Ovarian Cancer: New Horizons and Treatments

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SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

Washington University in St. Louis
School of Medicine

Disclosure

- Advisory Board: Celsion, Genentech, Iovance
- Speaker's bureau: Tesaro and Merck
- Institutional Grant: Merck and Tesaro

Objectives

- Symptoms and Diagnosis
- Standard of care therapy: surgery and neoadjuvant chemotherapy
- Novel therapies
  - Immunotherapy
  - PARP inhibitors
  - Anti-angiogenic

2018 US Estimates *

Women	New Cases 852,630	Deaths 282,500
	30% Breast	25% Lung & bronchus
	12% Lung & bronchus	14% Breast
	8% Colon & rectum	8% Colon & rectum
	7% Uterine corpus	7% Pancreas
	5% Thyroid	**5% Ovary**
	4% Non-Hodgkin	4% Leukemia
	4% Melanoma of skin	4% Uterine corpus
	3% Ovary	3% Non-Hodgkin lymphoma
	3% Pancreas	3% Liver & bile duct
	3% Leukemia	2% Brain & other nervous system
	20% All Other Sites	22% All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2018.

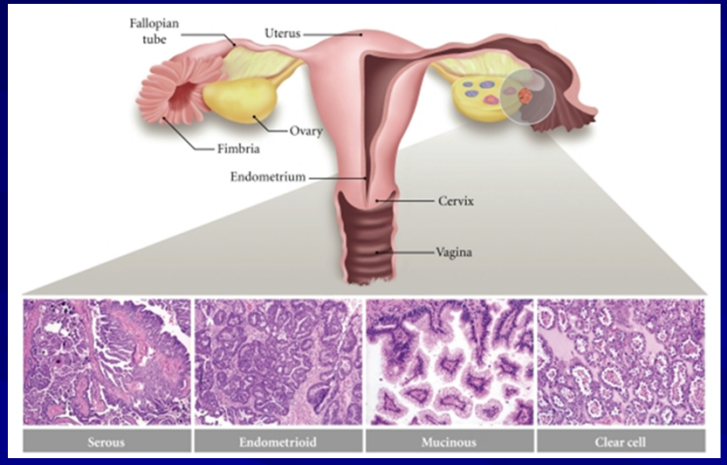
Epidemiology

- 239,000 new incidence annually worldwide. Incidence stable since 1970s
- Median age at diagnosis 63
- Fourth commonest cause of cancer death in women in developed countries
- >60% of women diagnosed with Stage III/IV
  - symptoms of abdominal pain, bloating, distension, constipation, back pain usually happen in advanced stage
- To date, no mortality benefit demonstrated with CA-125 and TVUS screening.

Stage at diagnosis

Stage I	**Confined to the Ovary**
I_A	Growth limited to one ovary, no ascites, capsule intact, no surface tumor extension
I_B	Same as I_A but involves both ovaries
I_C	I_A or I_B but with positive washings or ruptured capsule
Stage II	**Extends to True Pelvis**
II_A	Involves fallopian tube or uterus
II_B	Extension to other pelvic tissues
II_C	Either II_A or II_B but with positive washings or ruptured capsule
Stage III	**Extends Beyond the True Pelvis**
III_A	Tumor limited to true pelvis but microscopic positive biopsy outside the pelvis
III_B	Abdominal implants up to 2 cm
III_C	Positive lymph nodes or abdominal implants > 2 cm
Stage IV	**Distant Disease**

US 5 Yr Relative Survival Rates (%) from 2007-2013



	All subtypes	Serous	Endometrioid	Mucinous	Clear Cell
All stages	47	44	82	69	67
Localized	93	90	98	93	90
Regional	74	75	87	81	74
Distant	30	35	48	18	26

American Cancer Facts & Figures 2018

Ovarian Cancer Risk Factors

- 50 years of age or older
- Familial factors
  - Family history of breast, ovarian, endometrial or colon cancers
  - Personal history of breast or colon cancer
  - Familial cancer syndrome (10%)
    - BRCA (breast cancer) gene mutation
    - Hereditary nonpolyposis colon cancer (HNPCC)
- Other potential risk factors
  - Early menarche (younger than 12 years of age)
  - Late menopause (older than 52 years of age)
  - Hormone replacement therapy
  - First pregnancy at older than 30 years of age
  - Infertility, endometriosis
  - (fertility Rx does not increase risk)

Ovarian Cancer and Early Detection

- Certain factors may reduce a woman's risk of developing ovarian cancer :
  - Taking birth control pills for more than 5 years
  - Breastfeeding
  - Pregnancy
  - A hysterectomy or a tubal ligation

Lifetime Risk of Cancers Associated With Specific Genes

Cancer, %	BRCA1	BRCA2	MMR*
Breast	35-60	30-55	0
Ovarian	35-45	15-25	6-20
Endometrial	0	0	40-60

*MMR (mismatch repair) = HNPCC

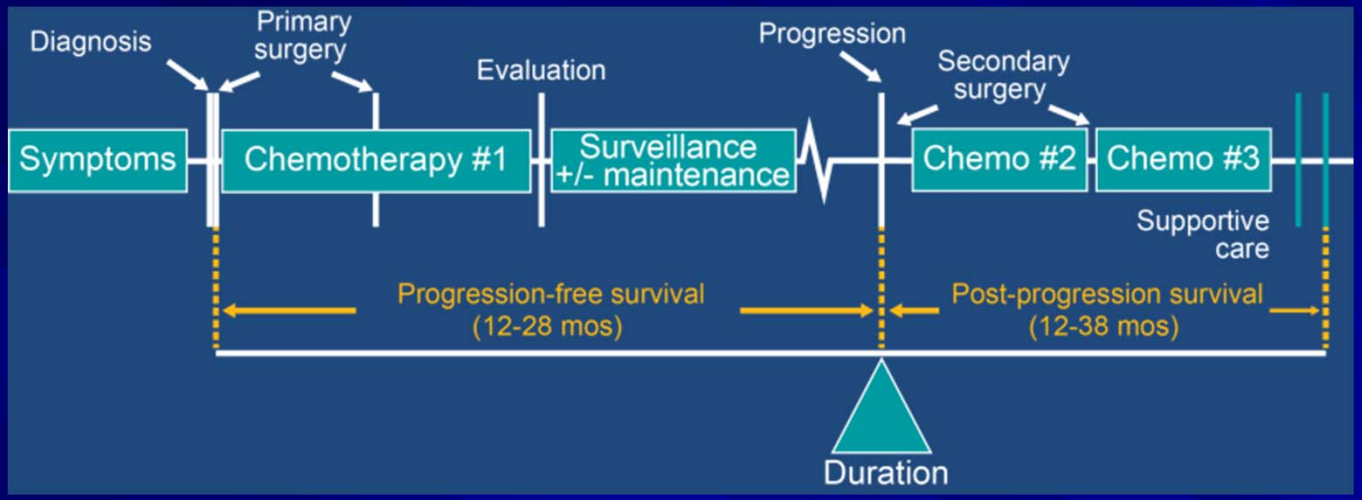
Chen S, et al. J Clin Oncol. 2007:25:1329-1333.
Aarnio M, et al. Int J Cancer. 1999:81:214-218.

Ovarian Ca Screening for general population: PLCO trial

- 68557 participants 55-74yo w/o prior hx of oophorectomy
- annual Ca125 for 6 years and TVUS for 4 years in intervention grp
- Median f/u:12.4 years
- Results:
  - Similar detection rate (5.7 v 4.7 per 10000 person-yrs), HR 1.21 CI:0.99-1.48
  - <60% of ovarian ca detected were high grade serous subtype.
  - No difference in ovarian ca mortality (3.1 v 2.6 per 10000 person-years) HR 1.18 CI:0.82-1.71.
  - Harm from false-positive screen: 3285 cases with 15% major complication rate from surgical intervention.

JAMA 2011:305 (22):2295-2303

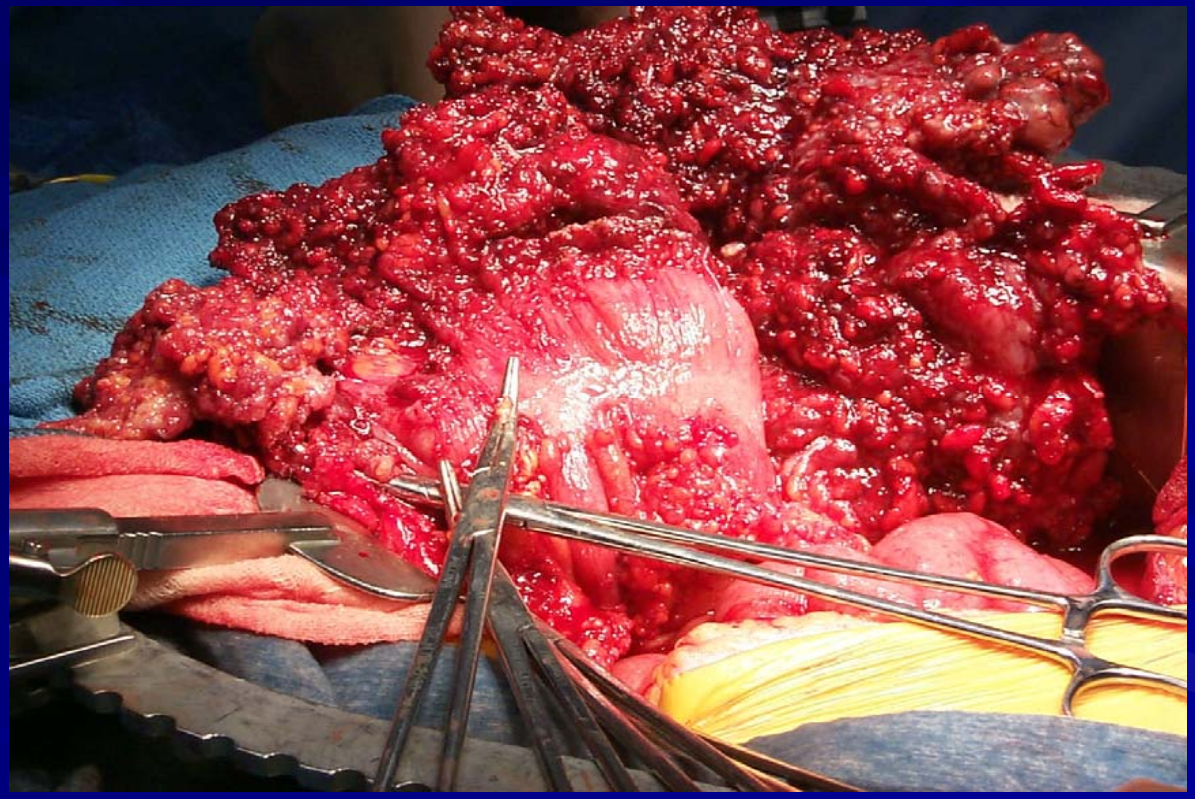
Treatment Landscape Overview for Advanced Ovarian Cancer



- Surgical goal is complete cytoreduction of all macroscopic visible disease[1]
- Standard adjuvant chemotherapy is an IV or IP taxane/platinum combination[1]
- Despite optimal upfront surgery and adjuvant chemotherapy, approximately 80% of patients will relapse[2]
- Unknowns: maintenance therapy, antiangiogenic therapy, role of IP therapy, and dose-dense schedule

EOC, epithelial ovarian cancer; IV, intravenous; IP, intraperitoneal.
Image curtesy of Dr. Robert Coleman
1. Ledermann et al. Ann Oncol. 2013;24 Suppl 6:vi24-32.
2. du Bois. Cancer. 2009;115(6):1234-44.

