Ovarian Cancer: New Horizons and Treatments

Premal H. Thaker, M.D.
Director of Gynecological Oncology Clinical Research
Professor in Gynecologic Oncology
Washington University School of Medicine

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

Washington University in St. Louis
School of Medicine

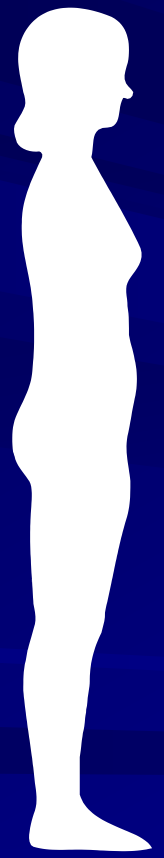
Disclosure

- Advisory Board: Celsion, Genentech, Iovance, Eisai, Stryker, Genelux, Unleash Oncolytics, Immunogen, Tesaro, Astra Zeneca, Merck
- 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
  - Anti-angiogenic
  - PARP inhibitors
  - Immunotherapy

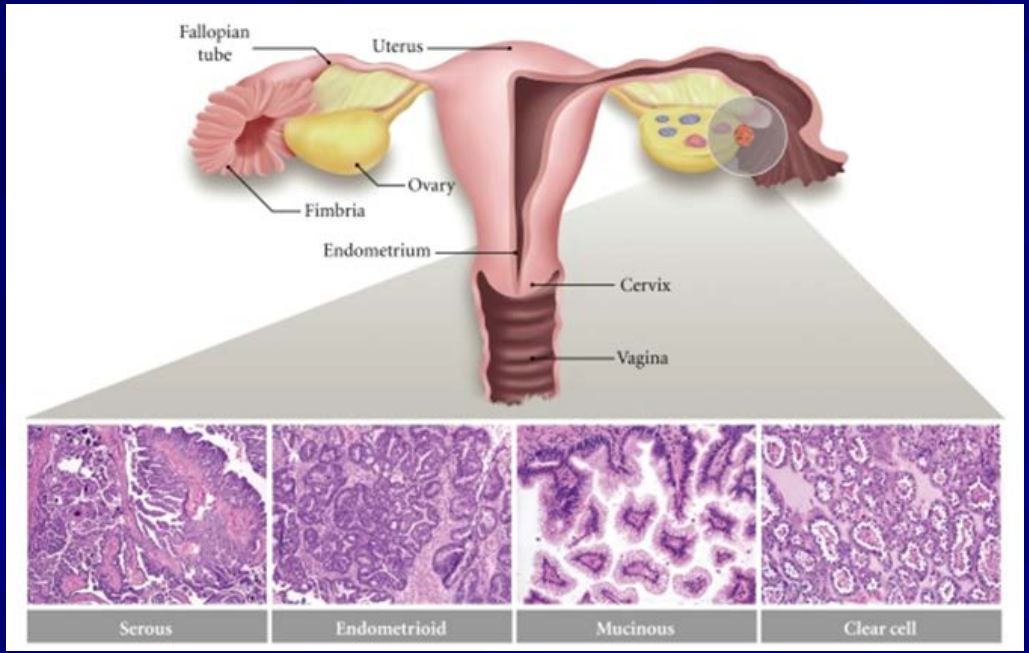
2019 US Estimates *



Women	New Cases		Deaths	
	891,480		**285,210**	
30%	Breast		23%	Lung & bronchus
13%	Lung & bronchus		15%	Breast
7%	Colon & rectum		8%	Colon & rectum
7%	Uterine corpus		8%	Pancreas
5%	Melanoma		**5%**	**Ovary**
4%	Non-Hodgkin lymphoma		4%	Uterine corpus
4%	Thyroid		4%	Liver & bile duct
2.5%	**Ovary**		3%	Non-Hodgkin lymphoma
3%	Pancreas		3%	Leukemia
3%	Leukemia		3%	Brain & other nervous system
21.5%	All Other Sites		24%	All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2019.

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

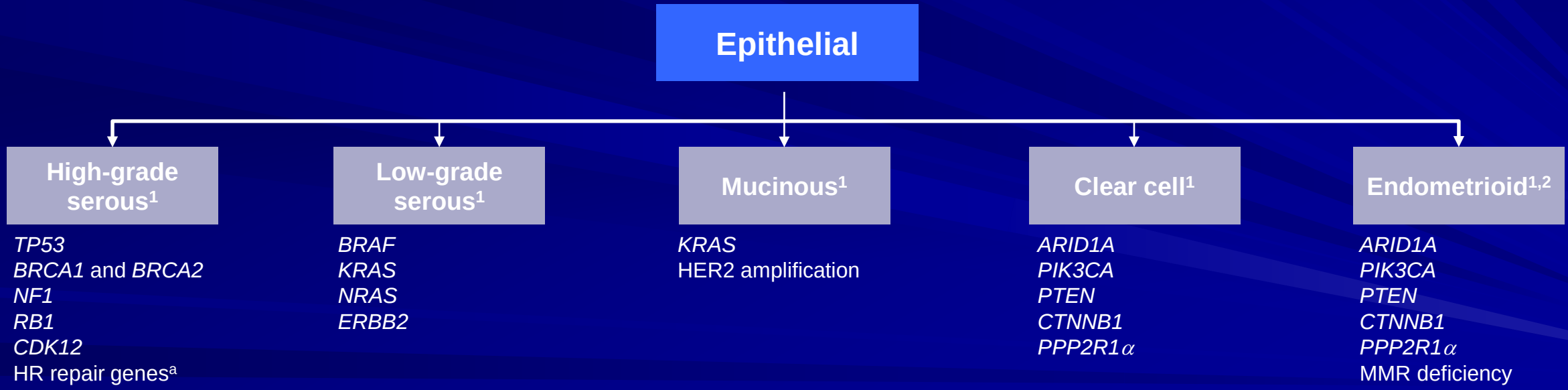


	All Subtypes	Serous	Endometrioid	Mucinous	Clear Cell
All stages	47	44	82	69	67
Localized	93	90	98	93	90
Regional	74	75	87	81	74
Distant	30	35	48	18	26

American Cancer Facts & Figures 2018

Epithelial Ovarian Cancer Subtypes Are Associated With Different Mutations and Molecular Aberrations

- Epithelial ovarian cancer can be characterized as a heterogeneous disease, not only histologically, but through identification of distinct molecular pathway alterations



[a] *CHK2*, *BARD1*, *BRIP1*, *PALB2*, *RAD50*, *RAD51C*, *ATM*, *ATR*, *EMSY*, and Fanconi anemia genes.

HR, homologous recombination; MMR, mismatch repair.

1. Banerjee S, et al. *Clin Cancer Res.* 2013;19(5):961-8. **2.** McConechy MK, et al. *Mod Pathol*. 2014;27(1):128-34.

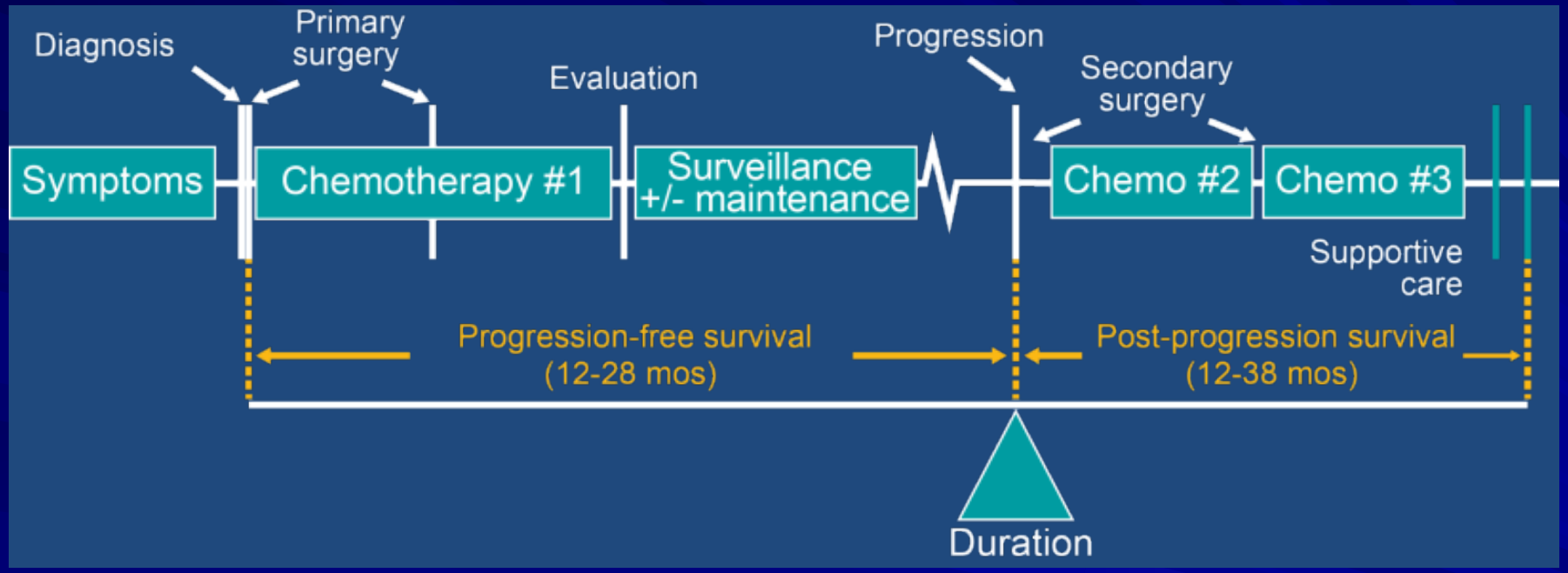
Lifetime Risk of Cancers Associated With Specific Genes

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.

