recommended outside of a clinical trial

Tew, ..., Kohn *J Clin Oncol* 2020
asco.org/gynecologic-cancer-guidelines

ASCO® Guidelines

The NEW ENGLAND JOURNAL of MEDICINE 2011

ORIGINAL ARTICLE

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., et al., for the Gynecologic Oncology Group*

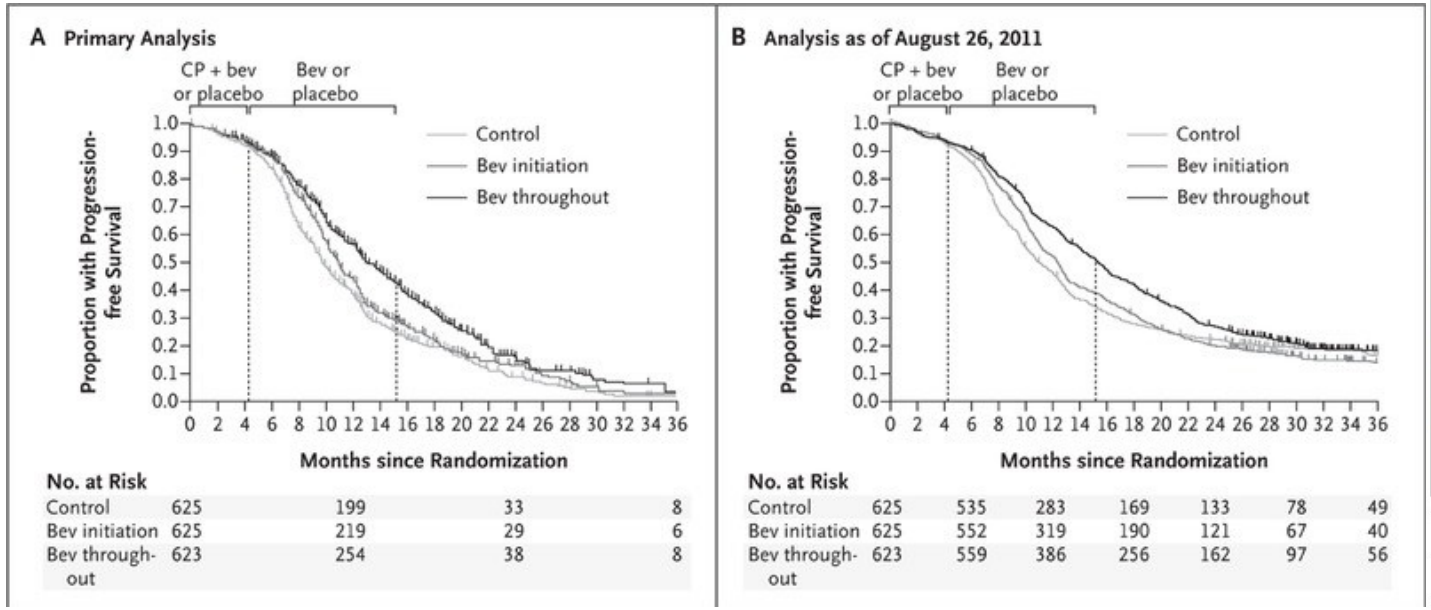


Table 2. Selected Adverse Events among the Study Patients, According to Treatment Group.*

Event	Bevacizumab Initiation (N=607)	Bevacizumab Throughout (N=608)	Control (N=601)
	number of patients (percent)		
Gastrointestinal events (grade ≥2)†	17 (2.8)	16 (2.6)	7 (1.2)
Hypertension (grade ≥2)‡	100 (16.5)§	139 (22.9)§	43 (7.2)
Proteinuria (grade ≥3)	4 (0.7)	10 (1.6)	4 (0.7)
Pain (grade ≥2)	252 (41.5)	286 (47.0)	250 (41.6)
Neutropenia (grade ≥4)	384 (63.3)	385 (63.3)	347 (57.7)
Febrile neutropenia	30 (4.9)	26 (4.3)	21 (3.5)
Venous thromboembolism	32 (5.3)	41 (6.7)	35 (5.8)
Arterial thromboembolism	4 (0.7)	4 (0.7)	5 (0.8)
Wound disruption	22 (3.6)	18 (3.0)	17 (2.8)
CNS bleeding	0	2 (0.3)	0
Non-CNS bleeding (grade ≥3)	8 (1.3)	13 (2.1)	5 (0.8)
Reversible posterior leukoencephalopathy syndrome	1 (0.2)	1 (0.2)	0

* Adverse events were those with onset between cycle 2 and 30 days after the date of the last treatment. CNS denotes central nervous system.
† Gastrointestinal events of grade 2 or greater were gastrointestinal-wall disruption: perforation, fistula, necrosis, or anastomotic leak.
‡ Hypertension of grade 2 or greater consisted of recurrent or continuous hypertension for a period of more than 24 hours or symptomatic increase in blood pressure by more than 20 mm Hg (diastolic) or to over 150/100 mm Hg if the blood pressure was previously within the normal range.
§ $P<0.05$ for the comparison with the control group.