Surgical Cytoreduction

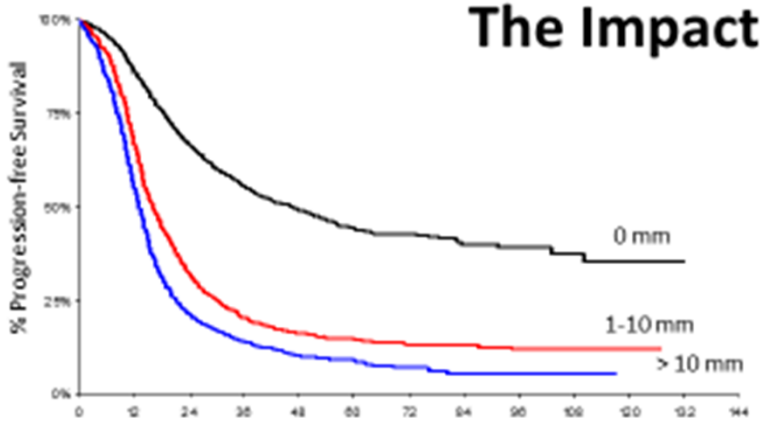


Adequate Surgery is Vital in Treating Ovarian Cancer

- Maximal effort at primary cytoreduction
  - Goal is R0 (complete resection = optimal)
  - Imaging and perhaps laparoscopy to assess feasibility
  - Decision requires gynecologic oncology input
- 3 cycles of neoadjuvant chemotherapy and interval debulking in unique circumstances
  1. Infirm and elderly unlikely to tolerate extensive surgery
  2. Carcinomatosis where R0 is unlikely

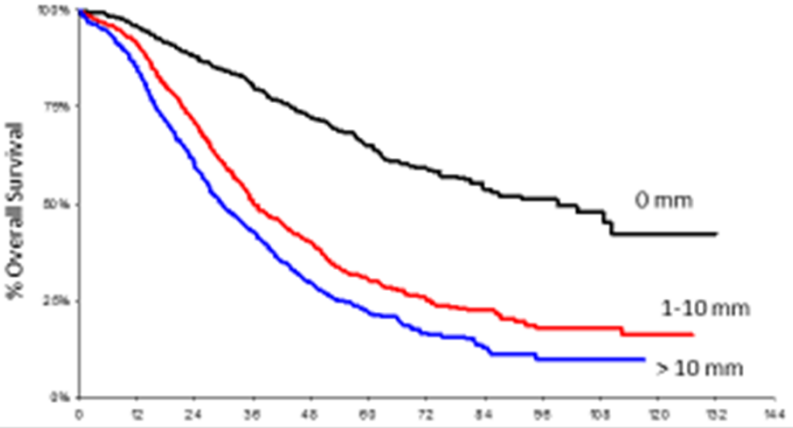
Wright AA, et al. J Clin Oncol. 2016 Oct 1;34(28):3460-73.

The Impact of Optimal Debulking



	HR	(95%CI)
1-10 mm vs. 0 mm:	2.52	(2.26;2.81)
>10 mm vs. 1-10 mm:	1.36	(1.24;1.50)

log-rank: p < 0.0001



Generated from 3 prospective Phase III trials (OVAR 3,5, & 7) N = 3126 pts

	HR	(95%CI)
1-10 mm vs. 0 mm:	2.70	(2.37; 3.07)
>10 mm vs. 1-10 mm:	1.34	(1.21; 1.49)

log-rank: p < 0.0001

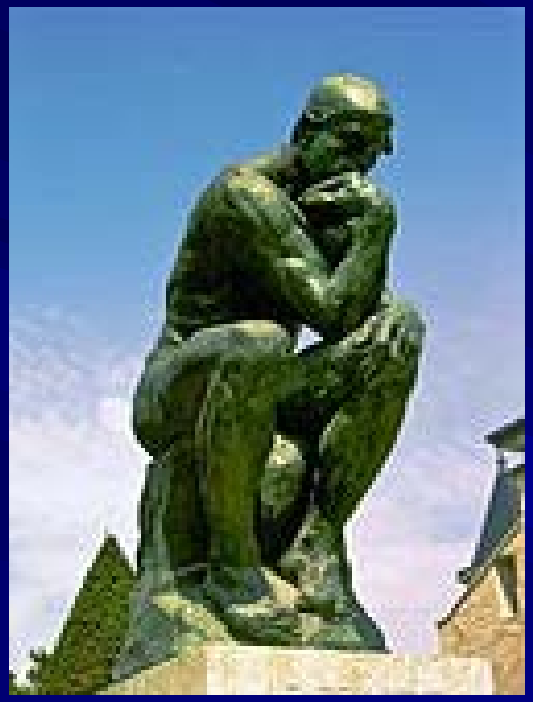
DuBois, Cancer (2009)115:1234

Laparoscopic Predictive Index

Table 2 | Laparoscopic predictive index value to determine disease distribution[51]

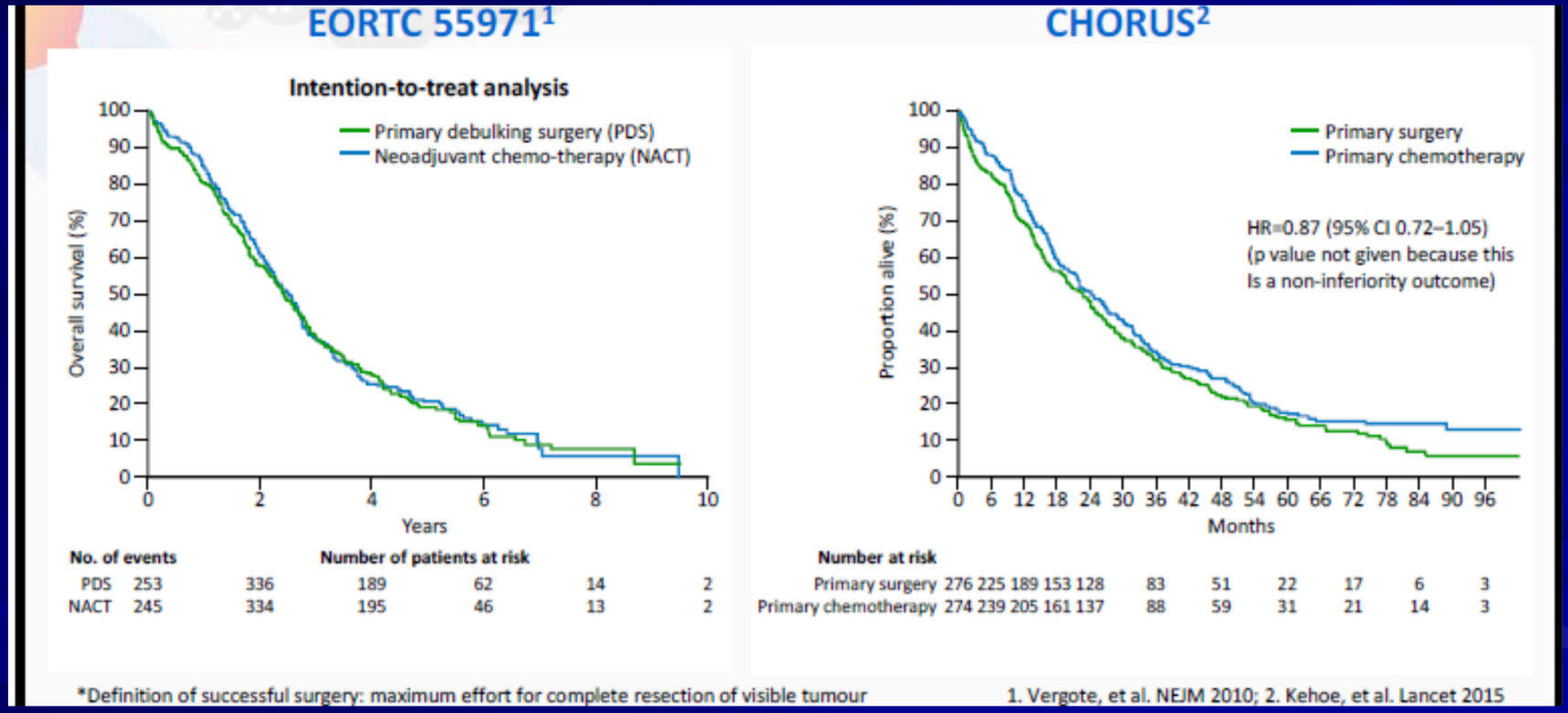
Tumour site distribution	Laparoscopic predictive index score = 2	Laparoscopic predictive index score = 0
Peritoneal carcinomatosis	Unresectable massive peritoneal involvement plus miliary pattern of distribution	Carcinomatosis involving a limited area surgically removable by peritonectomy
Diaphragmatic disease	Widespread infiltrating carcinomatosis or confluent nodules to most of the diaphragmatic surface	Isolated diaphragmatic disease
Mesenteric disease	Large infiltrating nodules or involvement of the root of the mesentery assumed based on limited movements of various intestinal segments	Small nodules potentially treatable with argon-beam coagulation
Omental disease	Tumour diffusion up to the large curvature of the stomach	Isolated omental disease
Bowel infiltration	Bowel resection assumed to be required or miliary carcinomatosis at the mesenteric junction	No bowel resection required and no miliary carcinomatosis at the mesenteric junction
Stomach infiltration	Obvious neoplastic involvement of the gastric wall	No obvious neoplastic involvement of the gastric wall
Liver metastasis	Any surface lesions	No surface lesions

Nick, A. M. *et al.* (2015) A framework for a personalized surgical approach to ovarian cancer
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2015.26



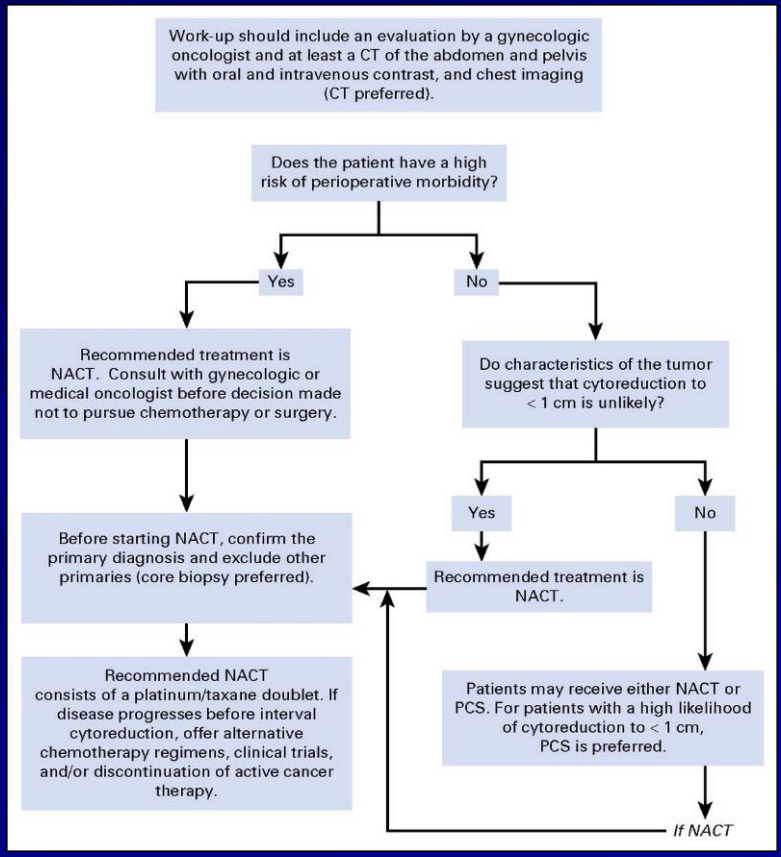
Chemotherapy vs Surgery?

Design of 2 Phase III Trials Addressing NACT



Algorithm for the clinical evaluation and treatment of women with suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