Treatment Landscape Overview for Advanced Ovarian Cancer



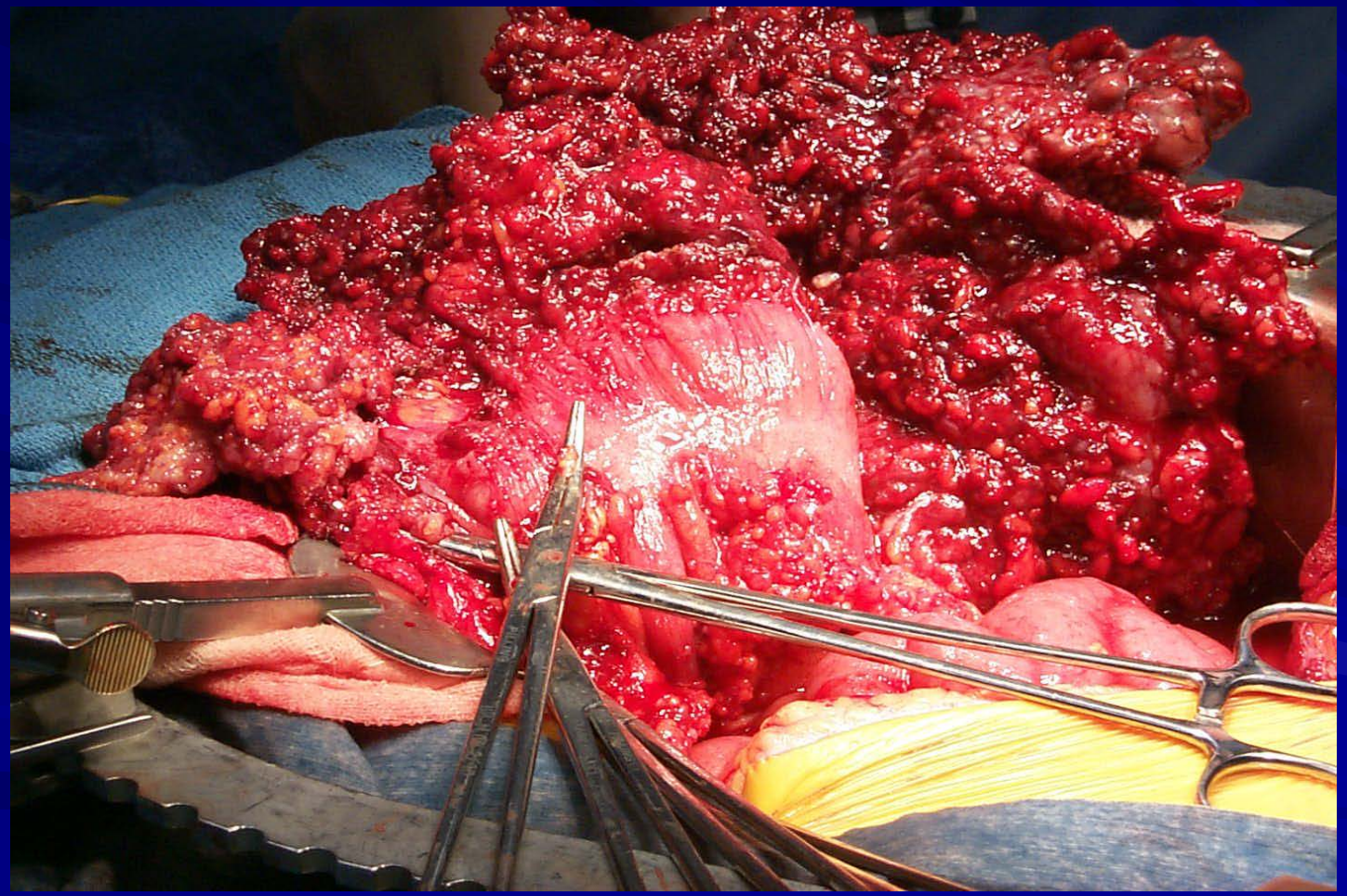
- Surgical goal is complete cytoreduction of all macroscopic visible disease[1]
- Standard adjuvant chemotherapy is an IV or IP taxane/platinum combination[1]
- Despite optimal upfront surgery and adjuvant chemotherapy, approximately 80% of patients will relapse[2]
- Unknowns: maintenance therapy, antiangiogenic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



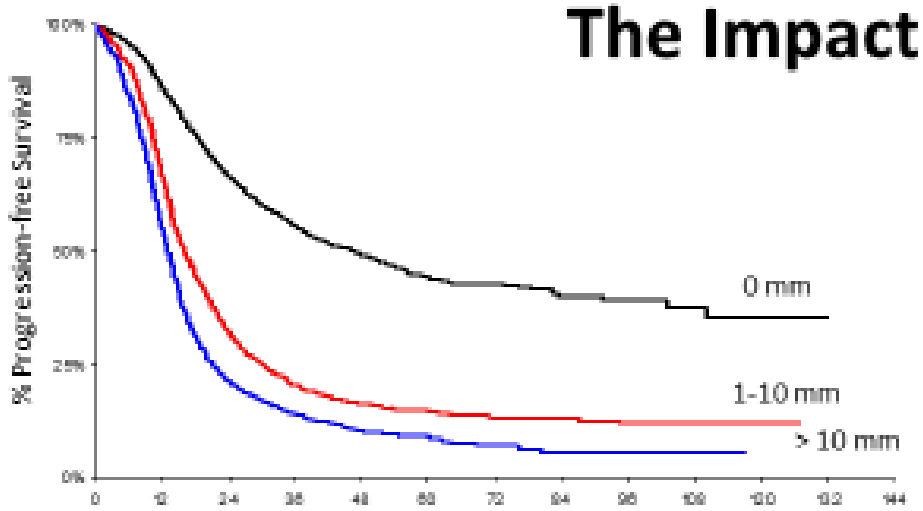
Adequate Surgery is Vital in Treating Ovarian Cancer

- 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

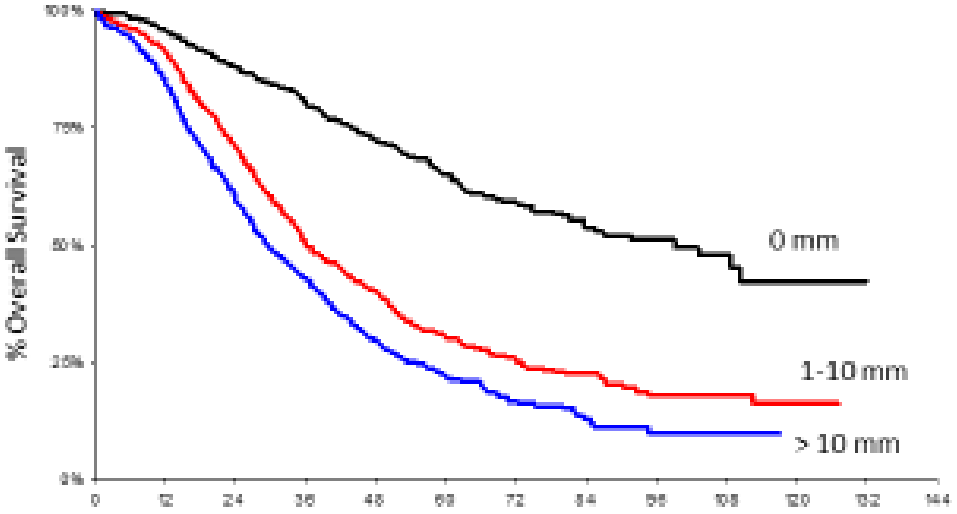
Wright AA, et al. J Clin Oncol. 2016 Oct 1;34(28):3460-73.