The NEW ENGLAND JOURNAL of MEDICINE

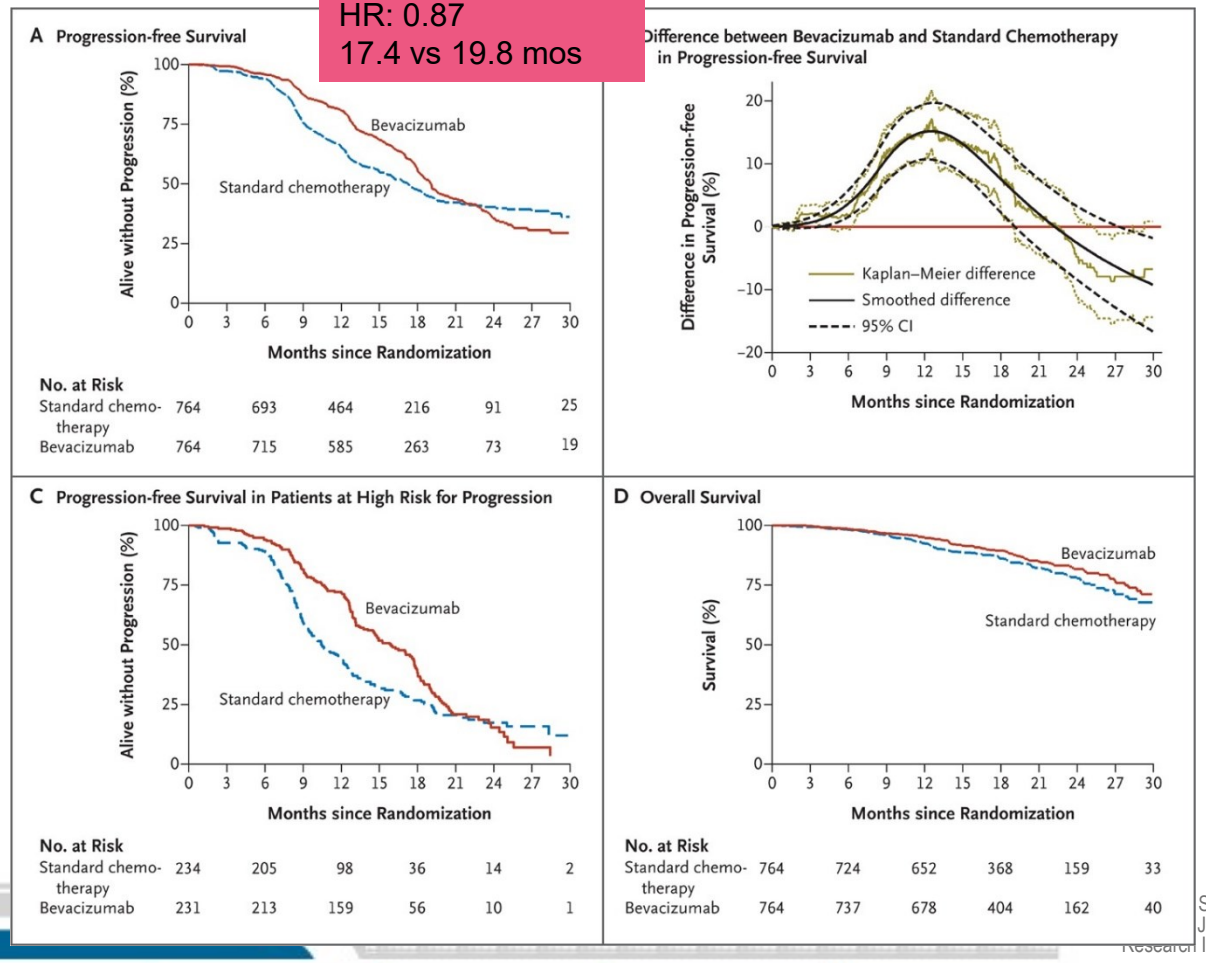
2011

ORIGINAL ARTICLE

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., et al., for the ICON7 Investigators*

HR: 0.87
17.4 vs 19.8 mos



Bevacizumab may provide some benefit in PFS

Use was adopted by some in “higher” risk patients
-Stage IV
-Suboptimal debulking

Patients with ascites

Some use upfront, some don’t….

Combination with Olaparib in HRD+ tumors

Recurrent Ovarian Cancer

- Recurrence management dictated on platinum-free interval
- > 6 months since last platinum treatment = PLATINUM SENSITIVE
- ≤6 months since last platinum treatment = PLATINUM RESISTANT
- Progression on platinum = PLATINUM REFRACTORY

- No longer “curable” but still treatable
- Regimens often dictated on prior toxicities
- Clinical trials

Does Surgery Play A Role in Recurrence?