ASCO & SGO Guidelines August 2016



Alexi A. Wright et al. JCO doi:10.1200/JCO.2016.68.6907

JOURNAL OF CLINICAL ONCOLOGY ASCO

NACT Trends

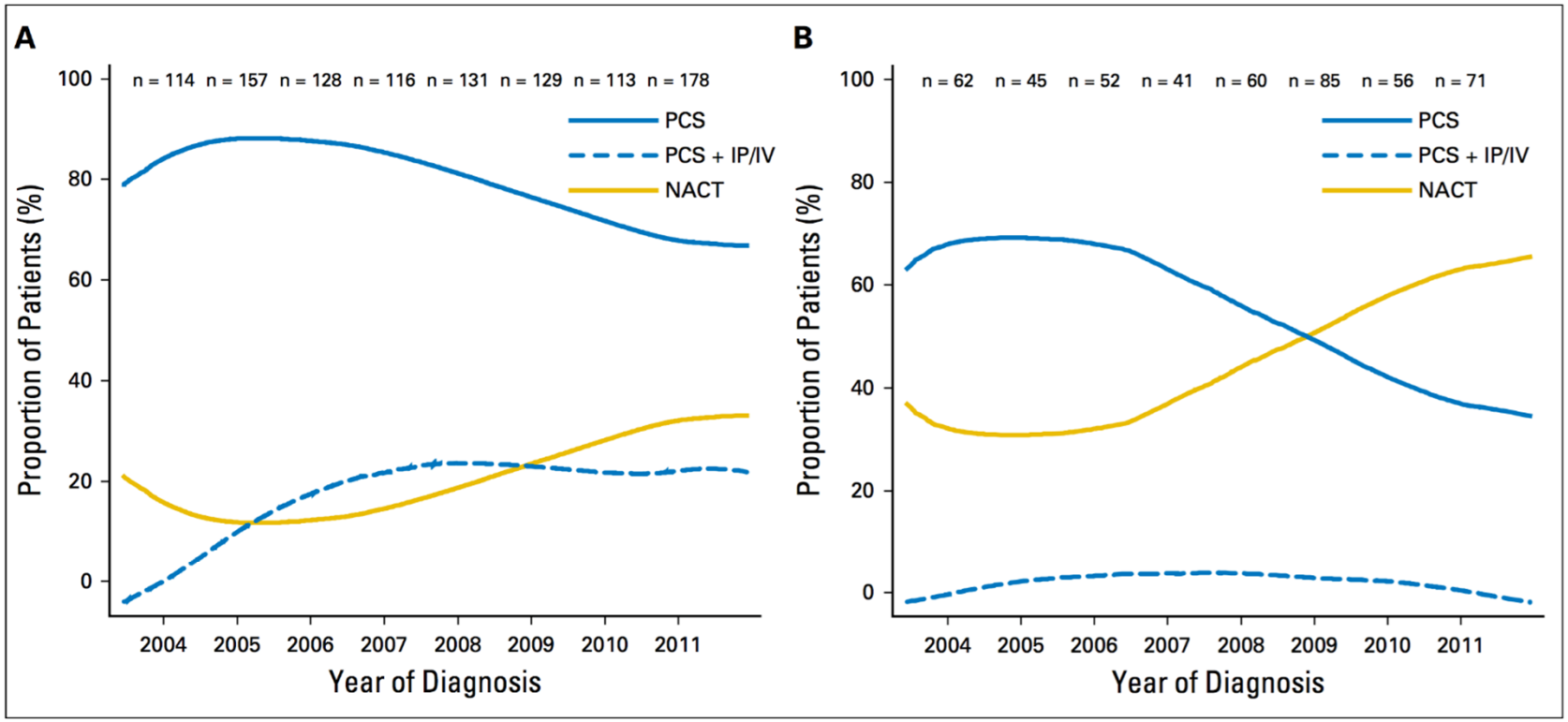
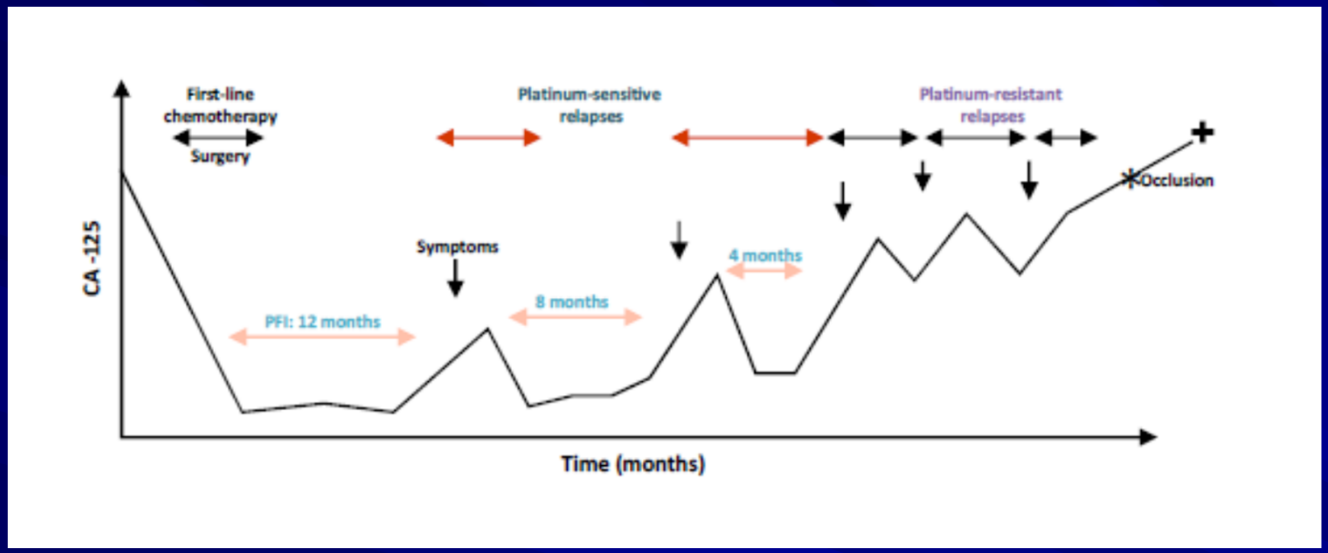


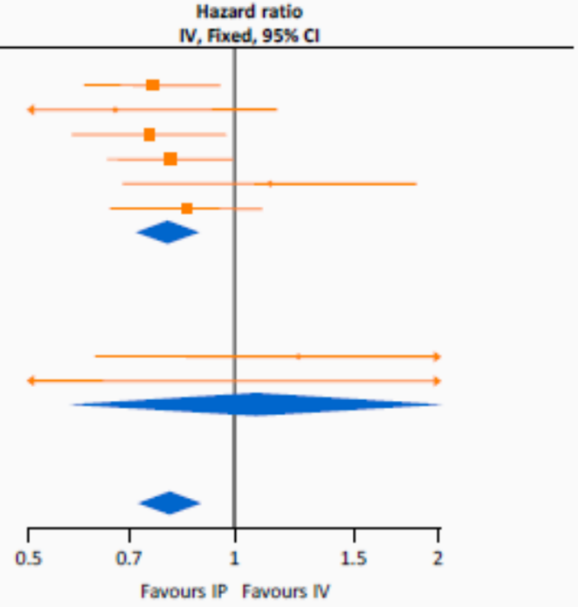
Fig 1. (A) Stage IIIC disease. (B) Stage IV disease. Use of neoadjuvant chemotherapy (NACT) increased significantly over time ($P_{trend} < .001$ for both groups). Intraperitoneal and intravenous (IP/IV) chemotherapy is shown for comparison. Three patients with stage IIIC disease and one with stage IV who were diagnosed in 2003 are included in the estimate for 2004. Twenty-three patients with stage IIIC disease and seven with stage IV who were diagnosed in 2012 are included in the estimate for 2011. PCS, primary cytoreductive surgery.



STANDARD OF CARE THERAPY

Chemotherapy choices: intraperitoneal therapy improves OS, but toxicity is increased

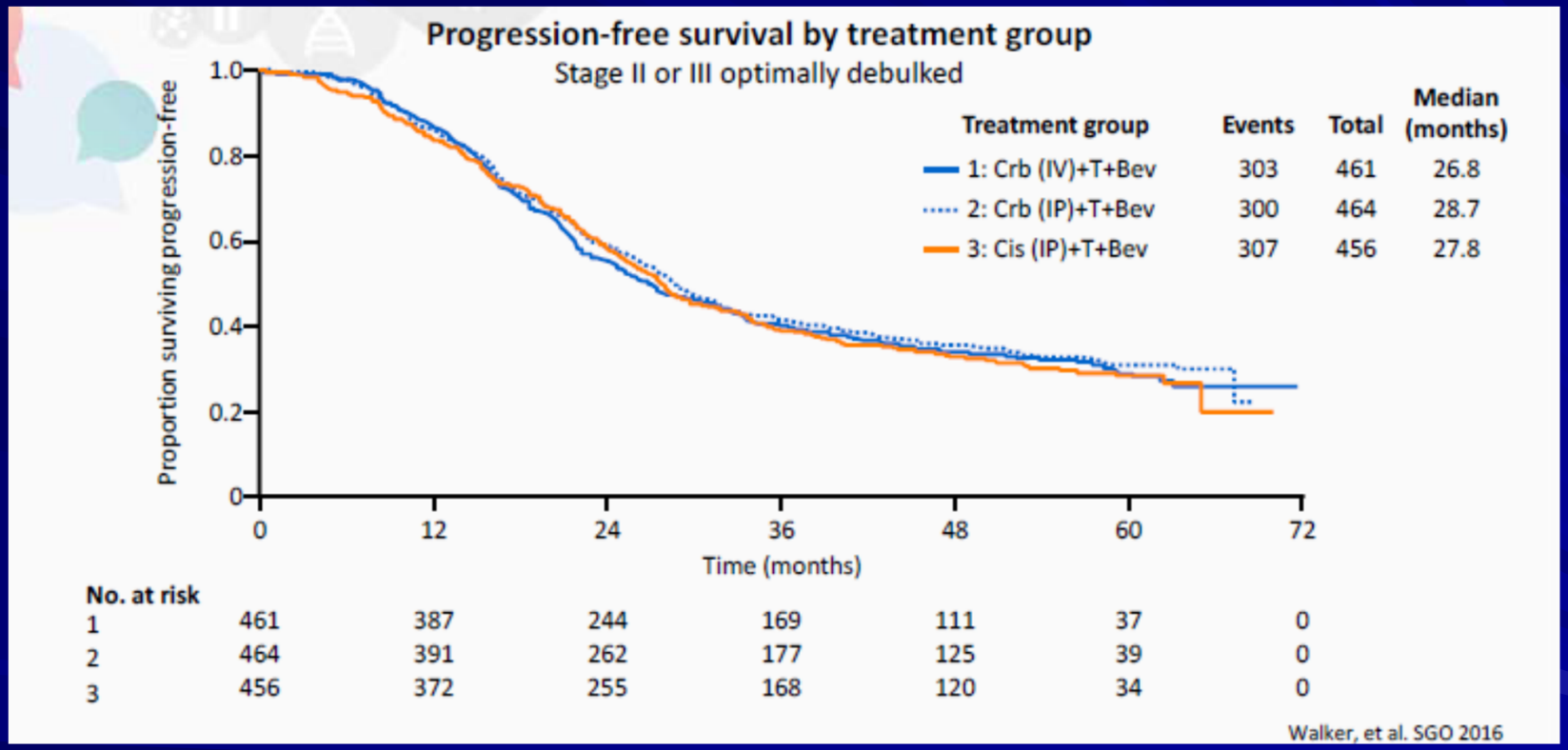
Study or Subgroup	log [Hazard ratio]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
1.1.1 High quality trials				
Alberts 1996	-0.2744	0.1157	23.9%	0.76 [0.61, 0.95]
Gadducci 2000	-0.4025	0.2776	4.2%	0.67 [0.39, 1.15]
GOG 172	-0.2877	0.1312	18.6%	0.75 [0.58, 0.97]
Markman 2001	-0.2107	0.1099	26.5%	0.81 [0.65, 1.00]
Yen 2001	0.1222	0.253	5.0%	1.13 [0.69, 1.86]
Yen 2009	-0.163	0.13	18.9%	0.85 [0.66, 1.10]
Subtotal (95% CI)			**97.1%**	**0.80 [0.72, 0.90]**
Heterogeneity: $Chi^2 = 2.95$, df = 5 (p = 0.71); $I^2 = 0\%$				
Test for overall effect: Z = 3.88 (p = 0.0001)				
1.1.2 Low quality trials				
Kirmani 1994	0.2175	0.3508	2.6%	1.24 [0.62, 2.47]
Zylberberg 1986	-1.227	1.1249	0.3%	0.29 [0.03, 2.66]
Subtotal (95% CI)			**2.9%**	**1.09 [0.57, 2.11]**
Heterogeneity: $Chi^2 = 1.50$, df = 1 (p = 0.22); $I^2 = 33\%$				
Test for overall effect: Z = 0.27 (p = 0.79)				
Total (95% CI)			**100.0%**	**0.81 [0.72, 0.90]**
Heterogeneity: $Chi^2 = 5.29$, df = 7 (p = 0.62); $I^2 = 0\%$				
Test for overall effect: Z = 3.78 (p = 0.0002)				
Test for subgroup differences: $Chi^2 = 0.85$, df = 1 (p = 0.36), $I^2 = 0\%$				



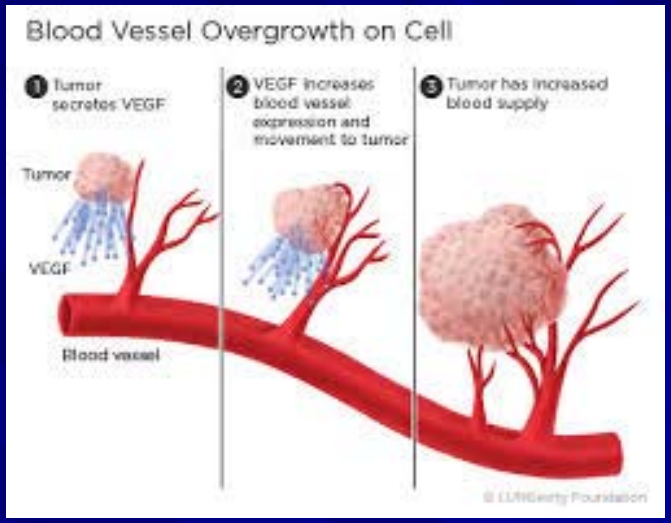
- However, use is limited by delivery issues and toxicity
- In GOG-0172, only 42% of patients received all 6 cycles of intraperitoneal chemotherapy[2]

1. Jaaback, et al. Cochrane Database System Rev 2016; 2. Armstrong, et al. N Engl J Med 2006

GOG 252: PFS optimal stages II & III



ANGIOGENESIS



Maintenance therapy results from past/old frontline studies: positive,modest (218, ICON7, Pazopanib)