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

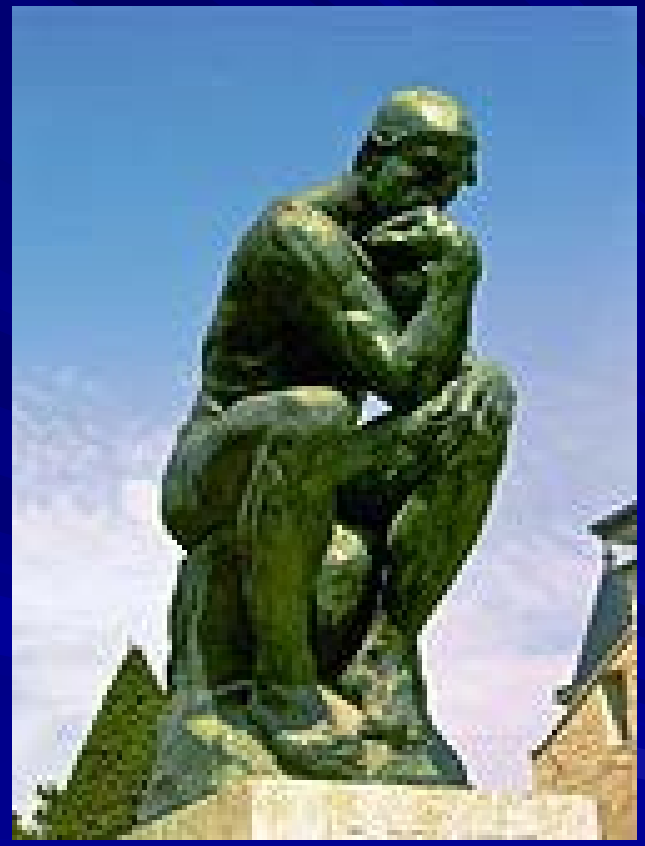
Laparoscopic Predictive Index

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

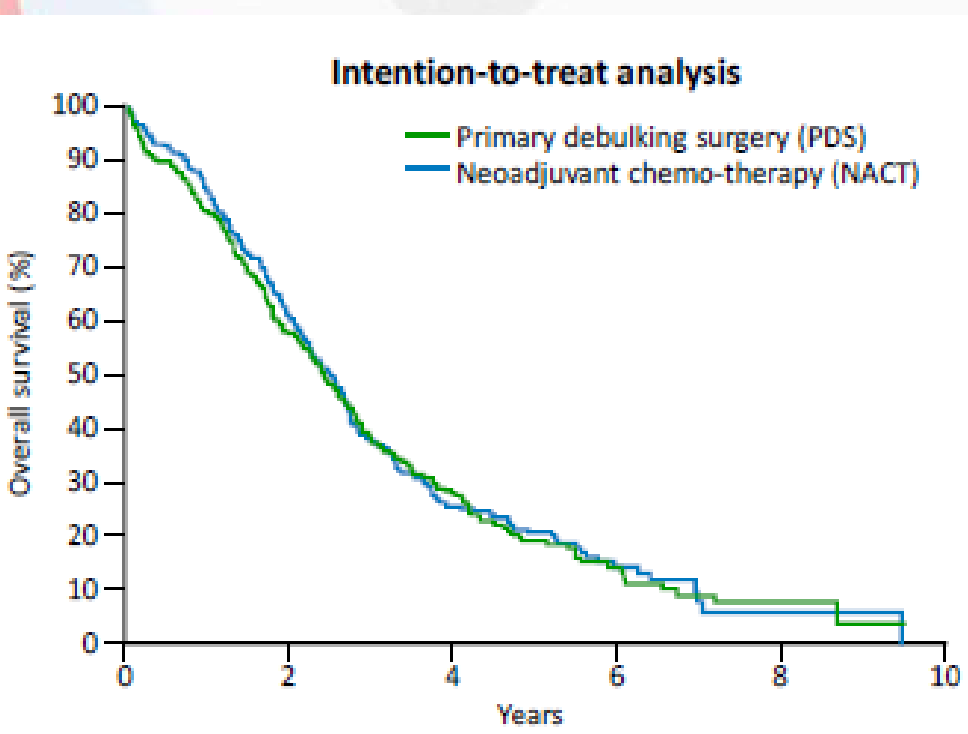
Nick, A. M. *et al.* (2015) A framework for a personalized surgical approach to ovarian cancer *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2015.26

CHEMOTHERAPY VS SURGERY?



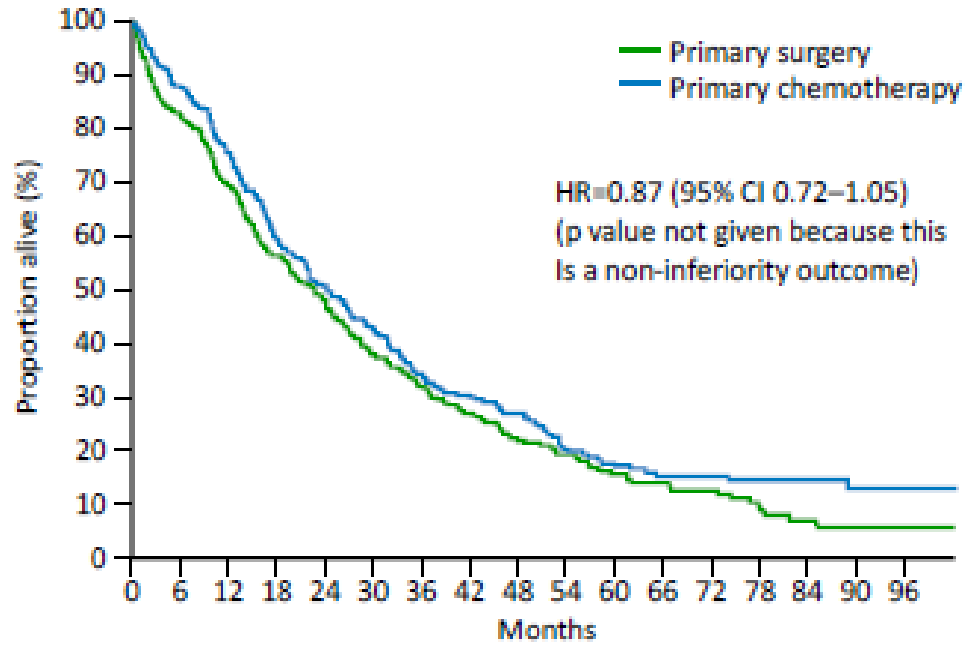
Design of 2 Phase III Trials Addressing NACT

EORTC 55971[1]



No. of events		Number of patients at risk				
PDS	253	336	189	62	14	2
NACT	245	334	195	46	13	2

CHORUS[2]