The NEW ENGLAND JOURNAL of MEDICINE

2019

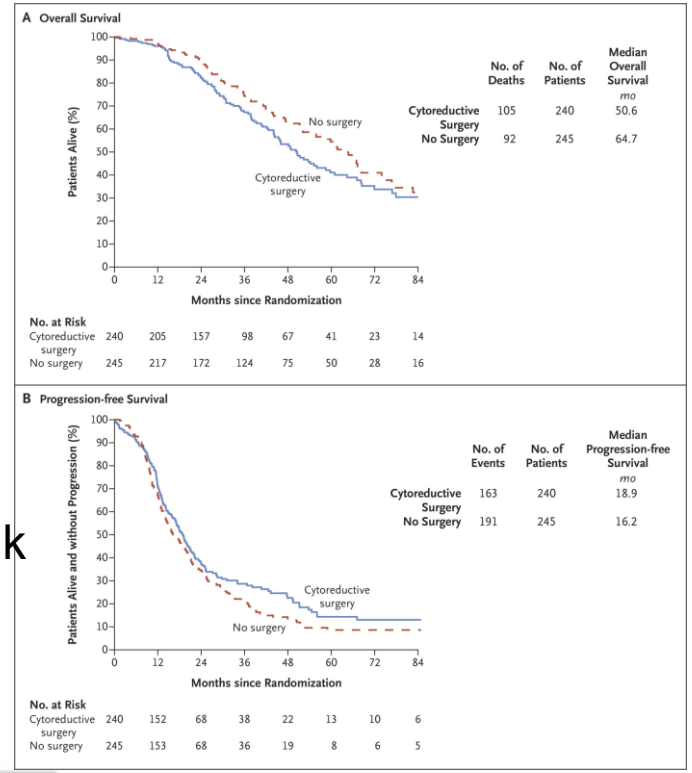
ORIGINAL ARTICLE

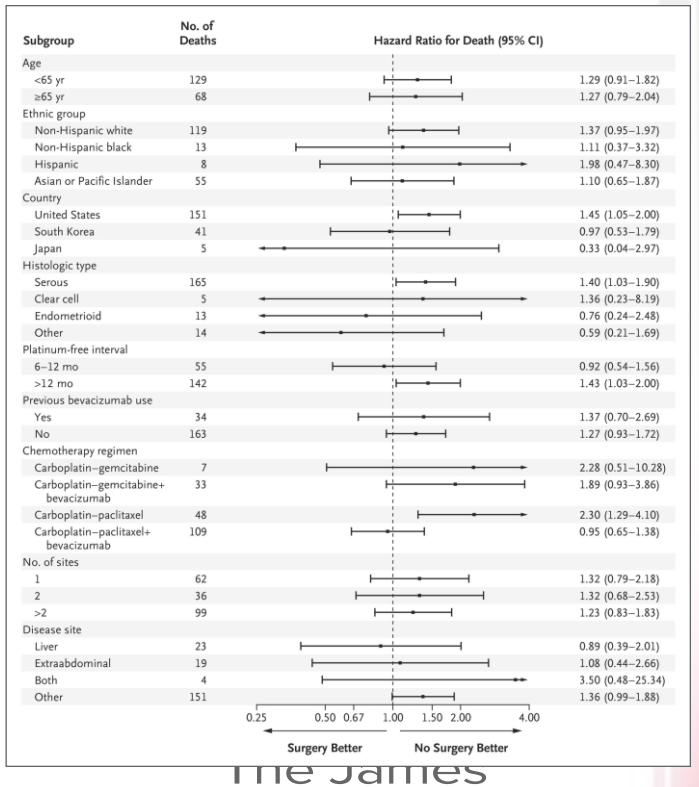
Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer

Robert L. Coleman, M.D., Nick M. Spirtos, M.D., Danielle Enserro, Ph.D., Thomas J. Herzog, M.D., Paul Sabbatini, M.D., Deborah K. Armstrong, M.D., Jae-Weon Kim, M.D., Sang-Yoon Park, M.D., Byoung-Gie Kim, M.D., Joo-Hyun Nam, M.D., Keiichi Fujiwara, M.D., Joan L. Walker, M.D., et al.

GOG213 –
Platinum Sensitive
Assessed bevacizumab
Assessed secondary surgery
Chemotherapy to follow

“Lenient” criteria – Surgeon thinks they can debulk





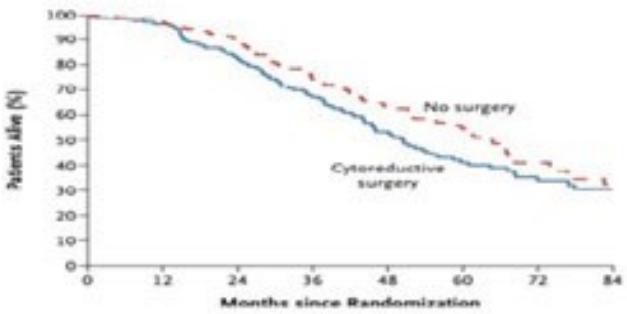
Does Surgery Play A Role in Recurrence?

DESKTOP III
Presented at ASCO 2020

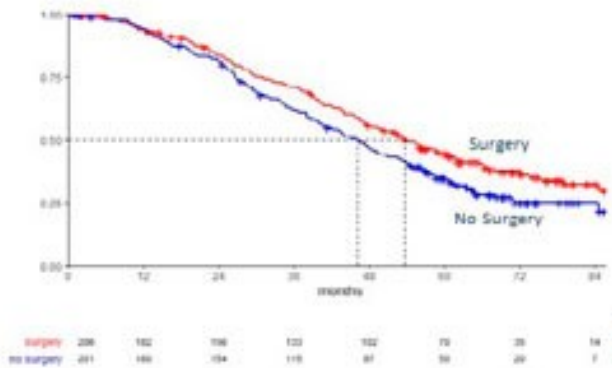
Positive AGO-score (PS ECOG 0, ascites ≤500 ml, and complete resection at initial surgery)

	GOG-213	AGO Desktop III	SGOG SOC-1
OS – Surgery (median)	53.6 mos	53.7 mos	58.1 mos
OS - No Surgery (median)	65.7 mos	46.0 mos	53.9 mos
HR, 95% CI	1.28 (0.92-1.78) P = NS	0.75 (0.58-0.96) P = 0.04	0.82 (0.57-1.19) P = NS

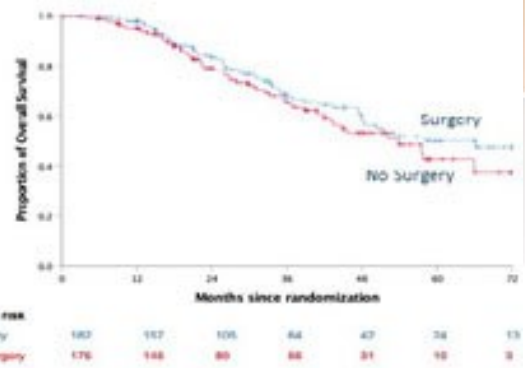
GOG-213



DESKTOP III



SOC-1



Verdict? Secondary surgery may provide benefit for SELECT cases

Platinum Sensitive Recurrent Ovarian Cancer

- Re-Challenge with Platinum-containing regimen
  - Doublet with – Pegylated Liposomal Doxorubicin (PLD), Gemcitabine, Paclitaxel