Anti-vascular therapy as maintenance in Front Line EOC Therapy

	GOG 218 First Line with Maintenance[1]	ICON 7 First Line with Maintenance[2]	Pazopanib Maintenance[3]
Primary Endpoint	PFS (RECIST/CA 125/ clinical)	PFS (RECIST)	PFS (RECIST)
Secondary Endpoint	OS	OS, RR	OS, Safety, PFS by GCIG, 3 yr PFS, QOL
Maintenance duration	15 months maximum	12 months maximum	24 months maximum
Stopping rules	GCIG (CA125)	RECIST PD	RECIST PD
Results (PFS in Δ months)	6 months (censored for CA125 only events)	5.4 months (high risk subgroup)	5.6 months
Results (OS)	NS	NS (all stages)	NS (immature)

1 = Burger et al. NEJM 356: 2011, 2 = Perren et al. NEJM 365: 2011, Dubois et al. LBA 5503

Presented By Paul Sabbatini, MD at 2013 ASCO Annual Meeting

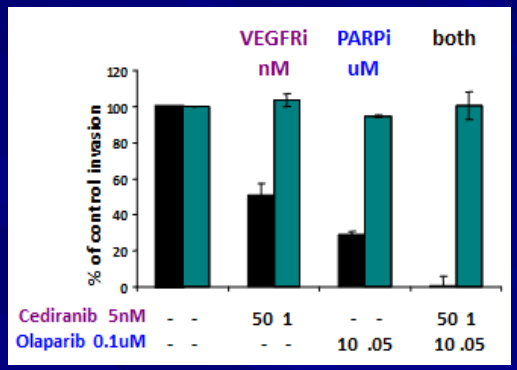
Cediranib

- Angiogenesis Inhibitor
  - a potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases and has some c-Kit and PDGF activity
- Oral
- Similar Side Effects of Olaparib
  - Fatigue, nausea, diarrhea, hypertension

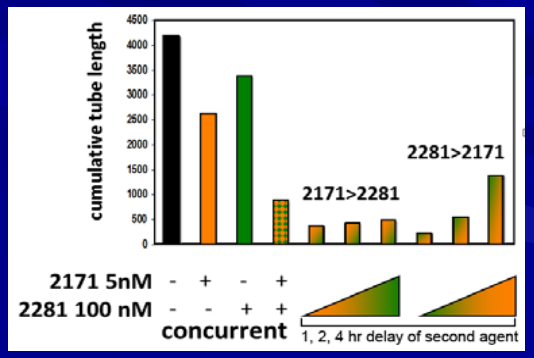
Rationale for combination of olaparib and cediranib

- PARP-inhibitors and anti-angiogenics with known activity in ovarian cancer
- Pre-clinical data suggesting potential synergy between PARPi and anti-angiogenics
- Pre-clinical data demonstrating *in vitro* synergy between cediranib and olaparib

Effect of ced/olap on cell invasion:



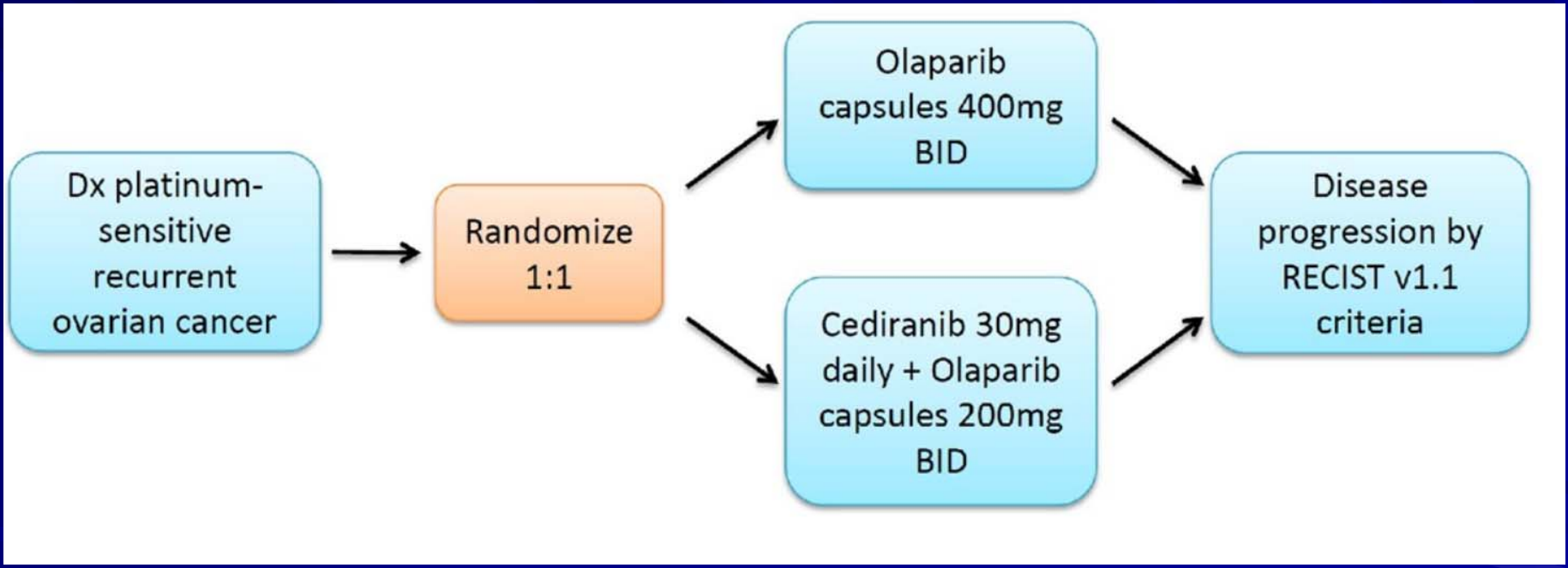
Effect of ced/olap on microvascular cell tube organization:



[1]Tentori et al., *Eur J Cancer* 2007, 43(14): 2124-33
[2]Hegan et al., *PNAS* 2010, 107(5): 2201-6

Data courtesy Elise Kohn, NCI/CTEP

Overall Survival and Updated PFS results from a randomized phase 2 trial comparing the combination of olaparib and cediranib against olaparib alone in recurrent platinum sensitive ovarian cancer
Liu et al. Abst 5535



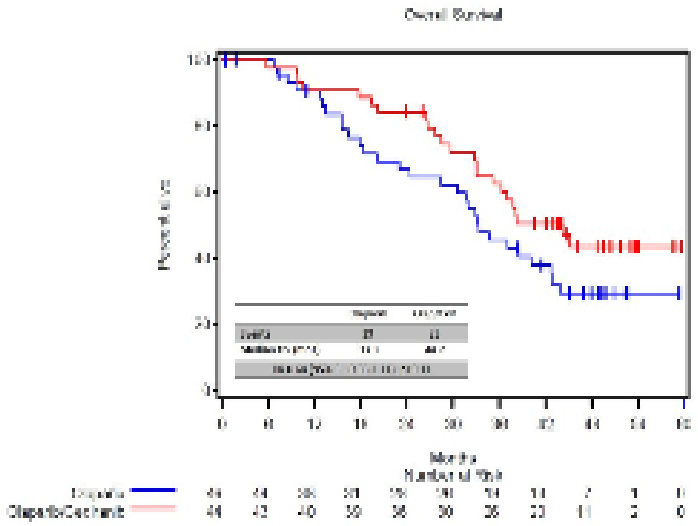
Phase 2 trial comparing the combination of olaparib and cediranib against olaparib alone in recurrent platinum sensitive ovarian cancer

Patient Characteristics:

	Olaparib (N=46)	Cediranib/olaparib (N=44)	p-value
Age, median (range)	58.1 (32.7-81.9)	57.8 (41.9-85.6)	0.33
ECOG performance status			0.82
0	34 (73.9%)	31 (70.5%)	
1	12 (26.1%)	13 (29.5%)	
BRCA mutation status			0.92
Mutation carrier	24 (52.2%)	23 (52.3%)	
Non-carrier	11 (23.9%)	12 (27.3%)	
Unknown	11 (23.9%)	9 (20.5%)	
Prior anti-angiogenic therapy			1.00
No	40 (87.0%)	38 (86.4%)	
Yes	6 (13.0%)	6 (13.6%)	
Prior platinum-free interval			0.83
6-12 months	26 (56.5%)	23 (52.3%)	
>12 months	20 (43.5%)	21 (47.7%)	
Number of prior lines			0.11
1	17 (37.0%)	26 (59.1%)	
2	18 (39.1%)	10 (22.7%)	
3+	11 (23.9%)	8 (18.2%)	

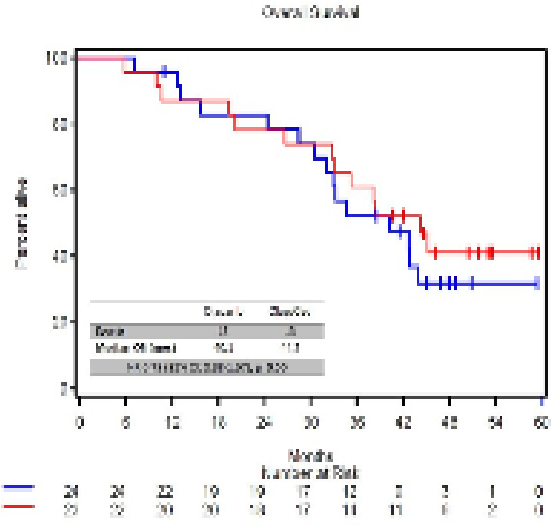
Phase 2 trial comparing the combination of olaparib and cediranib against olaparib alone in recurrent platinum sensitive ovarian cancer

All patients (n=90)



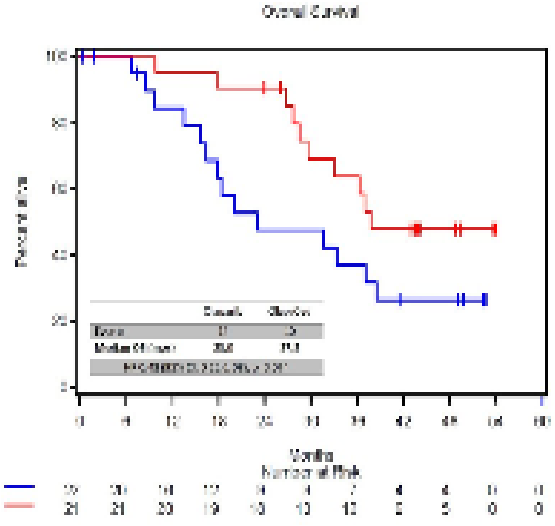
Median OS 33.3 vs. 44.2
HR 0.64
(95% CI 0.36-1.11; p=0.11)

*g*BRCA mutation carrier (n=47)

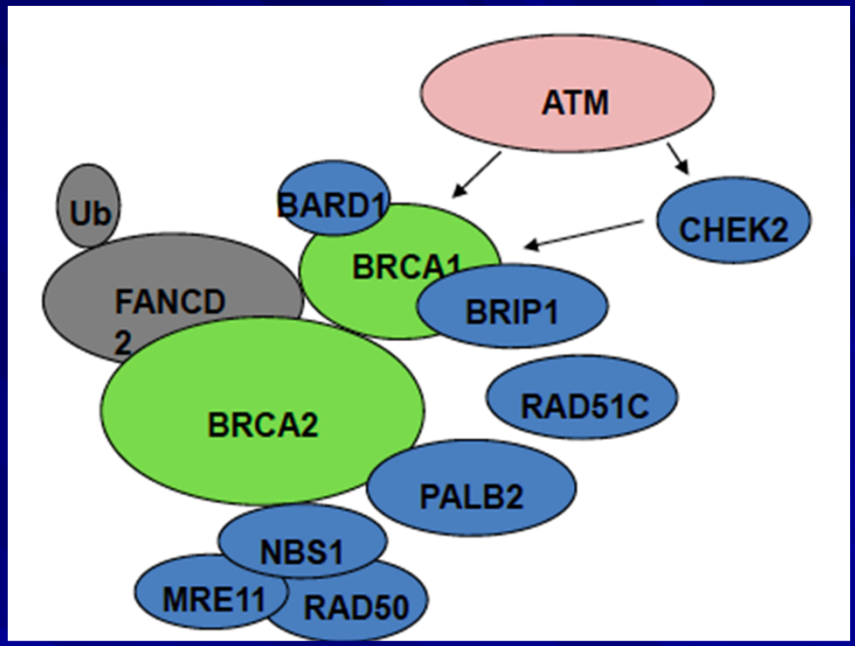


Median OS 40.1 vs. 44.2
HR 0.79
(95% CI 0.38-1.67; p=0.55)

*g*BRCA non-carrier/status unknown (n=43)