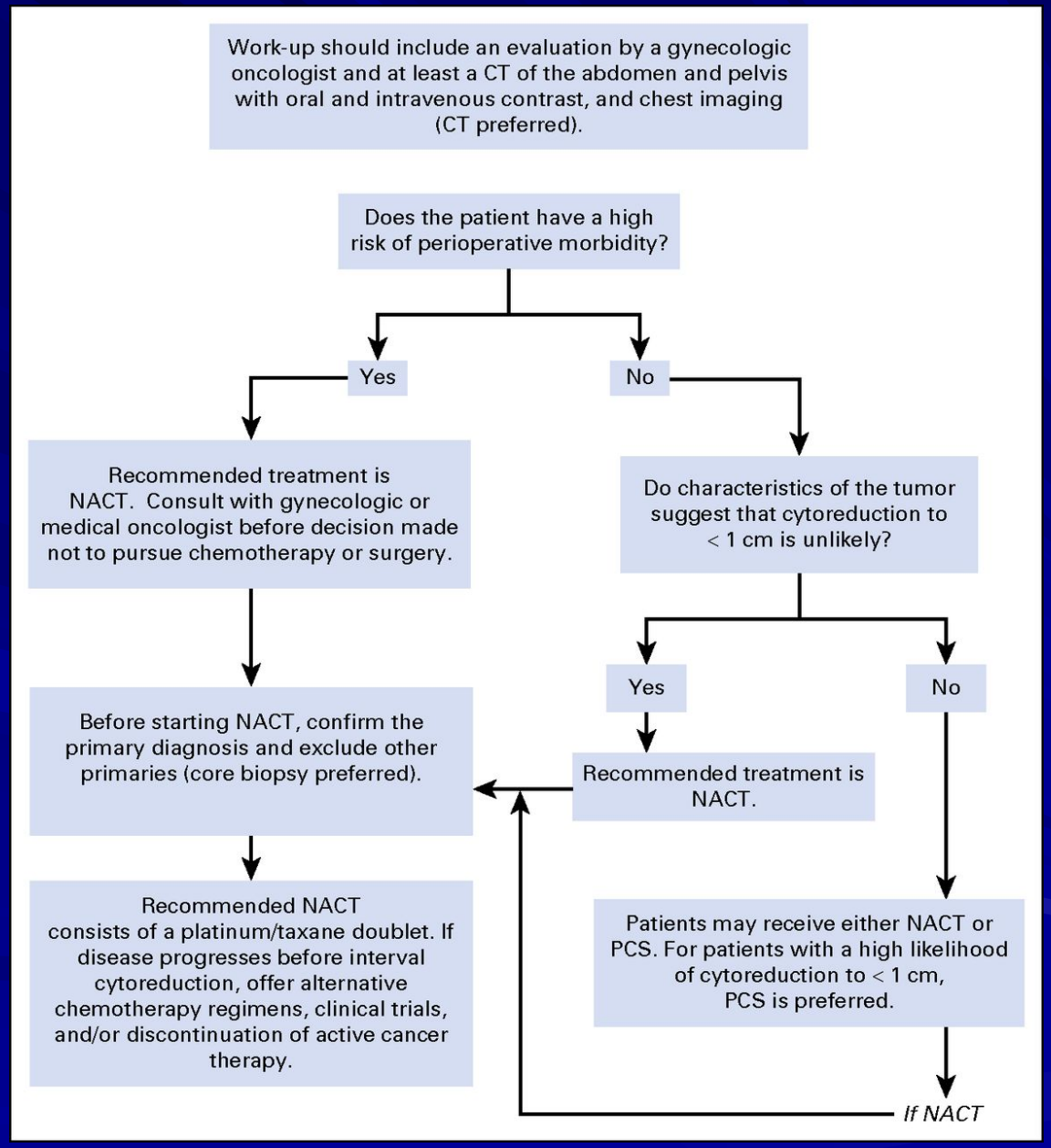
Number at risk											
Primary surgery	276	225	189	153	128	83	51	22	17	6	3
Primary chemotherapy	274	239	205	161	137	88	59	31	21	14	3

*Definition of successful surgery: maximum effort for complete resection of visible tumour

1. Vergote, et al. NEJM 2010; 2. Kehoe, et al. Lancet 2015

ASCO & SGO Guidelines August 2016

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.



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

NACT Trends

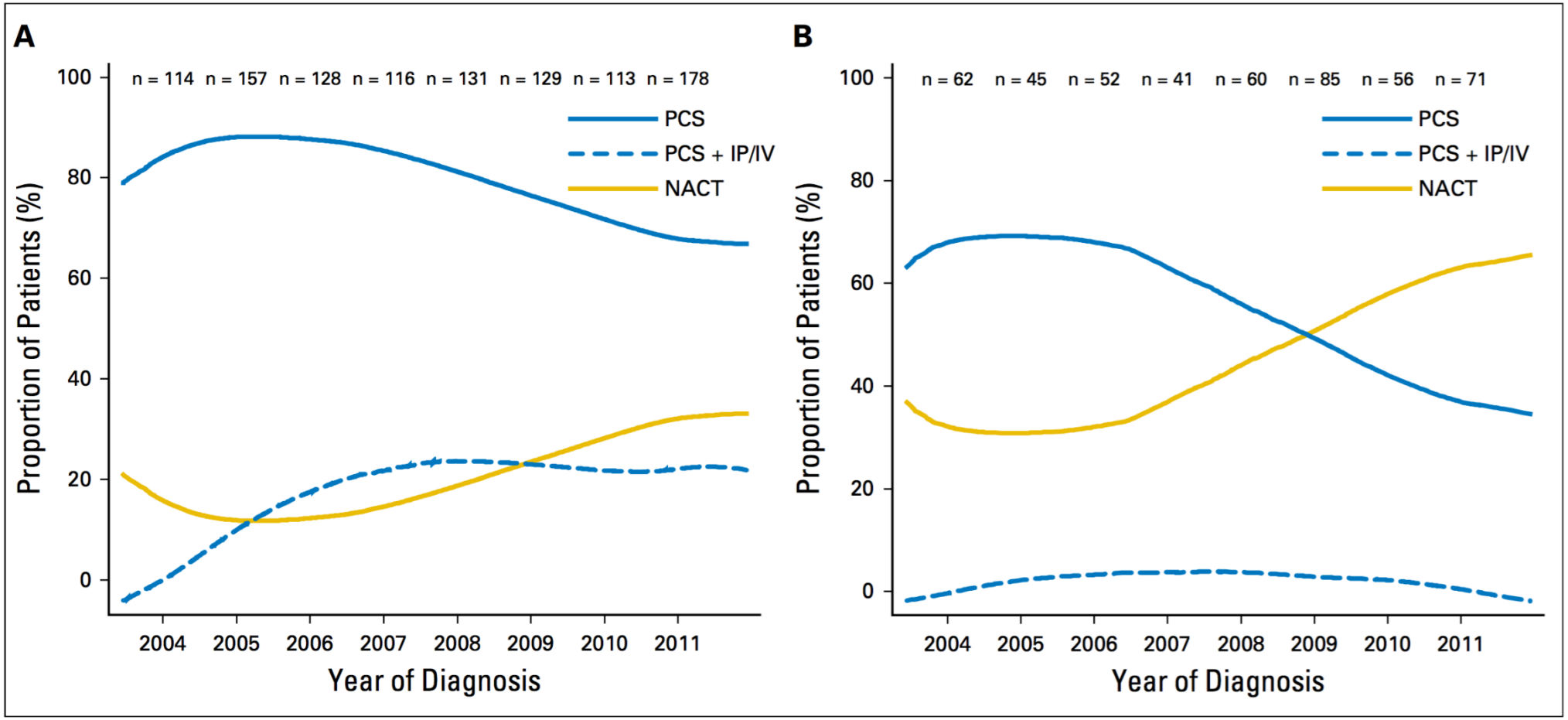
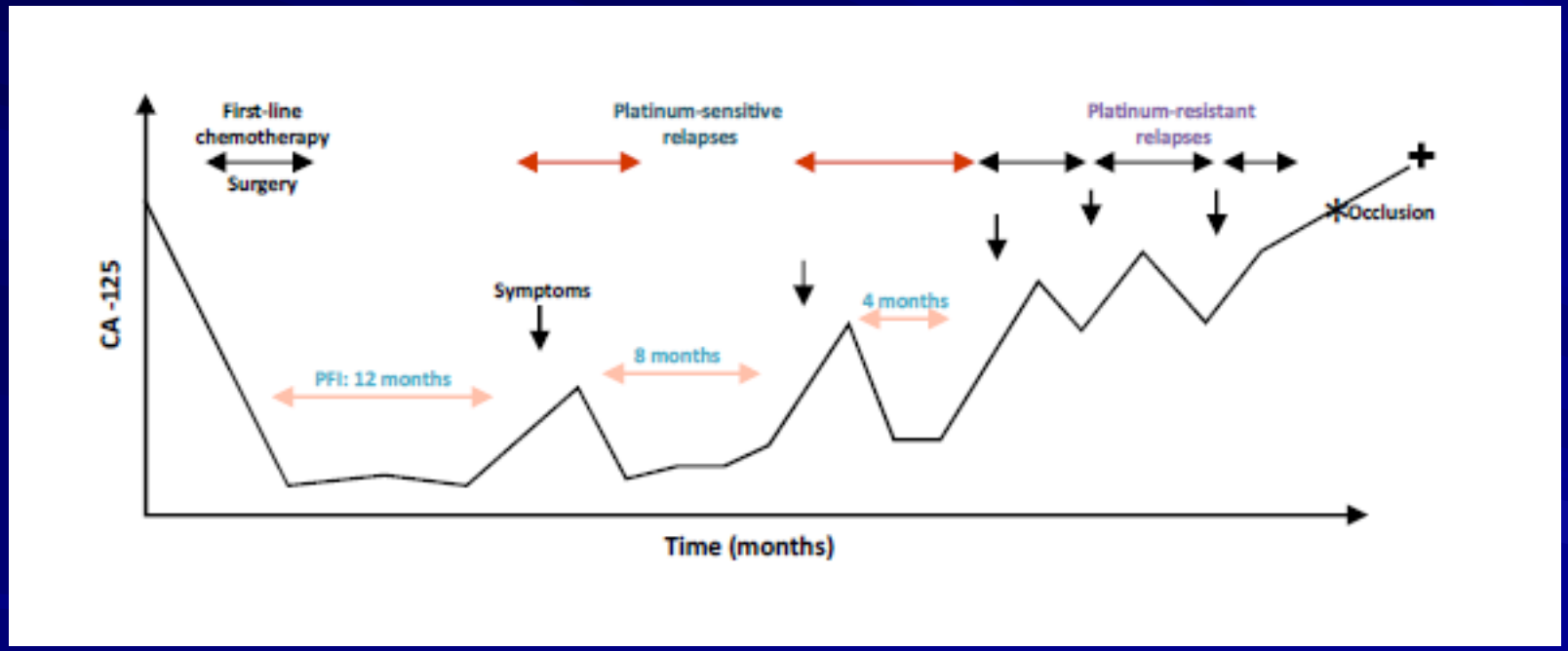