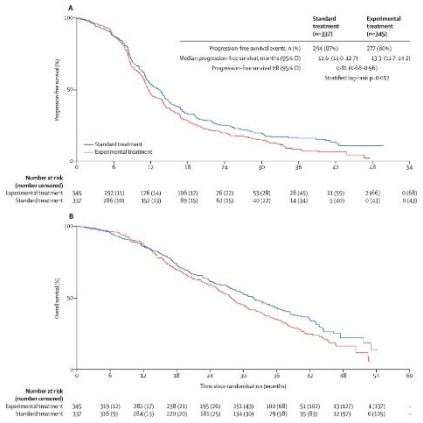
THE LANCET Oncology

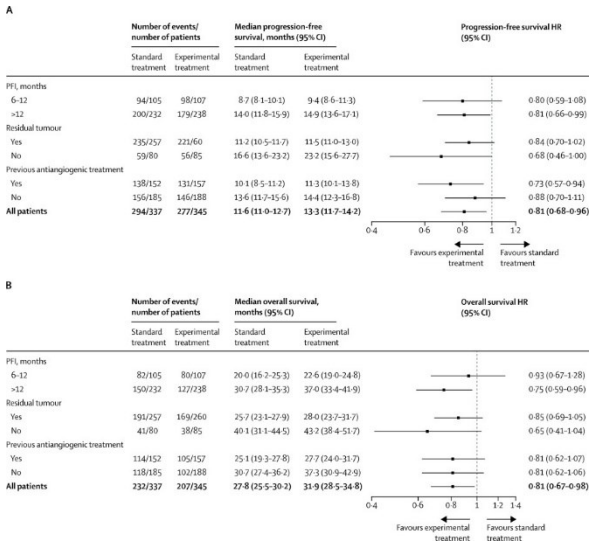
ARTICLES | VOLUME 21, ISSUE 5, P699-709, MAY 01, 2020

Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial

Prof Jacobus Pfisterer, MD • Catherine M Shannon, MBBS • Klaus Baumann, MD • Joern Rau, MSc • Philipp Harter, MD • Prof Florence Joly, MD • et al. Show all authors • Show footnotes

PLD>Gem





VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pegylated Liposomal Doxorubicin and Carboplatin Compared With Paclitaxel and Carboplatin for Patients With Platinum-Sensitive Ovarian Cancer in Late Relapse

Eric Pujade-Lauraine, Uwe Wagner, Elisabeth Aavall-Lundqvist, Val Gebski, Mark Heywood, Paul A. Vasey, Birgit Volgger, Ignace Vergote, Sandro Pignata, Annamaria Ferrero, Jalid Sehouli, Alain Lortholary, Gunnar Kristensen, Christian Jackisch, Florence Joly, Chris Brown, Nathalie Le Fur, and Andreas du Bois

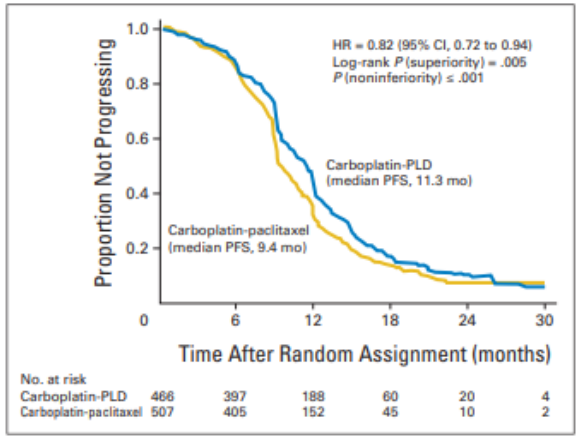


Fig 2. Progression-free survival (PFS). HR, hazard ratio; PLD, pegylated liposomal doxorubicin.

PLD>Taxol
***** <neuropathy**

Platinum Sensitive – Maintenance (PARP)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

Mansoor R. Mirza, M.D., Bradley J. Monk, M.D., Jørn Herrstedt, M.D., D.M.Sc., Amit M. Oza, M.D., Sven Mahner, M.D., Andrés Redondo, M.D., Ph.D., Michel Fabbro, M.D., Jonathan A. Ledermann, M.D., Domenica Lorusso, M.D., Ignace Vergote, M.D., Ph.D., Noa E. Ben-Baruch, M.D., Christian Marth, M.D., et al., for the ENGOT-OV16/NOVA Investigators*

THE LANCET Oncology

LUME 18, ISSUE 9, P1274-1284, SEPTEMBER 01, 2017

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

Prof Eric Pujade-Lauraine, MD • Prof Jonathan A Ledermann, MD • Frédéric Selle, MD • Prof Val Gebski, FRANZCR • Richard T Penson, MD • Prof Amit M Oza, MD • et al. Show all authors • Show footnotes

THE LANCET

ARTICLES | VOLUME 390, ISSUE 10106, P1949-1961, OCTOBER 28, 2017

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Prof Robert L Coleman, MD * • Prof Amit M Oza, MD • Domenica Lorusso, MD • Carol Aghajanian, MD • Ana Oaknin, MD • Andrew Dean, MD • et al. Show all authors • Show footnotes

	STUDY 19[1] ITT	SOLO-2[2] g*BRCA*m	NOVA[3] g*BRCA*m	NOVA[3] Non-g*BRCA*m	ARIEL3[4] *BRCA*m	ARIEL3[4] ITT
Agent	Olaparib	Olaparib	Niraparib	Niraparib	Rucaparib	Rucaparib
Difference in mPFS, mo	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; *P* < .001)	0.53 (95% CI, 0.41-0.68; *P* < .001)	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* < .001)	0.45 (95% CI, 0.34-0.61; *P* < .001)	0.20 (95% CI, 0.13-0.32; *P* < .0001)	0.35 (95% CI, 0.28-0.45; *P* < .0001)

Olaparib, Rucaparib, Niraparib all have approval as maintenance in platinum sensitive recurrence (if response to platinum) as maintenance

Platinum Sensitive – Maintenance (Bev)

VOLUME 30 · NUMBER 17 · JUNE 10 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Carol Aghajanian, Stephanie V. Blank, Barbara A. Goff, Patricia L. Judson, Michael G. Teneriello, Amreen Husain, Mika A. Sovak, Jing Yi, and Lawrence R. Nycum