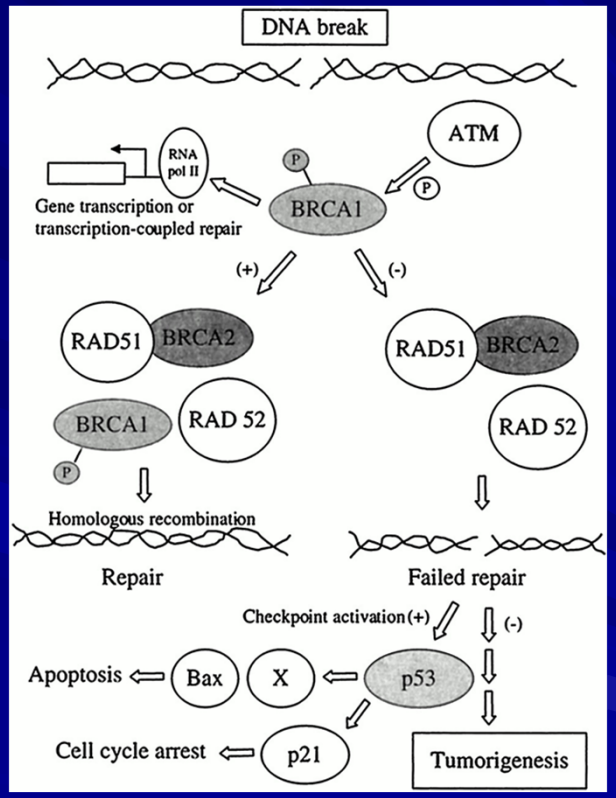
Median OS 23.0 vs. 37.8
HR 0.48
(95% CI 0.21-1.08; p=0.074)



PARP INHIBITORS

BRCA 1 and BRCA 2 Pathway

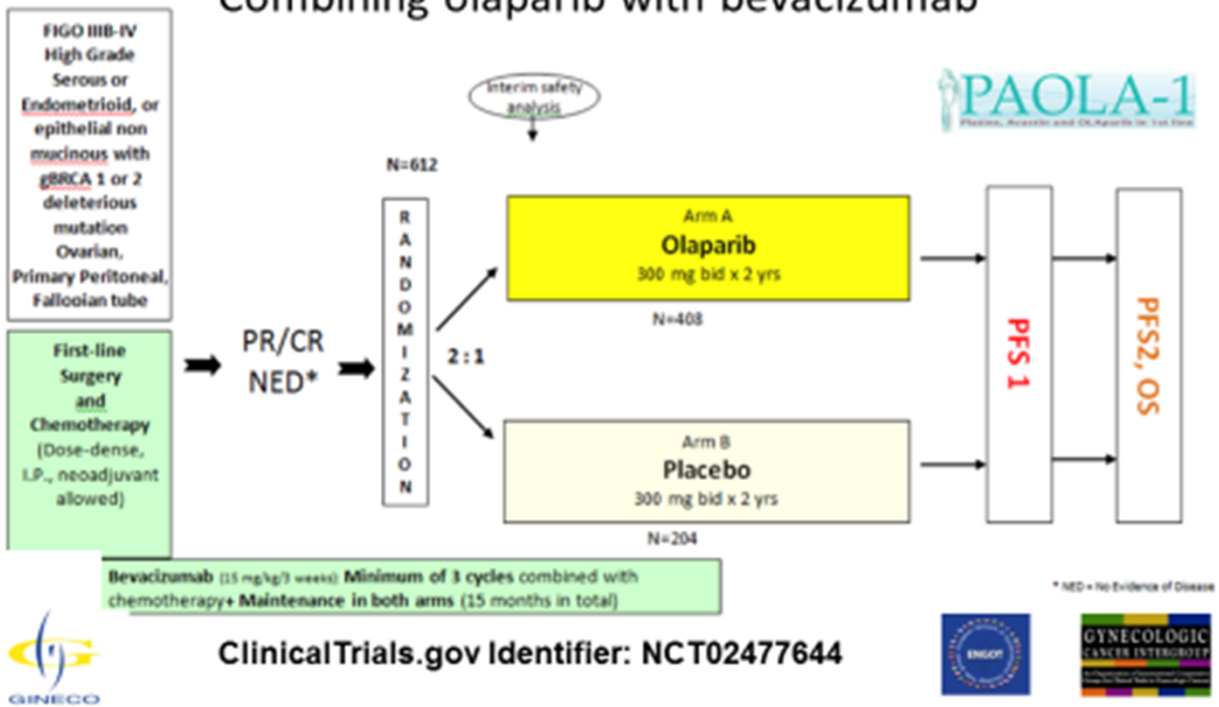
- Homologous recombination pathway:
- repair of double-stranded DNA
- tumors with *BRCA* mutations cannot repair DNA as well; tend to be more responsive to chemo, ionizing radiation, and PARP inhibitors



Combining PARP inhibitors with anti-angiogenic therapy

Platine, Avastin and OLAparib in 1st Line (PAOLA-1)

Combining olaparib with bevacizumab

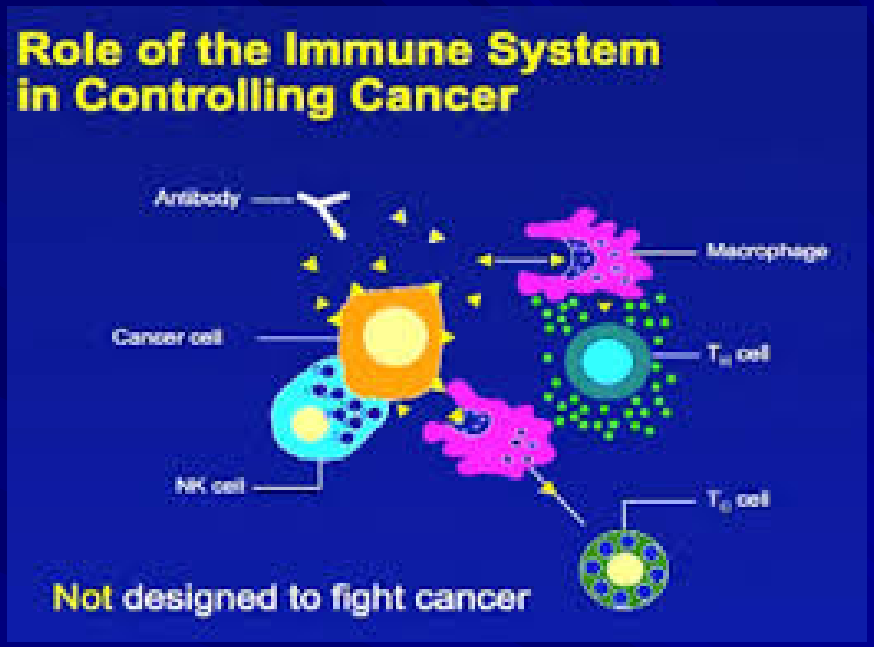


ClinicalTrials.gov Identifier: NCT02477644

PARP Inhibitor Summary: Indications and Efficacy

	Olaparib	Rucaparib	Niraparib
Current Label	**Monotherapy for g*BRCA*+ patients with 3+ prior lines of therapy (4L induction)**	**Monotherapy for somatic or g*BRCA*+ patients with ≥2 prior regimens (3L induction)**	**Maintenance for recurrent OC in response to treatment (2L+ PS maintenance)**
Trial Name	SOLO-2 (phase III)	ARIEL3 (phase III)	NOVA (phase III)
Study Design, Population	Maintenance olaparib vs placebo, PSOC with 2+ prior lines and in response *BRCA*+ (all had germline, some also somatic)	Maintenance rucaparib vs placebo, PSOC 2+ prior regimens, PSOC, unrestricted measurable disease, *BRCA*+ (germline 58.2%, somatic 17.2%, unknown origin 24.6%)	Maintenance niraparib vs placebo, ≥2 prior regimens, in response, *BRCA*+ (germline 36.7%, somatic 8.5%) or *BRCA* WT
Median PFS, mos	*BRCA*+: 19.1 vs 5.5, HR=0.3	BRCA+: 16.6 vs 5.4, HR=.23 HRD +:13.6 vs 5.4, HR .32 ITT: 10.8 vs. 5.4, HR .36	g*BRCA*+: 21.0 vs 5.5 HR=0.27 Non-g*BRCA*: 9.3 vs 3.9, HR=0.45

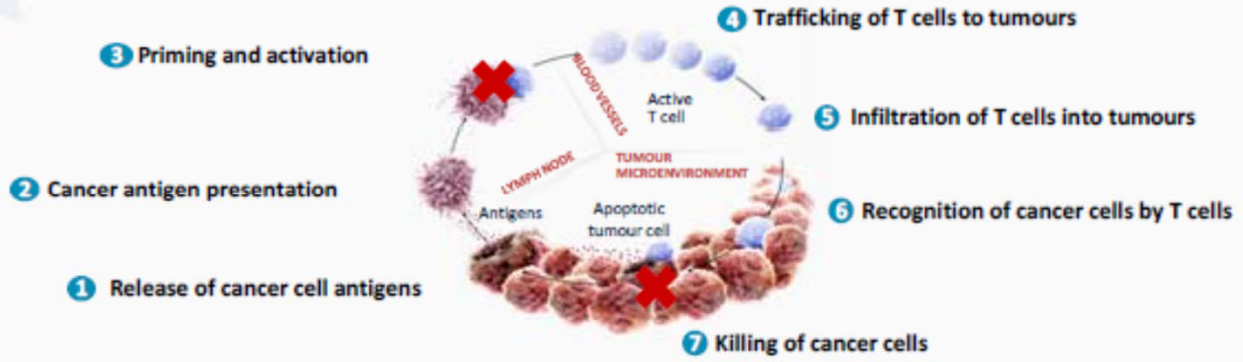
Mahner S, et al. Presented at: SGO. 2017. Pujade-Lauraine E, et al. Presented at: SGO. 2017 (abstr LBA2). Konecny GE, et al. Presented at: SGO. 2017 (abstr 1)., Lederman J, et al. Presented at ESMO 2017



IMMUNOTHERAPY

The immune system can recognize tumors and mount an active immune response

The cancer-immunity cycle describes the process by which the immune system recognises, targets and kills cancer cells

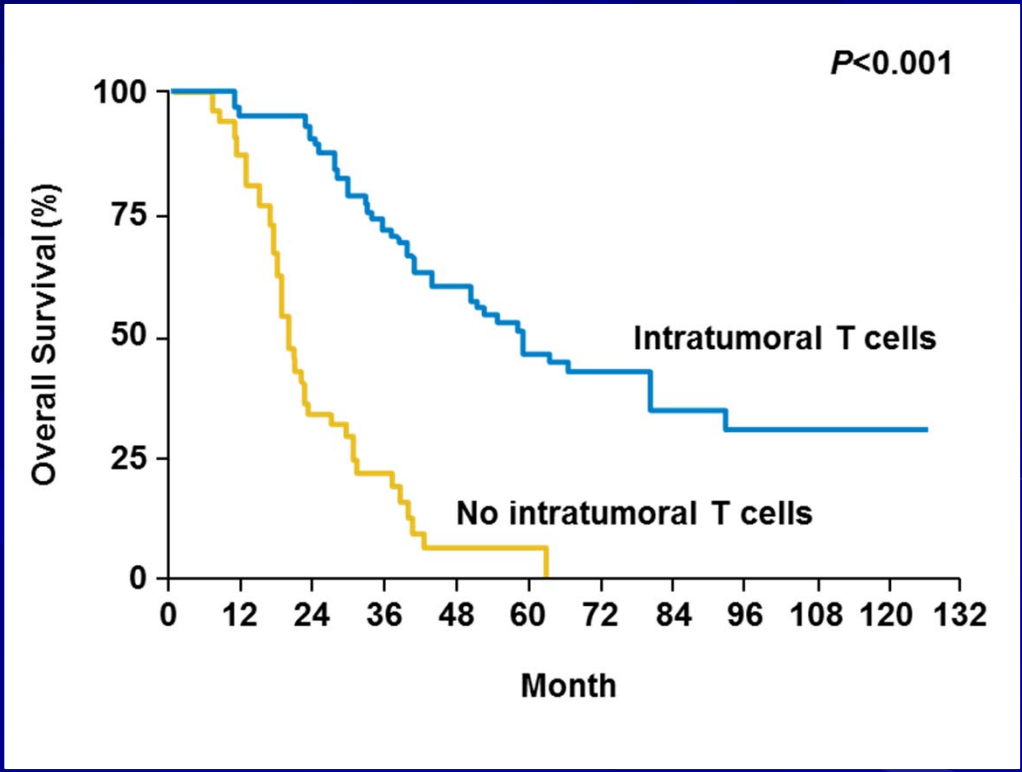


Tumours can inhibit the anti-tumour immune response by disrupting the balance of the cancer-immunity cycle via immune checkpoints[1,2]