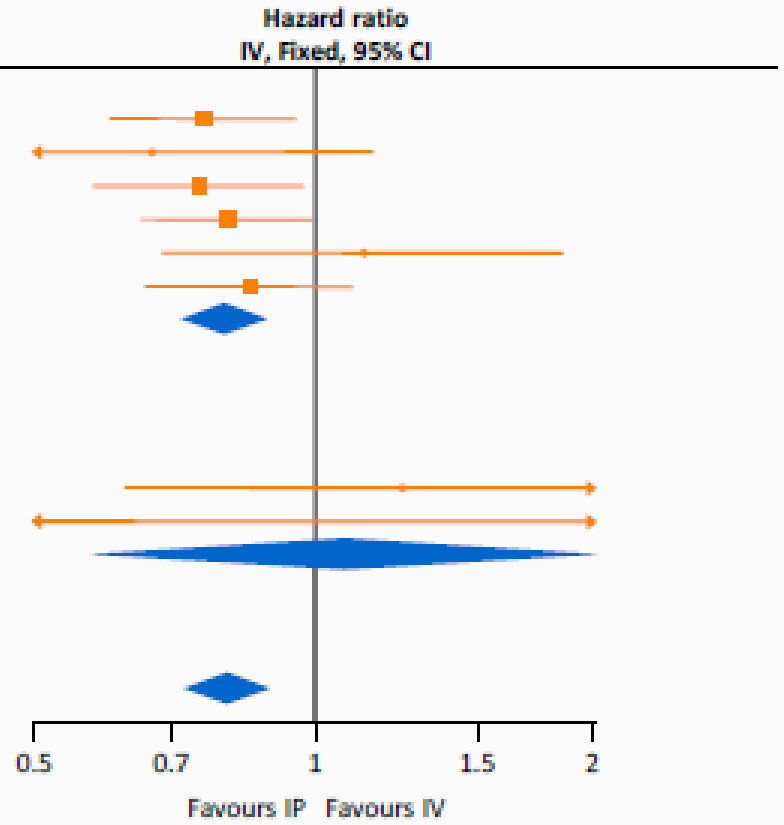
Fig 1. (A) Stage IIIC disease. (B) Stage IV disease. Use of neoadjuvant chemotherapy (NACT) increased significantly over time ($P_{trend} < .001$ for both groups). Intraperitoneal and intravenous (IP/IV) chemotherapy is shown for comparison. Three patients with stage IIIC disease and one with stage IV 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

Addition of HIPEC to Interval Cytoreductive Surgery Improves Outcomes in Advanced Ovarian Cancer

- Intraperitoneal chemotherapy during surgery delivered under hyperthermic conditions is termed HIPEC
  - Hyperthermia increases penetration of chemotherapy at the peritoneal surface and is thought to increase chemosensitivity by interfering with DNA repair
- A recent randomized phase 3 study investigated whether HIPEC with cisplatin improved outcomes in patients with stage III epithelial ovarian cancer who had at least stable disease after 3 cycles of neoadjuvant carboplatin + paclitaxel
- Addition of HIPEC to interval cytoreductive surgery resulted in longer mRFS and mOS
  - HIPEC did not result in increased rates of side effects and did not affect health-related QoL

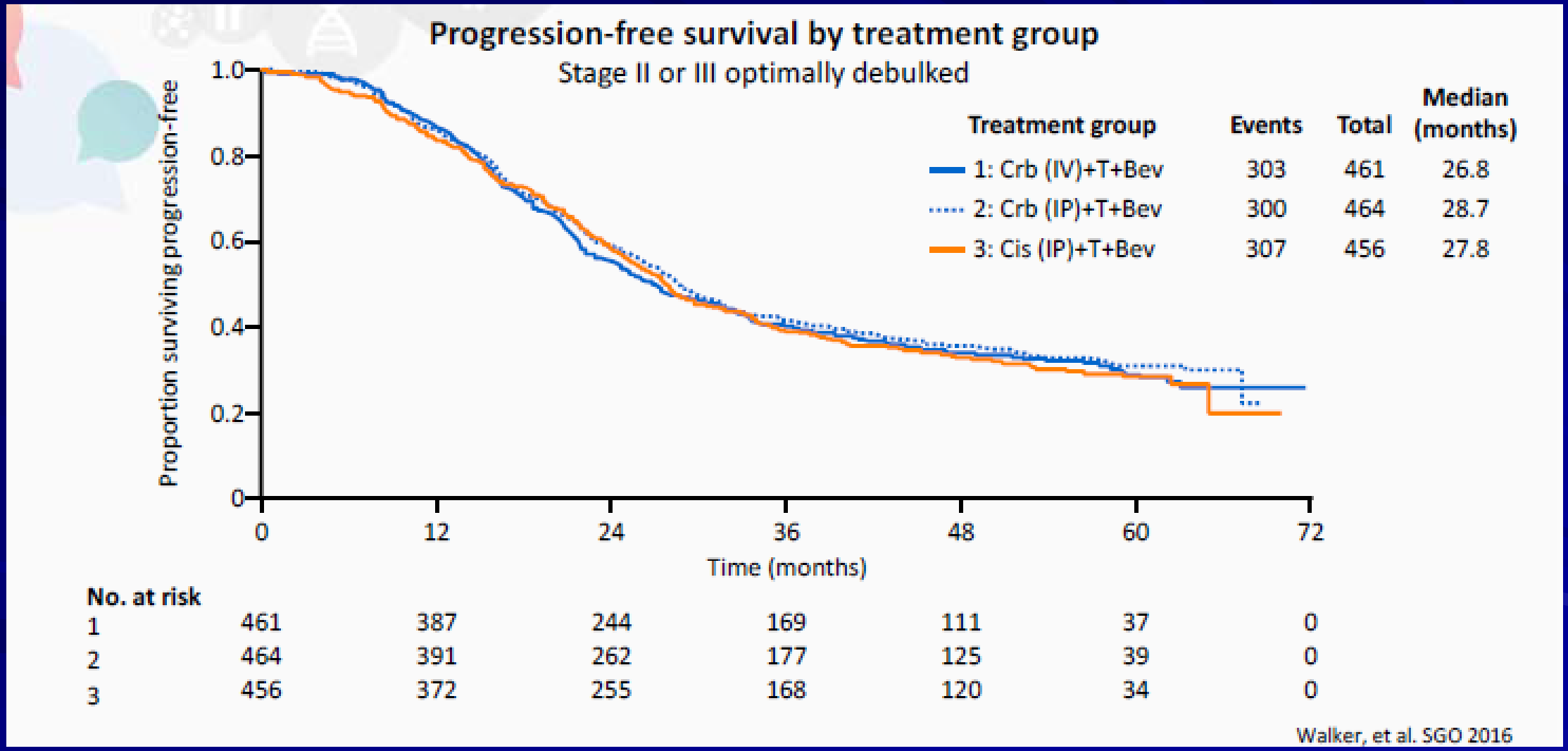
Endpoint	Surgery Alone (n=123)	HIPEC + Surgery (n=122)
mRFS, mo (95% CI)[a]	10.7	14.2
HR (95% CI)	0.66 (0.50–0.87), *P*=0.003[b]	
mOS, mo (95% CI)[c]	33.9	45.7
HR (95% CI)	0.67 (0.48–0.94), *P*=0.02[b]	
Grade 3/4 AEs, %	25	27

[a] Primary endpoint. [b] Stratified *P* value. [c] Secondary endpoint.