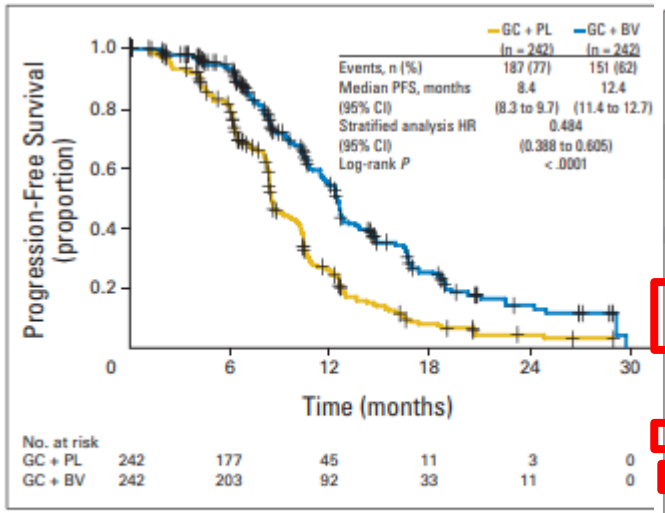


Table 3. Safety Summary and Selected AEs*

Type of AE	GC + PL (n = 233)† No.	%	GC + BV (n = 247)‡ No.	%
Any	233	100.0	247	100.0
Grades 3 to 5	192	82.4	221	89.5
Grade 5	1	0.4	1	0.4
Serious	58	24.9	86	34.8
Grades 3 to 5	47	20.2	72	29.1
Leading to study drug (BV/PL) discontinuation	11	4.7	49	19.8
Special interest (any grade)	198	85.0	233	94.3
Arterial thromboembolic event (any grade)	2	0.9	7	2.8
Bleeding				
CNS (any grade)	1	0.4	2	0.8
Non-CNS (grade ≥ 3)	2	0.9	14	5.7
LV systolic dysfunction/CHF (grade ≥ 3)	2	0.9	3	1.2
Febrile neutropenia (any grade)	4	1.7	4	1.6
Fistula/abscess (any grade)§	1	0.4	4	1.6
GI perforation (any grade)	0	0.0	0	0.0
Hypertension (grade ≥ 3)	1	0.4	43	17.4
Neutropenia (grade ≥ 4)	51	21.9	51	20.6
Proteinuria (grade ≥ 3)	2	0.9	21	8.5
RPLS (any grade)	0	0.0	3	1.2
Wound-healing complication (grade ≥ 3)	0	0.0	2	0.8
Venous thromboembolic event (grade ≥ 3)	6	2.6	10	4.0

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) based investigator assessment, censoring for non–protocol-specified therapy (random assigned patients). BV, bevacizumab; GC, gemcitabine plus carboplatin; HR, hazard ratio; PL, placebo.

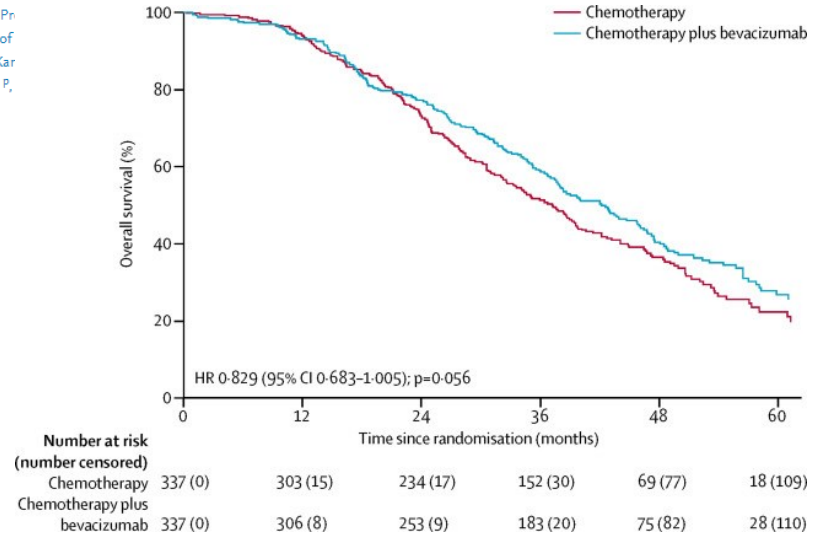
THE LANCET Oncology

Volume 18, Issue 6, June 2017, Pages 779-791

Articles

Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial

Prof Robert L Coleman MD [a], Prof Mark F Brady PhD [b], Prof Thomas J Herzog MD [c], Prof Paul Sabbatini MD [d], Prof Deborah K Armstrong MD [e], Pr
Prof Krishnansu S Tewari MD [l], Prof
Prof Paul DiSilvestro MD [m], Prof Kar
Spirtos MD [o], Raheela Ashfaq MD [p],



Platinum Resistant

VOLUME 32 · NUMBER 13 · MAY 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial

Eric Pujade-Lauraine, Felix Hilpert, Béatrice Weber, Alexander Reuss, Andres Poveda, Gunnar Kristensen, Roberto Sorio, Ignace Vergote, Petronella Witteveen, Aristotelis Bamias, Deolinda Pereira, Pauline Wimberger, Ana Oaknin, Mansoor Raza Mirza, Philippe Follana, David Bollag, and Isabelle Ray-Coquard