1. Hanahan & Weinberg. Cell 2011; 2. Chen & Mellman. Immunity 2013

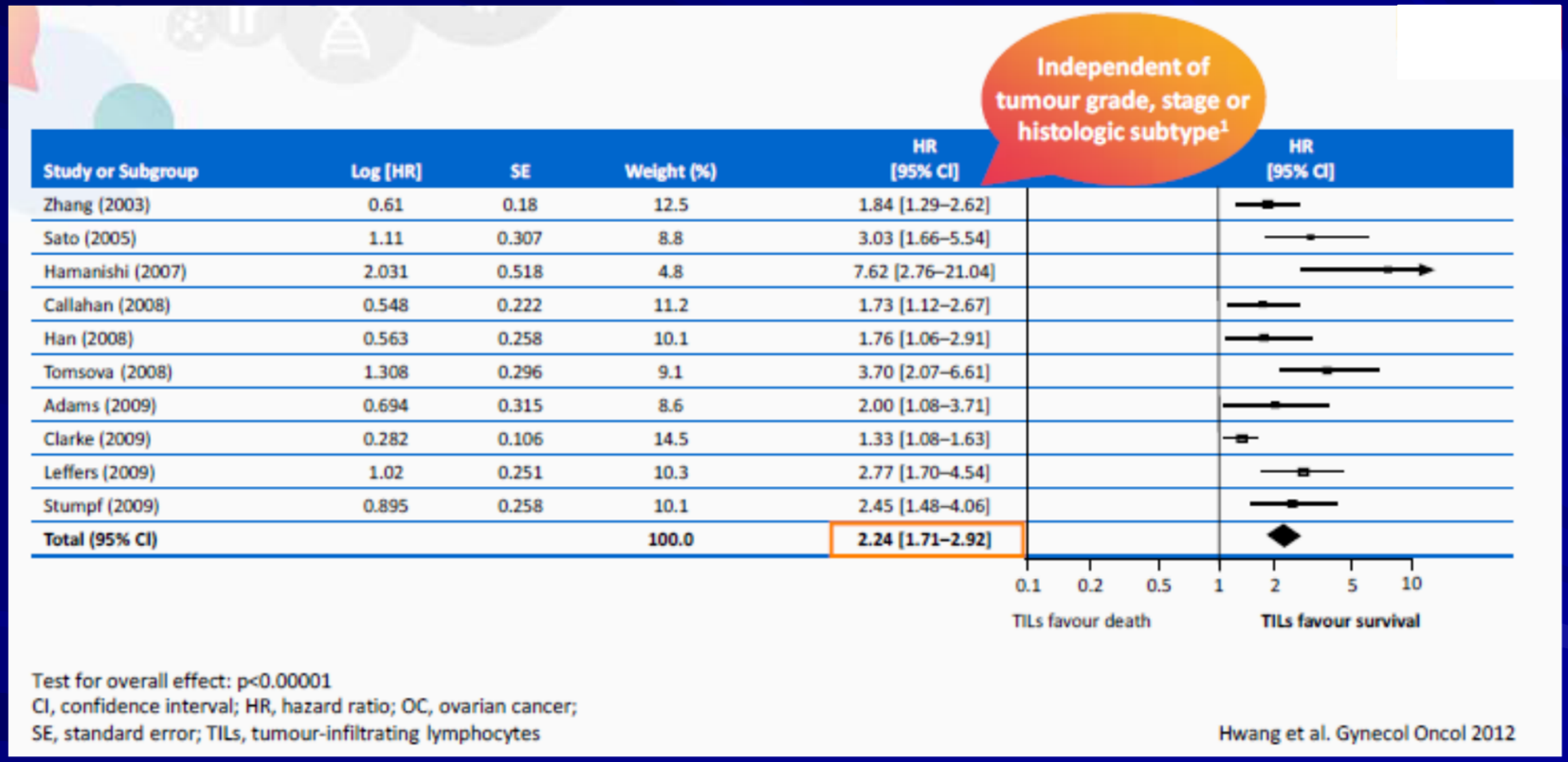
Role of Immune Cells in Ovarian Cancer

- OC is an immunogenic tumour[1-4]
  - Strong immunosuppressive environment present in OC
  - Spontaneous antitumor immune response can be detected in the form of tumor-reactive T cells and antibodies
- Analyses of OC patient samples showed presence of intratumoral T cells was associated with better clinical outcome[4]



1. Turner TB et al. *Gynecol Oncol*. 2016;142:349-356. 2. Coukos G et al. *Ann Oncol*. 2016;27(suppl 1):i11-i15. 3. Mandai M et al. *Int J Clin Oncol.* 2016;21:456-461. 4. Zhang L et al. *N Engl J Med.* 2003;348:203–213.

The correlation between TILS and survival is supported by multiple studies



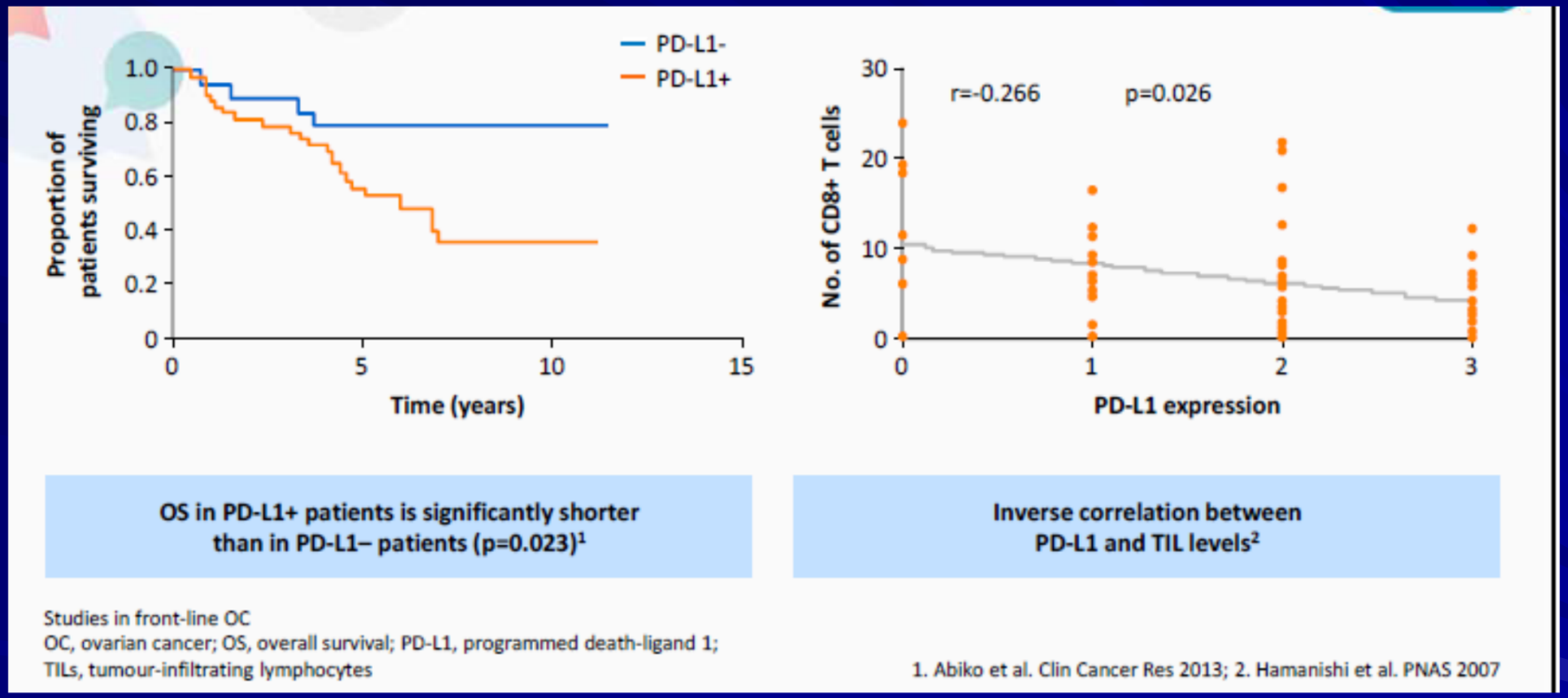
Study or Subgroup	Log [HR]	SE	Weight (%)	HR [95% CI]
Zhang (2003)	0.61	0.18	12.5	1.84 [1.29–2.62]
Sato (2005)	1.11	0.307	8.8	3.03 [1.66–5.54]
Hamanishi (2007)	2.031	0.518	4.8	7.62 [2.76–21.04]
Callahan (2008)	0.548	0.222	11.2	1.73 [1.12–2.67]
Han (2008)	0.563	0.258	10.1	1.76 [1.06–2.91]
Tomsova (2008)	1.308	0.296	9.1	3.70 [2.07–6.61]
Adams (2009)	0.694	0.315	8.6	2.00 [1.08–3.71]
Clarke (2009)	0.282	0.106	14.5	1.33 [1.08–1.63]
Leffers (2009)	1.02	0.251	10.3	2.77 [1.70–4.54]
Stumpf (2009)	0.895	0.258	10.1	2.45 [1.48–4.06]
Total (95% CI)			**100.0**	**2.24 [1.71–2.92]**

Test for overall effect: p<0.00001

CI, confidence interval; HR, hazard ratio; OC, ovarian cancer; SE, standard error; TILs, tumour-infiltrating lymphocytes

Hwang et al. Gynecol Oncol 2012

PD-L1 expression may represent a tumor resistance mechanism to TILS in OC



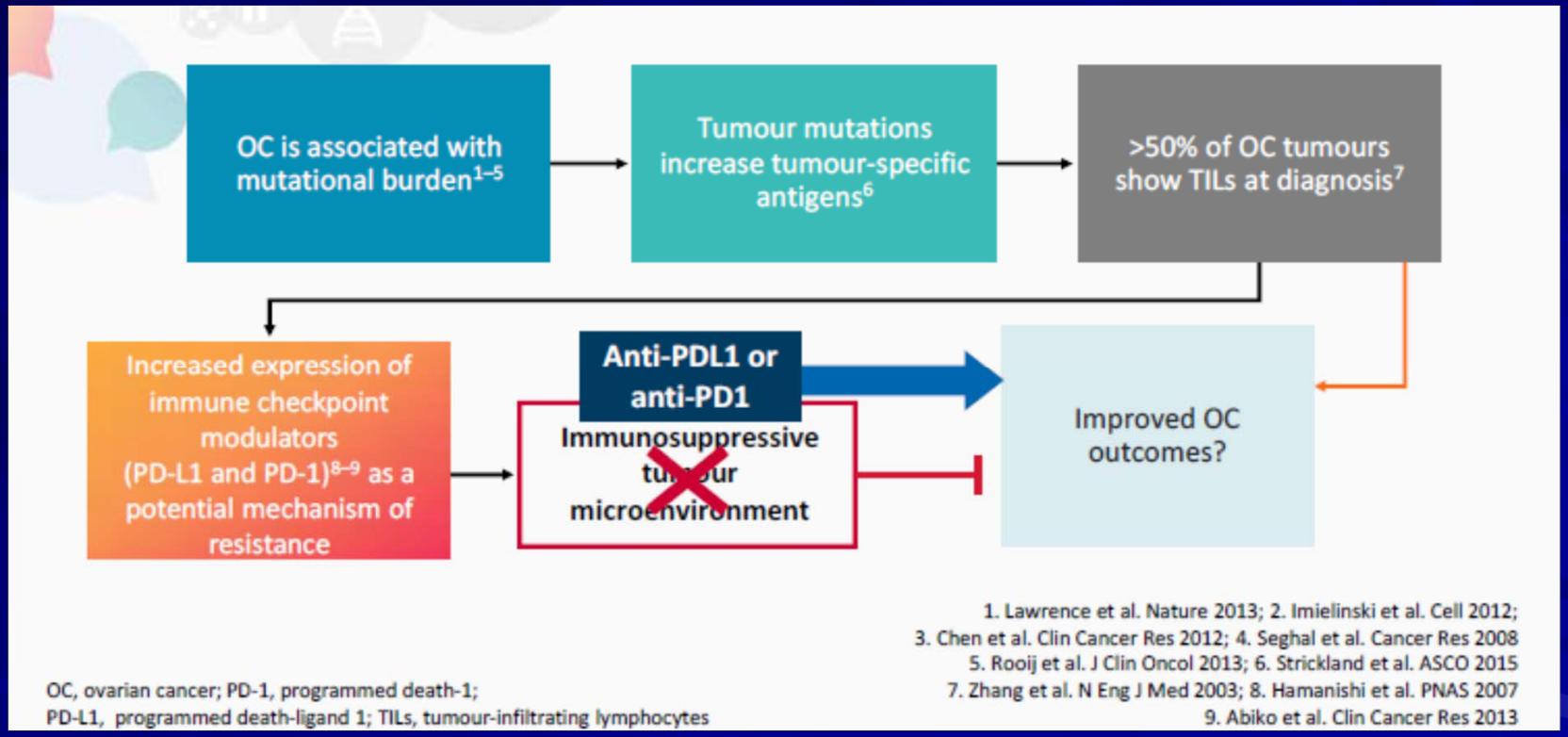
OS in PD-L1+ patients is significantly shorter than in PD-L1– patients (p=0.023)[1]

Inverse correlation between PD-L1 and TIL levels[2]

Studies in front-line OC
OC, ovarian cancer; OS, overall survival; PD-L1, programmed death-ligand 1; TILs, tumour-infiltrating lymphocytes

1. Abiko et al. Clin Cancer Res 2013; 2. Hamanishi et al. PNAS 2007

Rationale for targeting PD-L1 in OC



OC, ovarian cancer; PD-1, programmed death-1;
PD-L1, programmed death-ligand 1; TILs, tumour-infiltrating lymphocytes

1. Lawrence et al. Nature 2013; 2. Imielinski et al. Cell 2012;
3. Chen et al. Clin Cancer Res 2012; 4. Seghal et al. Cancer Res 2008
5. Rooij et al. J Clin Oncol 2013; 6. Strickland et al. ASCO 2015
7. Zhang et al. N Eng J Med 2003; 8. Hamanishi et al. PNAS 2007
9. Abiko et al. Clin Cancer Res 2013

Anti-PDL1/PD1 single agent therapy data in OC

Therapeutic agent	Phase and trial name	N	Setting	ORR, n/N (%)
Atezolizumab	Ia (PCD4989g)[1]	12	PR ROC	2/8 (25)[a,b]
Avelumab	Ib (JAVELIN solid tumour)[2]	75	ROC	8/75 (11)
Nivolumab	II (UMIN000005714)[3]	20	PR ROC	3/20 (15)
Pembrolizumab	Ib (KEYNOTE-028)[4]	26	ROC	3/26 (12)

a Efficacy-evaluable population included only patients who received ≥ 1 mg/kg (2 patients excluded; n = 10).
b An additional patient without measurable disease at baseline was excluded (n = 9).