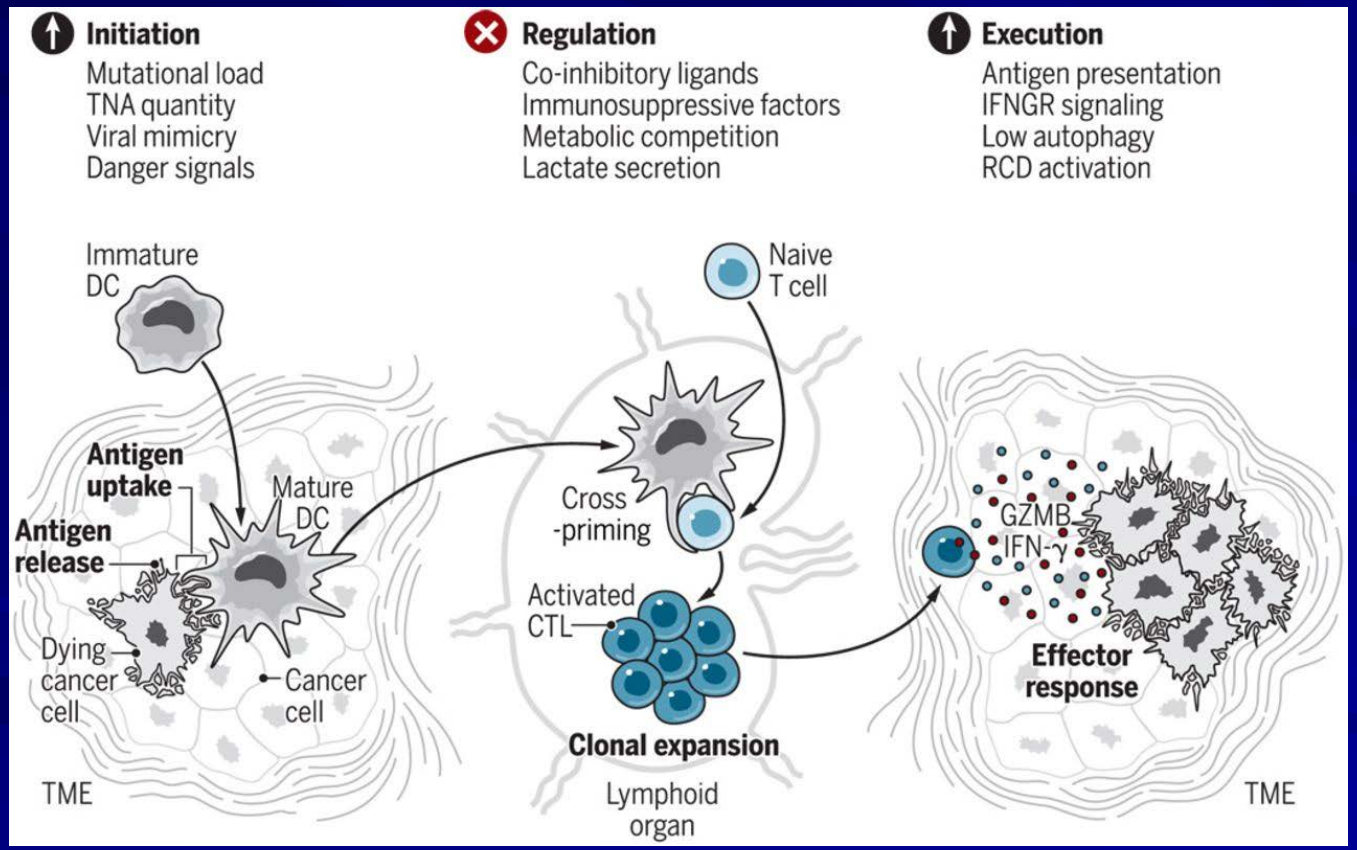
AE, adverse event; CI, confidence interval; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; mOS, median OS; mRFS, median relapse-free survival; OS, overall survival; QoL, quality of life.

van Driel WJ, et al. *N Engl J Med*. 2018;378(3):230-40.

GOG 252: PFS optimal stages II & III



IMMUNOTHERAPY



IL-12: A Powerful Immune-Modulating Agent

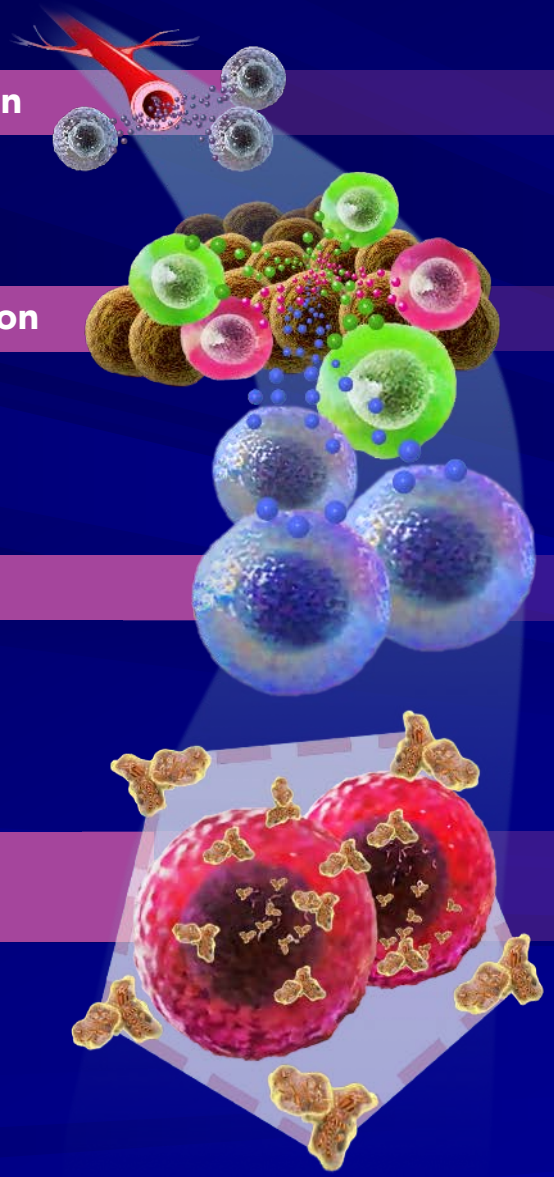
Interleukin 12 Can Induce Anti-cancer Immunity Through Multiple Mechanisms

Activation/Proliferation

Maturation/Proliferation

Anti-Angiogenesis

Inhibition of Immune Suppression



1 Stimulates the proliferation of CD-8 positive T-cells and natural killer (NK) cells and their cytotoxic activity against the tumor

2 Shifts the differentiation of naive CD-4 positive T-cells toward a TH-1 phenotype, further enhancing the immune response

Turns cold tumors into hot tumors

3 Promotes cellular production of the potent immune mediator IFN-γ and TNF-α. IFN-γ promotes the expression of anti-angiogenic molecules, halting the growth of new blood vessels that supply oxygen to the tumor

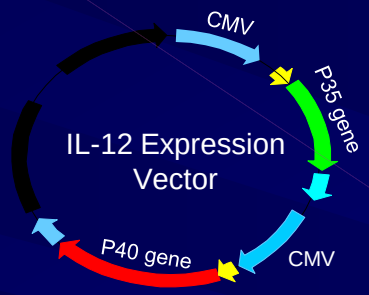
4 IL-12 may inhibit regulatory T-cells that suppress immune responses by "hiding" the tumor from the body's immune system

Celsion

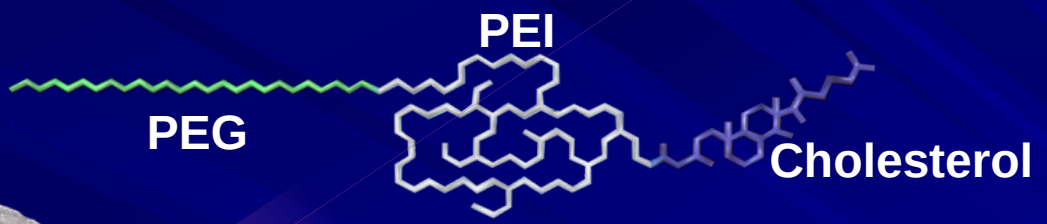
Clinical Experience with rhIL-12

- Hurteau *et al.*
  - GOG trial of recombinant human IL-12 in recurrent platinum resistant or refractory ovarian cancer
  - rhIL-12 250 ng/kg IV bolus on D#1 followed by a 2 week rest period, with subsequent daily dosing x 5 days
  - 26 evaluable patients with median of 2 cycles:
    - 1 PR, 13 SD
  - Grade 4 myelotoxicity of 21%
    - *Gynecol Oncol* 2001;82(1):7-10.