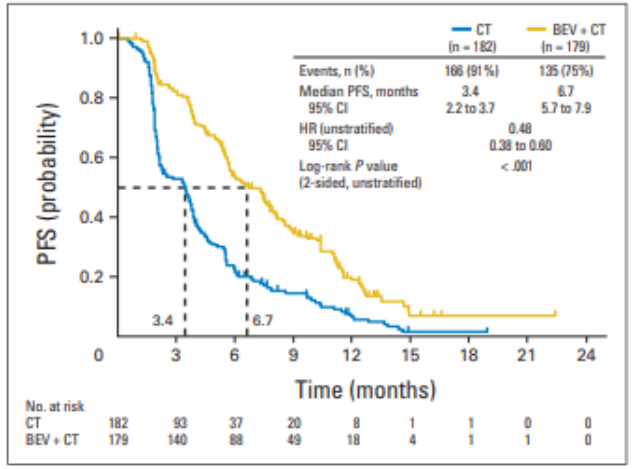
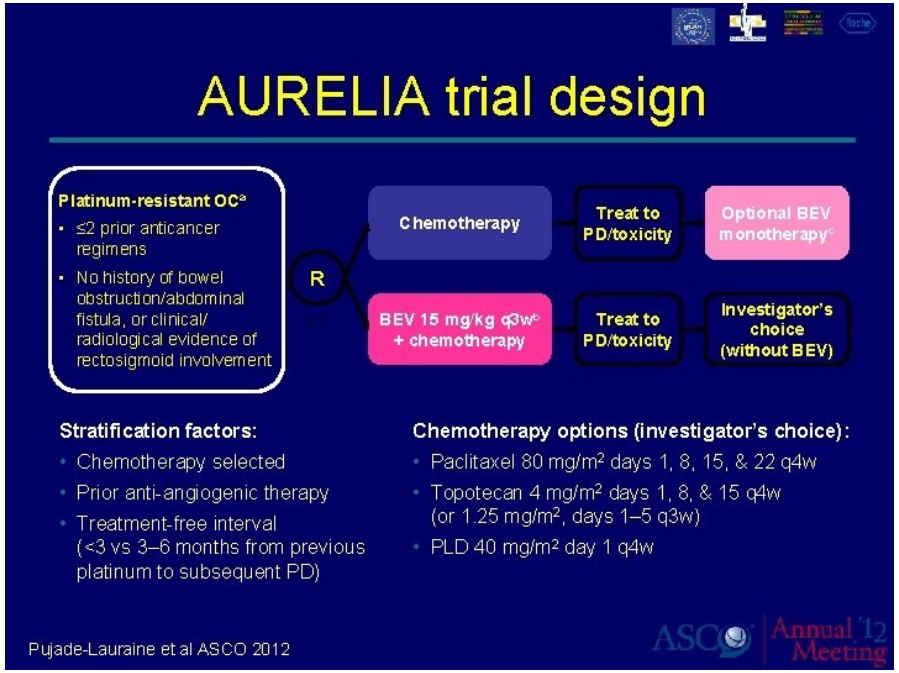
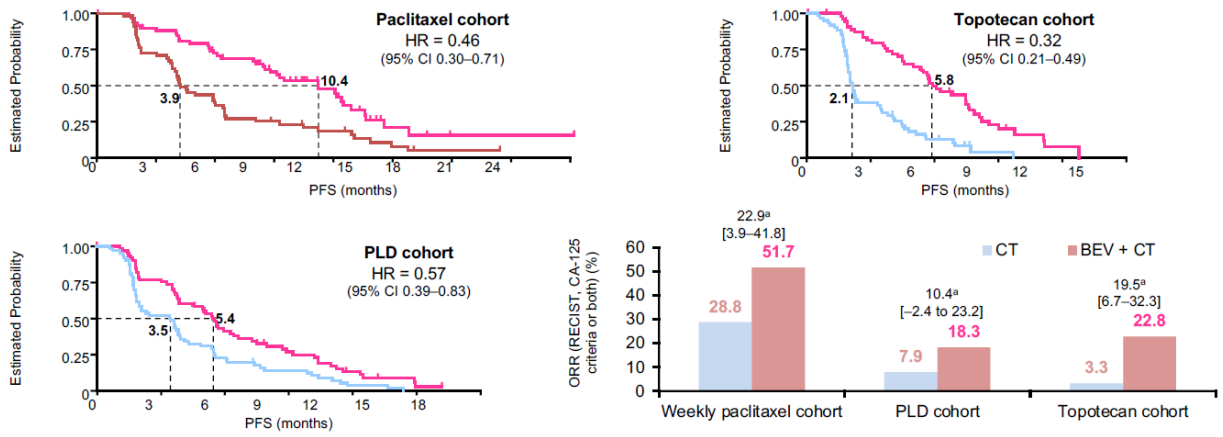


Fig 2. Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.





Poveda AM, et al; J Clin Oncol. 2015

What About Immunotherapy?

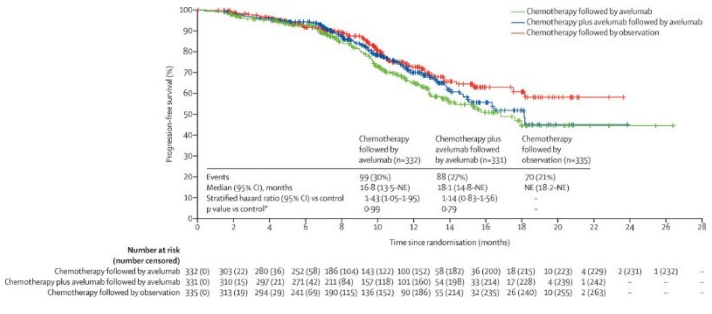
THE LANCET Oncology

ARTICLES | VOLUME 22, ISSUE 9, P1275-1289, SEPTEMBER 01, 2021

Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial

Prof Bradley J Monk, MD • Nicoletta Colombo, MD • Prof Amit M Oza, MD • Prof Keiichi Fujiwara, MD • Prof Michael J Birrer, MD • Prof Leslie Randall, MD • et al. Show all authors • Show footnotes

Although no new safety signals were observed, results do not support the use of avelumab in the frontline treatment setting. Alternative treatment regimens are needed to improve outcomes in patients with advanced epithelial ovarian cancer.