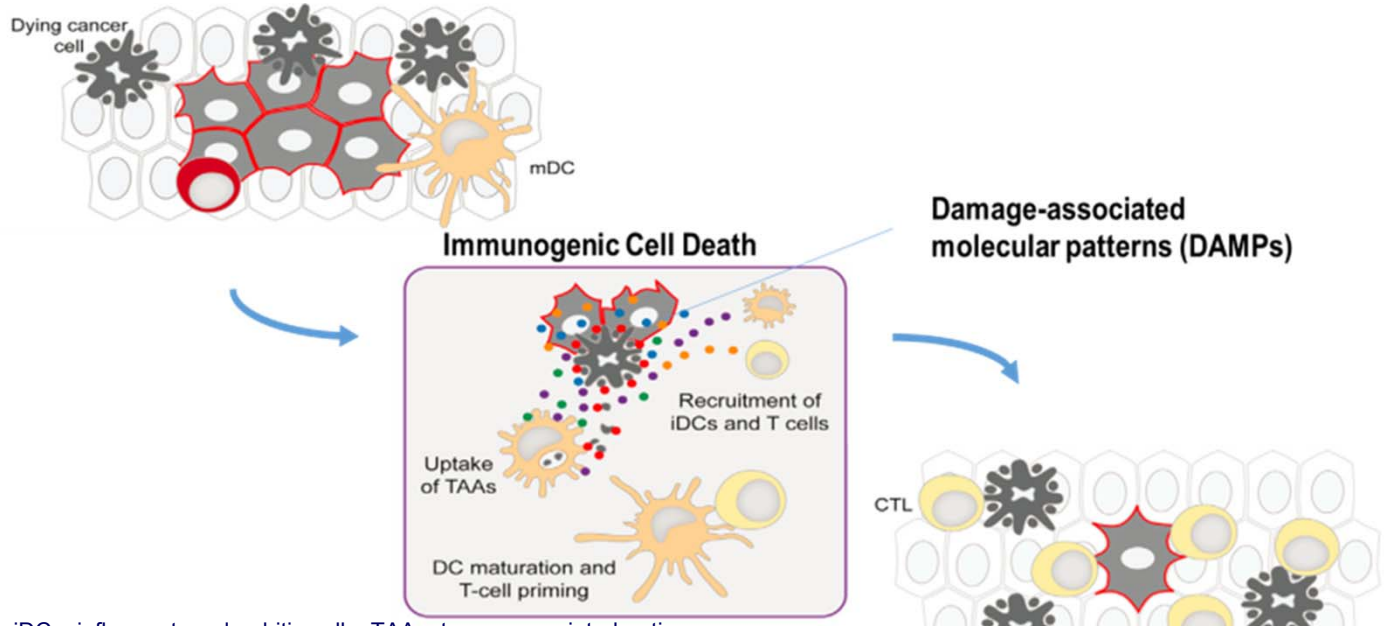
PD-L1/PD-1 inhibitors demonstrate encouraging but modest activity in ROC, suggesting an opportunity for combinations

1. Infante et al. ESMO 2016 (abs 871P); 2. Disis et al. J Clin Oncol 2015 (abs 5509)
3. Hamanishi et al. J Clin Oncol 2015 (abs 5570); 4. Varga et al. J Clin Oncol 2015 (abs 5510)

Immunogenicity of Chemotherapy

Chemotherapy has been shown to

- Enhance antigen presentation
- Enhance immunogenicity (release of adjuvants by cells)
- Increase susceptibility to immune attack



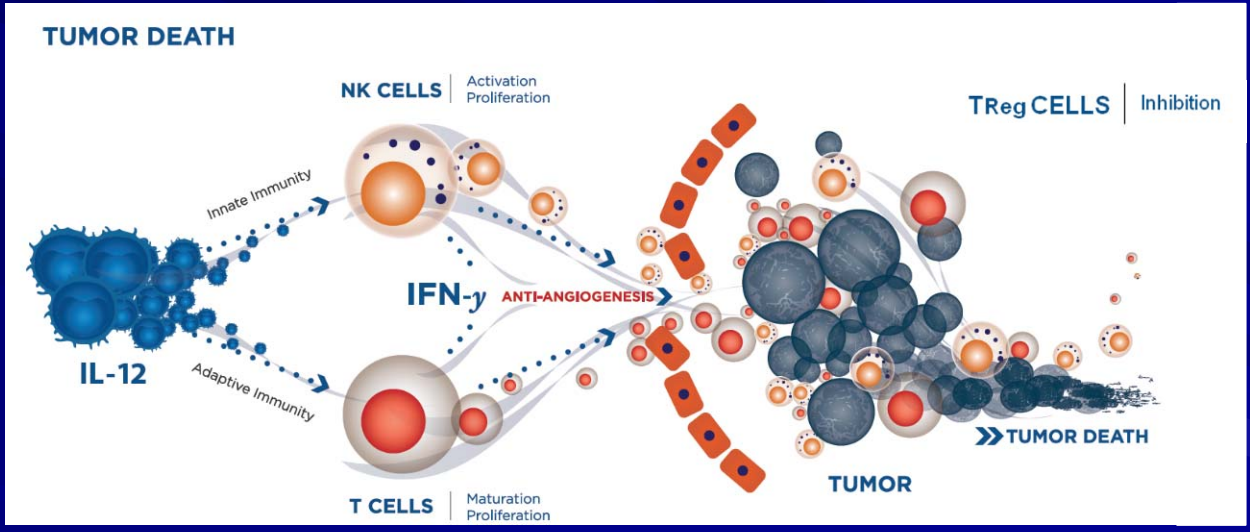
CTL, cytotoxic T lymphocytes; iDCs, inflammatory dendritic cells; TAAs, tumor-associated antigens.

Zitvogel L et al. *Immunity*. 2013;39:74-88.

IL-12: A Powerful Immune Modulating Agent with Multiple Mechanisms of Action

Mechanisms of Action

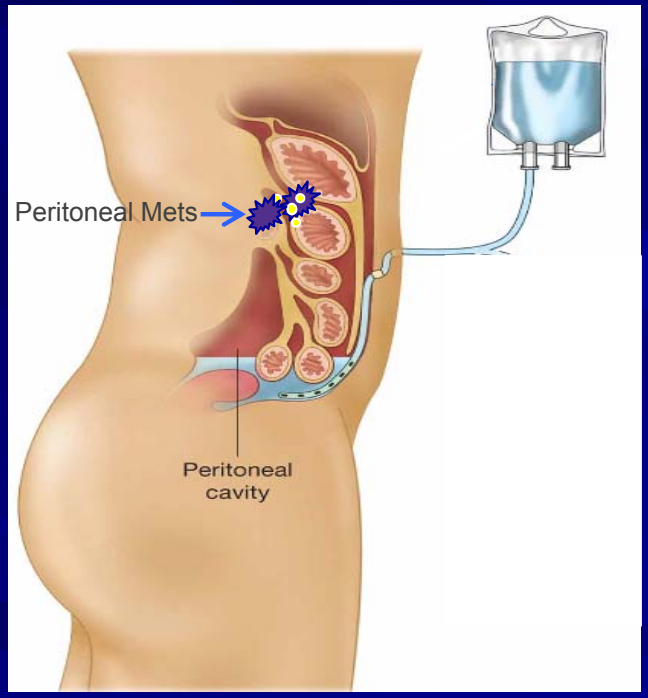
1. NK cell Activation
2. T cells Activation
3. Anti-angiogenesis
4. Treg suppression



Modulation of Immune Response by Local Production of a Powerful Immune Modulating Agent, IL-12

Persistent Delivery of IL-12 with a Single Administration of Formulated IL-12 Plasmid

(Distinct from IV Chemotherapy)



EGEN-001

Stable Nanoparticles for Local Delivery

- GEN-1causes the production of IL-12 at cancer site for several days
- IL-12 addresses cancer by recruiting the immune system, inducing powerful anti-cancer mechanisms

GEN-1 Prior Clinical Studies

Study	N	Platinum Sensitivity	IP Dose (mg/m2)	Dosing Schedule
EGEN-001-101	13	Resistant	.6, 3.0, 12, 24	Weekly x4
EGEN-001-201	13	Sensitive	12, 18, 24	Weekly x8
GOG-170Q	20	Resistant	24	Weekly until toxicity/progression
GOG-9928	16	Resistant	24, 36	Weekly until toxicity/progression
201-14-101	18	First Line (Neoadjuvant)	36, 47, 61, 79	Weekly x8
Total Subjects	80			

Phase I Trial of GEN-1 + Neoadjuvant Chemo in Newly Diagnosed Ovarian Cancer Patients (The "OVATION" Trial)

PT

Primary Objective: Safety, tolerability, MTD

Secondary Objective: Objective Tumor Response Rate, pCR, PFS, OS

Translational Research

Newly Diagnosed Ovarian Cancer				
Cohort	Number of Subjects	GEN-1 (mg/m^2)	Carboplatin (AUC)	Paclitaxel (mg/m^2)
1	3-6	36	6	80
2	3-6	47	6	80
3	3-6	61	6	80
4	3-6	79	6	80

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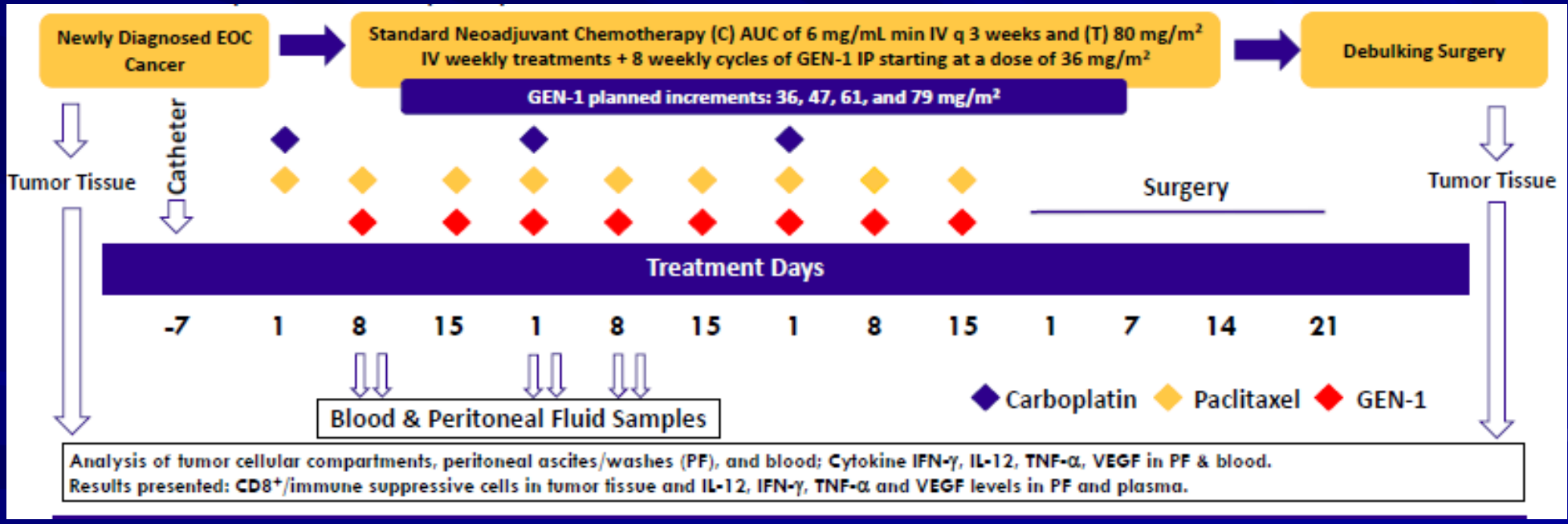
Washington University in St. Louis SCHOOL OF MEDICINE

OVATION (Protocol 201-14-101) Phase 1
Study Design and Methods

- Standard 3+3 design with approximate 30% dose increments between successive cohorts of patients. Dose levels of GEN-1 in conjunction with standard carboplatin (C) and paclitaxel (T)
- Tolerated dose is confirmed when 3-6 patients are treated at a dose level and <2 patients experience dose-limiting toxicities (DLTs)



OVATION (Protocol 201-14-101)
Study Population

- Patients newly diagnosed with EOC were eligible; patients who received prior radiotherapy or chemotherapy to any portion of the abdominal cavity and/or pelvis were excluded.
- Candidates for neoadjuvant chemotherapy
- A majority of the patients were Stage IIIC (10, 63%), followed by Stage IV (5, 31%) and one patient was Stage IIIB (1, 6%).
- All but one patient had high grade serous adenocarcinoma (15, 94%); the exception being clear cell adenocarcinoma (1, 6%).
- The median baseline CA-125 reported was 683 (78 – 4348) across all 4 cohorts.