GEN-1: Designed for IP Administration



Immune Agent



PEG-PEI-Chol (PPC)
(IP Delivery System)

GEN-1
Nanoparticles
~150 nm

GEN-1

GEN-1 intraperitoneally (IP) produces durable local levels of IL-12 and related cytokines after a single injection and is delivered safely for several weeks for modulation of TME

- Plasmid vector encoding the p35 and p40 subunits of human IL-12 gene
- Synthetic lipopolymer delivery system

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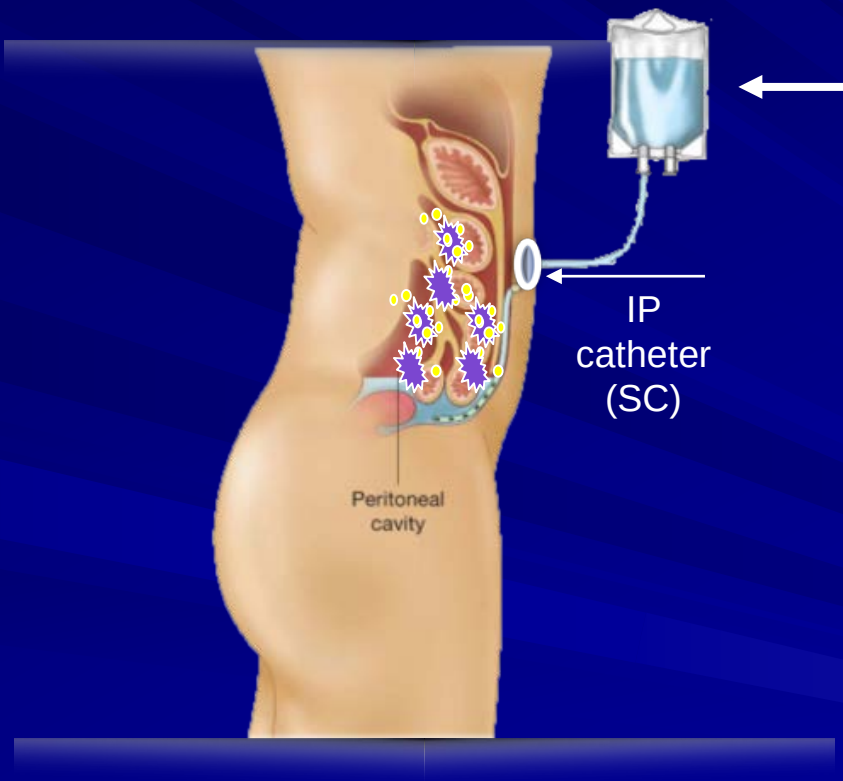
GEN-1 Design Concepts

- PEI condenses DNA into nanoparticle to escape endosomes
- Cholesterol is designed to facilitate uptake by cellular membrane
- PEG improves *in vivo* stability (weekly dosing)



Peritoneal Mets
(Ovarian/Primary)

GEN-1

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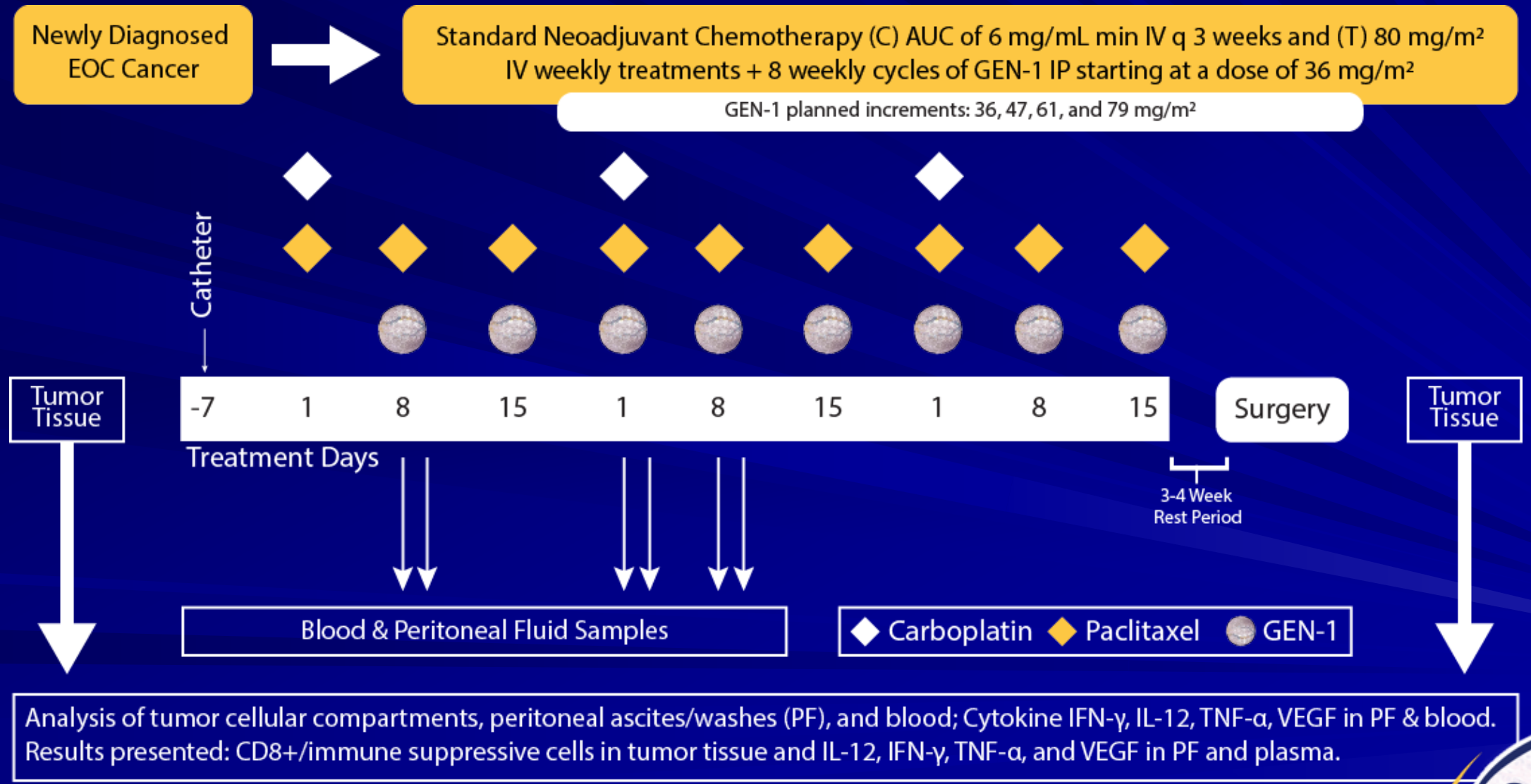
Rationale for GEN-1 in Newly Diagnosed Ovarian Cancer Patients

- Relatively healthier immune system than recurrent population
  - Tumor and immune system naïve to any cancer therapy
- Accessibility to primary tumor tissue for translational studies
  - Neoadjuvant population allows for examining tissue before and after treatment
- Better prospects of generating comprehensive translational data and understanding biological response to dose escalation

Hypothesis:

- GEN-1 when added to standard doublet chemotherapy may stimulate a potent immune response in ovarian cancer patients
  - Resulting in improved R0 resection rates
  - Reduced immunosuppression in the tumor microenvironment
  - Enhanced T cell anti-tumor activity

Phase I Study Design



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Study Endpoints

- Primary Objectives: To determine safety, feasibility, and dose in targeted patient population
- Secondary Objectives: pathological CR, PFS
- Translational Objectives: IFN-y, IL-12, VEGF, and tumor-specific T-cell response of CD4+ and CD8+

Study Population

Patients	Dates of C1D1	Age (yrs.)	Histology	Stage	Performance Status	Baseline CA-125 (U/mL)
18 (ITT)	Range: 05Oct2015 – 17May2017	Median: 63 Range: 48-79	Serous: 95% Clear Cell: 5%	IIIC: 67% IV: 33%	0: 34% 1:55% 2:11%	Median: 565 Range: 78 - 2252
14 (Per Protocol)	Range: 05Oct2015 – 15Feb2017	Median: 62 Range: 48-79	Serous: 100%	IIIC: 71% IV: 29%	0: 36% 1: 64% 2: 0%	Median: 988 Range: 245-2252

Results: Safety (n=15)

Most Common AEs Attributed to GEN-1	Total (n, %)	Grade 1 & Grade 2 (n,%)	Grade 3 (n,%)	Grade 4 (n, %)	Grade 5 (n, %)
Nausea	9, 60%	9, 60%	0, 0%	0, 0%	0, 0%
Abdominal Pain/ Cramping	6, 40%	5, 33%	1, 6%	0, 0%	0, 0%
Fatigue	6, 40%	6, 40%	0, 0%	0, 0%	0, 0%
Vomiting	6, 40%	5, 33%	1, 6%	0, 0%	0, 0%
Diarrhea	5, 33%	3, 20%	2, 13%	0, 0%	0, 0%
Neutropenia	5, 33%	3, 20%	1, 6%	1, 6%	0, 0%