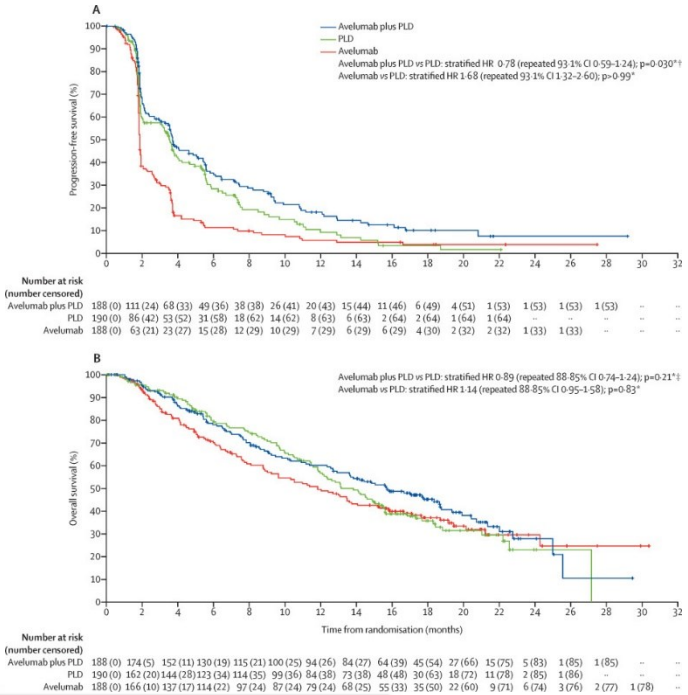


ARTICLES | VOLUME 22, ISSUE 7, P1034-1046, JULY 01, 2021

Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study

Prof Eric Pujade-Lauraine, MD • Prof Keiichi Fujiwara, MD • Prof Jonathan A Ledermann, MD • Prof Amit M Oza, MD • Rebecca Kristeleit, MD • Prof Isabelle-Laure Ray-Coquard, MD • et al. Show all authors

Neither avelumab plus PLD nor avelumab alone significantly improved progression-free survival or overall survival versus PLD. These results provide insights for patient selection in future studies of immune checkpoint inhibitors in platinum-resistant or platinum-refractory ovarian cancer.



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

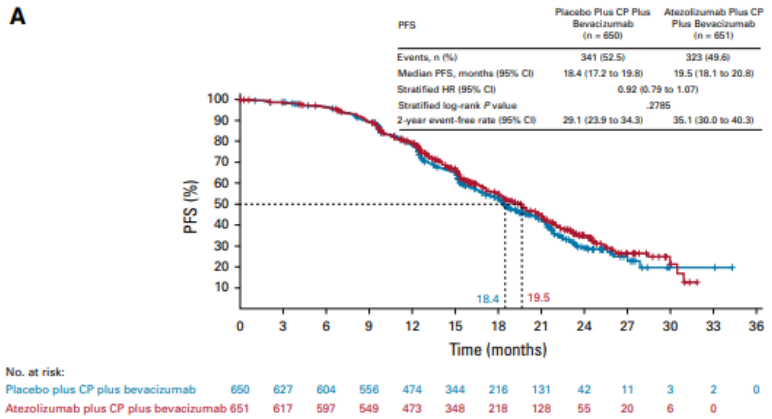
June 10, 2021

RAPID COMMUNICATIONS | Gynecological Cancer

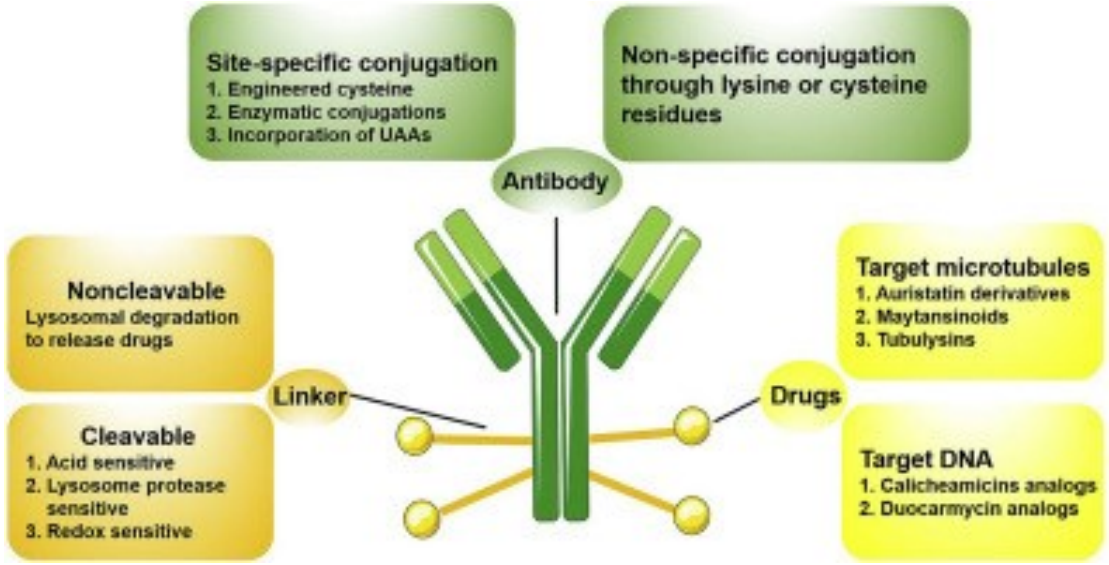
Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39)

Kathleen N. Moore, MD[1,2]; Michael Bookman, MD[3]; Jalid Sehouli, MD[4]; Austin Miller, PhD[5]; Charles Anderson, MD[6]; Giovanni Scambia, MD[7]; ...

Current evidence does not support the use of immune checkpoint inhibitors in newly diagnosed OC. Insight from this trial should inform further evaluation of immunotherapy in OC.