OVATION (Protocol 201-14-101)
Safety Results

- The safety evaluation period is based on the first 4 doses of GEN-1 administered to each patient. The DSMB has reviewed data from the first 4 cohorts of patients. To date, 15 patients have been evaluated for safety and no DLTs have been identified.
- Most common adverse events reported, regardless of causality, in descending order are nausea, constipation, fatigue, abdominal pain and cramping, neutropenia, anemia, anorexia, and vomiting.
- Most common toxicities reported, which can be attributed to GEN-1, in descending order include nausea, abdominal pain and cramping, fatigue, vomiting, neutropenia and diarrhea.
- A total of 5 patients discontinued GEN-1 treatments due to adverse events. Only one was GEN-1 related (altered taste).

OVATION (Protocol 201-14-101)
Safety Results – Grade 3 and 4 events

- Of the 15 patients evaluated for safety, the following Grade 3 and 4 events which can be attributed to GEN-1, in descending order include:
  - Neutropenia (5)
  - Leukopenia (2)
  - Diarrhea (2)
  - Vomiting (2)
  - Anemia (1)
  - Abdominal Pain / Cramping (1)
  - Hypokalemia (1)
  - Hyponatremia (1)
  - Vasovagal Reaction (1)

Clinical Results

RECIST Response	**Cohort 1 (n=3)**	**Cohort 2 (n=3)**	**Cohort 3 (n=3)**	**Cohort 4 (n=5)**	**Total (n=14)**
Complete Response	1, 33.3%	0, 0%	0, 0%	1, 20%	2, 14%
Partial Response	0, 0%	3, 100%	3, 100%	4, 80%	10, 72%
Stable Disease	2, 66.6%	0, 0%	0, 0%	0, 0%	2, 14%
Interval Debulking Status	**Cohort 1 (n=3)**	**Cohort 2 (n=3)**	**Cohort 3 (n=3)**	**Cohort 4 (n=5)**	**Total (n=14)**
R0	2, 66.6%	0, 0%	2, 66.6%	5, 100%	9, 64.3%
R1	1, 33.3%	2, 66.6%	0, 0%	0, 0%	3, 21.4%
R2	0, 0%	1, 33.3%	1, 33.3%	0, 0%	2, 14.3%
Pathological Response	**Cohort 1 (n=3)**	**Cohort 2 (n=3)**	**Cohort 3 (n=3)**	**Cohort 4 (n=5)**	**Total (n=14)**
cPR	1, 33.3%	0, 0%	0, 0%	0, 0%	1, 7%
micoPR	1, 33.3%	2, 66.6%	1, 33.3%	3, 60%	7, 50%
macroPR	1, 33.3%	1, 33.3%	2, 66.6%	2, 40%	6, 43%

Thaker et al. ASCO 2017

OVATION

Summary of Progression Data: As Treated

- **Current PFS Median – 21.0 months, 95%CI (9.2-24.5)**
  - *Assumes all ongoing patients censored February 21, 2018*
  - *Only patients treated according to protocol requirements*

Cohort	Pt ID	1st chemo	Date of progression or f/u	Time from chemo (d)	Time from chemo (m)
1	*OV01-06(17)*	*2/15/2017*	*1/19/2018*	*338*	*11.27*
1	*OV01-01(01)*	*10/5/2015*	*9/19/2016*	*350*	*11.67*
3	*OV04-04(10)*	*6/21/2016*	*8/16/2017*	*421*	*14.03*
4	OV04-07(16)	12/14/2016	2/20/2018	433	14.43
4	OV03-02(14)	10/10/2016	2/20/2018	498	16.60
4	OV04-06(15)	10/4/2016	2/20/2018	504	16.80
4	OV04-05(13)	9/28/2016	2/20/2018	510	17.00
3	OV02-02(12)	8/9/2016	2/20/2018	560	18.67
3	OV01-05(11)	7/6/2016	2/20/2018	594	19.80
1	*OV01-04(05)*	*2/8/2016*	*11/7/2017*	*638*	*21.27*
2	OV03-01(09)	4/13/2016	2/20/2018	678	22.60
2	OV04-02(07)	3/30/2016	2/20/2018	692	23.07
1	*OV01-02(02)*	*10/6/2015*	*10/19/2017*	*744*	*24.80*

Grey Row = Progression
Green Row= Median

Phase III NACT Trials

Table 1. Phase III RCTs of Neoadjuvant Chemotherapy in Stage III or IV Epithelial Ovarian Cancer

Author, Year, and Study	Enrollment Criteria	Primary End Point	Study Arm	No. of Patients	Age (years)	Stage IV	Operative Time (min)	No Residual Disease	Grade 3 to 4 Postoperative Complications	PFS (months)	OS (months)
Fagotti et al, 2016[34] SCORPION	Pathologically proven ovarian cancer, stage IIIC-IV. Intraoperative high tumor load (Fagotti's score of 8 to 12) assessed by staging laparoscopy.	Surgical complications	NACT PCS	55 55	55 54	7% 15%	275 451 $P = 0.0001$	58% 46% $P = 0.16$	6% 53%* $P = 0.0001$	Not yet reported	Not yet reported
Kehoe et al, 2015[2] CHORUS	Stages III or IV ovarian cancer based upon imaging or clinical evidence of pelvic mass with extrapelvic disease; CA-125 to CEA ratio > 25; if less, had to exclude gastrointestinal carcinoma.	OS	NACT PCS	274 276	65 66	25% 25%	120 120	39% 17% $P = 0.0001$	14% 24% $P = 0.007$	12.0 10.7 ITT analysis: HR, 0.91; 95% CI, 0.76 to 1.09	24.1 22.6 ITT analysis: HR, 0.87; 95% CI, 0.72 to 1.05 Upper bound of one-sided 90% CI = 0.98; excludes noninferiority boundary of 1.18
Onda et al, 2014[5] JCOG0602 Meeting abstract	Stage III or IV based on CT, MRI, and cytologic tests. CA-125 > 200 U/mL and CEA < 20 ng/mL	OS	NACT PCS	152 149	61 59	30% 32%	302 240 $P < 0.001$	63% 30% (includes ICS results in PCS arm)	5% 15% $P = 0.005$ (Nonhematologic adverse events)	Not yet reported	Not yet reported
Vergote et al, 2010[1] EORTC 55971	Biopsy-proven stage IIIC or IV. If no biopsy specimen, fine-needle aspirate showing adenocarcinoma was allowed under certain circumstances.	OS	NACT PCS	334 336	63 62	24% 23%	180 165	51% 19%	Hemorrhage NACT: 4% PCS: 7% Infections NACT: 2% PCS: 8% Venous NACT: 0 PCS: 3%	12 12 ITT analysis: HR, 1.01; 90% CI, 0.89 to 1.15	30 29 ITT analysis: HR, 0.98; 90% CI, 0.84 to 1.13 $P = 0.01$ for noninferiority

Abbreviations: CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; HR, hazard ratio; ICS, interval cytoreductive surgery; ITT, intent-to-treat; NACT, neoadjuvant chemotherapy; OS, overall survival; PCS, primary cytoreductive surgery; PFS, progression-free survival; RCT, randomized clinical trial.

*Two patients in the PCS group had grade 5 complications.

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OVATION PFS 21.0 months

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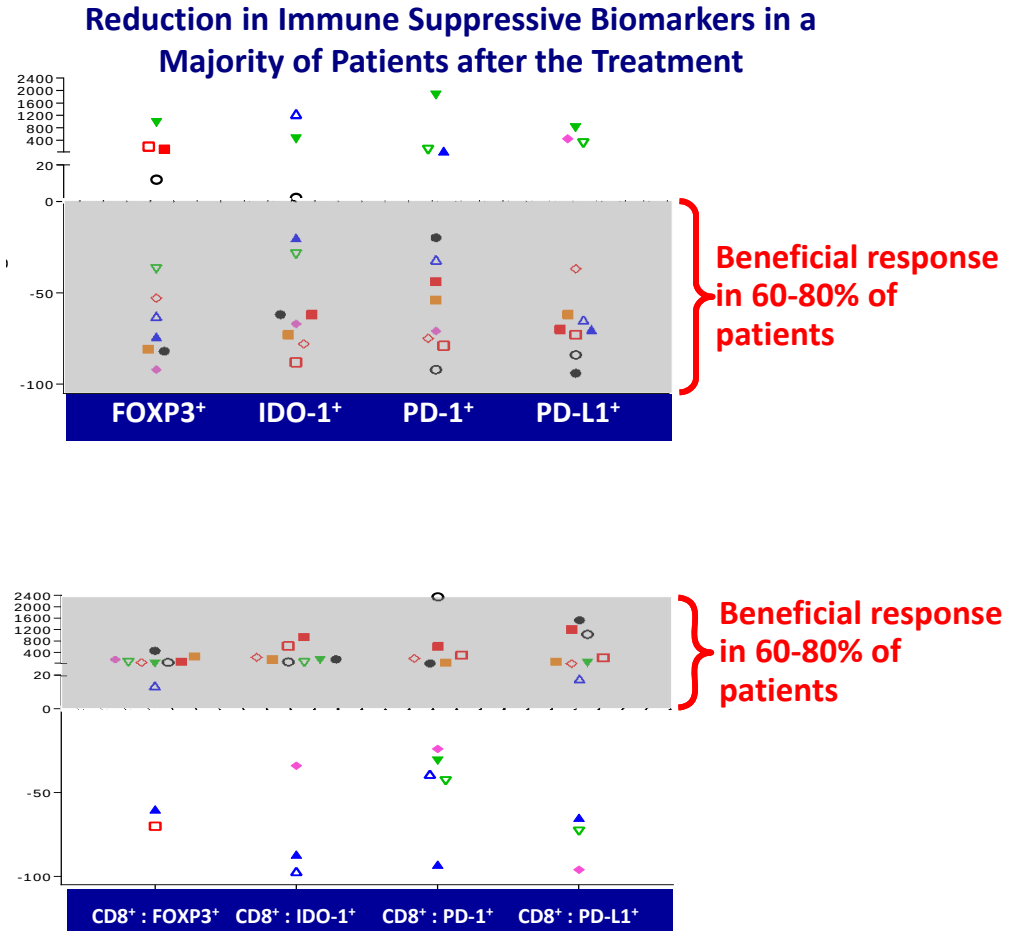
Translational Results



Thaker et al. ASCO 2017

Conclusion of TR Data

- GEN-1 IP + NAC treatment resulted in immunological changes that are consistent with the ability of GEN-1 to increase local (peritoneal) levels of IL-12 and its downstream anti-cancer cytokines and reduction in VEGF levels with little changes in systemic circulation.
- The increases in IL-12 and IFN-γ follows a dose response.
- Analysis of tumor tissue and ascites for immune cells populations shows a shift in local environment in favor of immune stimulation over immune suppression

Ovation II: A Phase I/II Study of NACT and GEN-1

Arm	Treatment	Before IDS									Interval Debulking Surgery	After IDS								
		C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	C3D1	C3D8	C3D15		C4D1	C4D8	C4D15	C5D1	C5D8	C5D15	C6D1	C6D8	C6D15
Arm 1	Carboplatin	X			X			X			X	X			X			X		
	Paclitaxel	X			X			X				X			X			X		
	GEN-1		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Arm 2 (control)	Carboplatin	X			X			X			X	X			X			X		
	Paclitaxel	X			X			X				X			X			X		
	GEN-1																			

Conclusion

- GEN-1 *IP* can shift the local microenvironment to favor *immunostimulation* without systemic side effects.
- Randomized phase I/II Ovation II study will build on GEN-1 development in the NACT population.

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A National Cancer Institute-Designated Cancer Center

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