Antibody Drug Conjugates



Zhao et al. Recent advances of antibody drug conjugates for clinical applications
Acta Pharmaceutica Sinica B
Volume 10, Issue 9, September 2020, Pages 1589-1600

ADC	Target antigen/ antibody	Cytotoxic payload and mechanism of action	Linker	DAR	Clinical outcomes	Phase of development	Most commonly reported adverse events
Mirvetuximab soravtansine (ImmunoGen, Inc)	Folate receptor α Humanized IgG1 (M9346A)	Soravtansine (Maytansinoid DM4) Microtubule inhibitor	Sulfo-PDB	3–4	ORR 24–46%[b,c] Median PFS 4.8–6.7 months[b,c] Combination therapy: • Carboplatin: ORR 71%[a] (80%[b]); PFS 15 months • Bevacizumab: ORR 41%[b]; PFS 7.1 months • Carboplatin + Bevacizumab: ORR 80%[a,c]	Phase III; Phase Ib/II for combination therapy ongoing (NCT02606305)	Diarrhea (34–44%), fatigue (30–32%), nausea (25–54%), neuropathy (28%), blurred vision (25–43%), keratopathy (26%), increased AST (24%), vomiting (22%) Combination therapy: Nausea (67%), diarrhea (61%), thrombocytopenia (61%), blurred vision (61%)
STRO-002 (Sutro Biopharma, Inc.)	Folate receptor α Human anti-FRα IgG1 antibody (SPB166)	Proprietary 3-aminophenyl hemiasterlin agent: SC209 Proprietary tubulin-targeting payload	Proprietary cleavable linker: SC239	4	ORR 7.7% (preliminary results; phase I dose escalation, ongoing)	Phase I dose escalation/ expansion ongoing (NCT03748186)	Nausea, vomiting, abdominal pain, fatigue, and insomnia (occurring in ≥20% of patients)
MORAb-202 (Eisai Inc.)	Folate receptor α Humanized anti-human FRα farletuzumab	Eribulin mesylate Microtubule inhibitor	Cathepsin B-cleavable linker	4	ORR 37.5% in entire cohort (3 ovarian cancer patients)	Phase I ongoing (NCT03386942)	Leukopenia (50%), neutropenia (50%)
XMT-1536 (Mersana Therapeutics)	NaPi2b Humanized monoclonal antibody (SLC34A2)	Proprietary auristatin derivative (auristatin F-HPA) Microtubule inhibitor	Proprietary hydrophilic polymer scaffold	10–12	33%[b,c] (also included NSCLC)	Phase I dose escalation/expansion ongoing (NCT03319628)	Nausea, fatigue, headache, vomiting, pyrexia, decreased appetite, diarrhea, anemia, thrombocytopenia, and increased aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase (occurring in ≥10% of patients)
Lifastuzumab vedotin (LIFA/DNIB0600A) (Genentech, Inc.)	NaPi2b Humanized monoclonal antibody (SLC34A2)	MMAE Microtubule inhibitor	Cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC)	3–4	ORR 36%[b,c]	Randomized phase II completed; further development discontinued	Fatigue (44%), nausea (46%), abdominal pain (46%), decreased appetite (37%), constipation (24%), diarrhea (35%), vomiting (26%), neutropenia (28%), anemia (22%), peripheral neuropathy (22%)
Tisotumab vedotin (HuMax-TF-ADC; TF011-MMAE) (Seattle Genetics, Inc.)	Tissue factor Fully human monoclonal antibody	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker		ORR 13.9%	Phase II ongoing (NCT03657043)	Epistaxis (69%), fatigue (56%), nausea (52%), alopecia (44%), conjunctivitis (43%), decreased appetite (36%), constipation (35%), diarrhea (30%), vomiting (29%), peripheral neuropathy (22%), dry eye (22%), and abdominal pain (20%).
Anetumab ravtansine (BAY 94-9343) (Bayer)	Mesothelin Fully human IgG1 (MF-T)	Ravtansine/ DM4 Microtubule inhibitor	Sulfo-PDB	3.2	ORR 9% with disease control rate of 59% Combination therapy: • PLD: ORR 52%; DCR 86%	Phase II combination with bevacizumab ongoing (NCT03587311)	Reversible keratopathy, asymptomatic liver function test increases, and gastrointestinal disorders (% not published) Combined therapy: Reversible corneal disorders, neutropenia, liver function test increases and gastrointestinal disorders (% not published)
DMOT4039A (RG7600) (Genentech, Inc.)	Mesothelin Humanized IgG1 antibody (h7D9.v3)	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker	3.5	ORR 30%[b]	Phase I completed (NCT01469793)	Fatigue (46%), nausea (26%), diarrhea (22%), alopecia (20%), peripheral neuropathy (19%), anorexia (11%), pyrexia (11%)
BMS-986148 (Bristol-Myers Squibb)	Mesothelin Fully human IgG1 monoclonal antibody	Duocarmycin-related DNA alkylation	Protease cleavable valine-citrulline linker	1.4	ORR 9%	Phase I/IIa ongoing (NCT02341625)	Increased AST (43%), increased ALT (41%), fatigue (37%), nausea (29%), decreased appetite (22%), and increased blood alkaline phosphatase (18%)
Sofituzumab vedotin (DMUC5754A) (Genentech, Inc.)	MUC16 Humanized IgG1 monoclonal antibody	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker	3.5	ORR 17%[b]	Phase I completed; further development discontinued	Fatigue (30–57%), peripheral neuropathy (39%), nausea (37%), decreased appetite (22–30%), vomiting (28%), diarrhea (22–24%), alopecia (20–22%), pyrexia (20%), anemia (35%), neutropenia (26%), hypomagnesemia (22%)
Anti-MUC16 TDC (DMUC4064A) (Genentech, Inc.)	MUC16 Humanized anti-MUC16 IgG1	MMAE Microtubule inhibitor	Cysteine-engineered THIOMAB™	2	ORR 45%[b]	Phase I completed (NCT02146313)	Blurred vision (65%), fatigue (40%), nausea (40%), peripheral neuropathy (35%), keratitis (30%), diarrhea (25%), and dry eyes (25%).

Calo (2021) Expert Opinion on Biological Therapy

GOG FOUNDATION® Transforming the standard of care GOG PARTNERS A GOG Foundation Program

Antibody Drug Conjugates as a New Class of Agents in Treating Recurrent Ovarian Cancer

Conclusions

- Suspected ovarian cancer should be evaluated by a gynecologic oncologist for surgery/timing of surgery
- Surgical staging/debulking remains a major part of treatment
- Genetic counseling/testing – germline (for ALL) and somatic (advanced stage)
- Maintenance therapy is considered for advanced stage cases
- Still many unclear answers
- Despite lots of literature… individualized care remains central
- **Clinical trials should be considered when possible**