- Four patients discontinued the study due to AEs
  - Dosing delays > 21 days
  - Declining performance status
  - Sepsis & congestive heart failure
  - Altered taste (GEN-1 treatment only)

Response Data

Response		Total	36 mg/m²	47 mg/m²	61 mg/m²	79 mg/m²
RECIST (Prior to IDS) (n=14)	CR	2	1	0	0	1
	PR	10	0	3	3	4
	SD	2	2	0	0	0
Debulking Status (n=14)	R0	9	2	0	2	5
	R1	3	1	2	0	0
	R2	2	0	1	1	0
Pathologic Response (n=14)	cPR	1	1	0	0	0
	Micro	8	1	2	1	4
	Macro	5	1	1	2	1

OVATION 1 Study: Improved Progression-Free Survival with GEN-1

Improvements vs Historic Outcomes in Comparable Patient Populations

Historical Estimated PFS* (Vergote, Kehoe) — 12 months

OVATION 1 – ITT — 17 months

Final Median PFS Per OVATION 1 Protocol — 21 months

Similar Baseline Patient Characteristics in the OVATION I Study vs Large NAC Trials

Name of Study	# of Patients	Age	Histology	Stage
OVATION 1	**18**	**Median: 63** **Range: 48-79**	**Serous: 95%** **Clear Cell: 5%**	**IIIC: 67%** **IV: 33%**
Vergote	670	Median: 63 Range: 33-81	Serous: 65% Undiff: 27%	IIIC: 76% IV: 24%
Kehoe	550	Median: 65 Range: 34-88	Serous*: 83% Clear Cell: 6%	IIC, IIIA/B: 12% IIIC: 71% IV: 15%

*Includes high-grade and "not specified"

Celsion

Decrease in Immunosuppressive Markers in the TME Post GEN-1/NACT

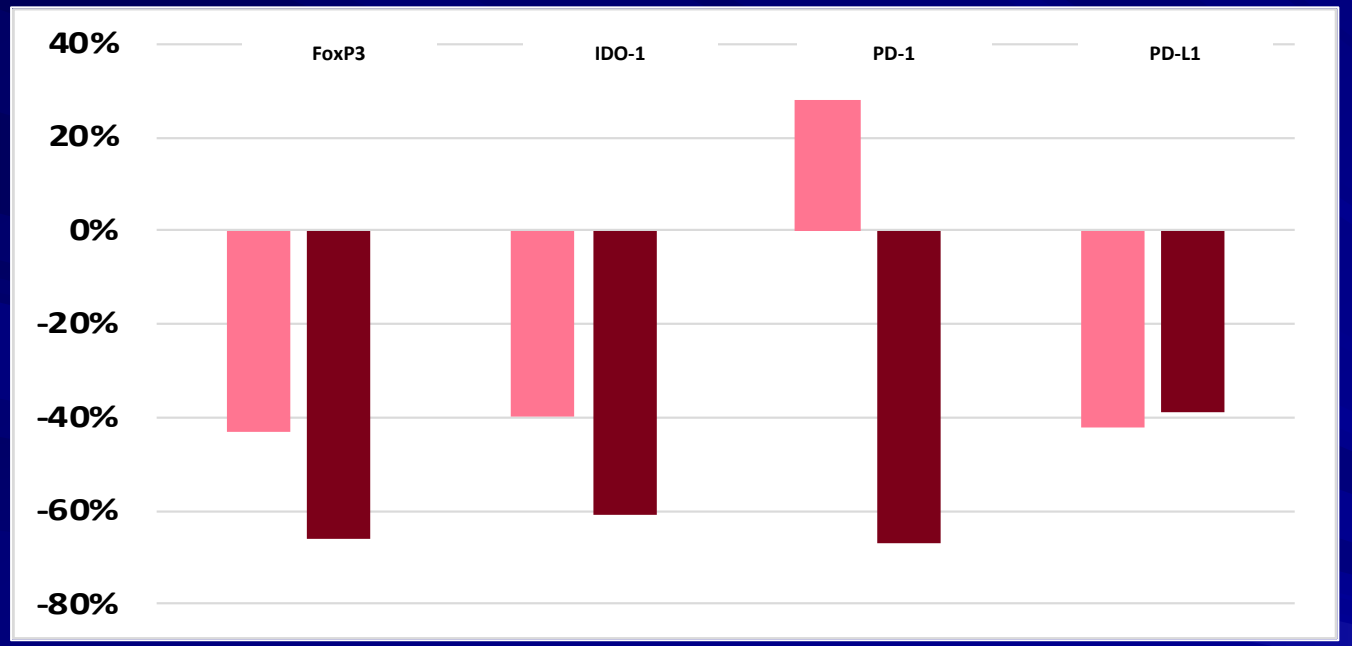


Figure 1. Changes in immunosuppressive markers in response to low and high doses of GEN-1.

* Data in Figures 1 and 2 from 12 patients treated per protocol

Celsion

Increase in the Ratio of Immune Activating Cells to Immune Suppressive Cells in the TME

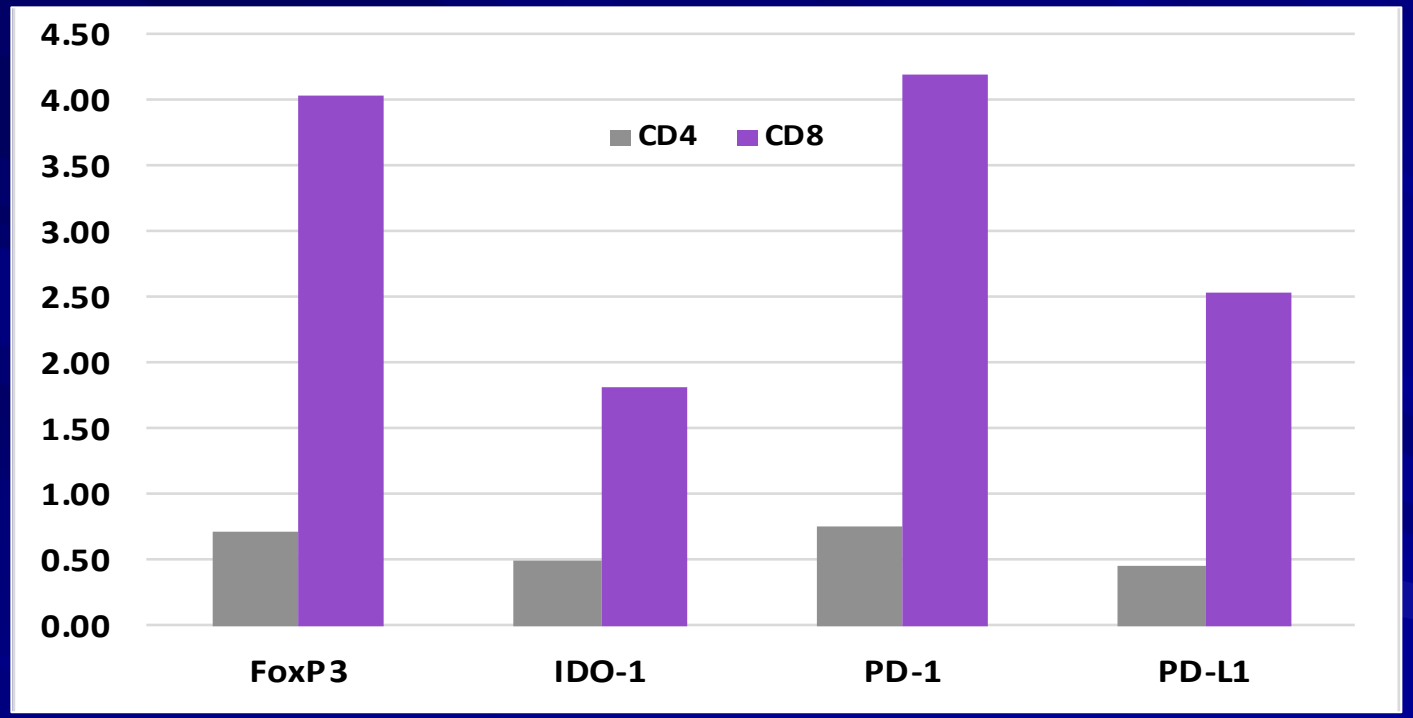
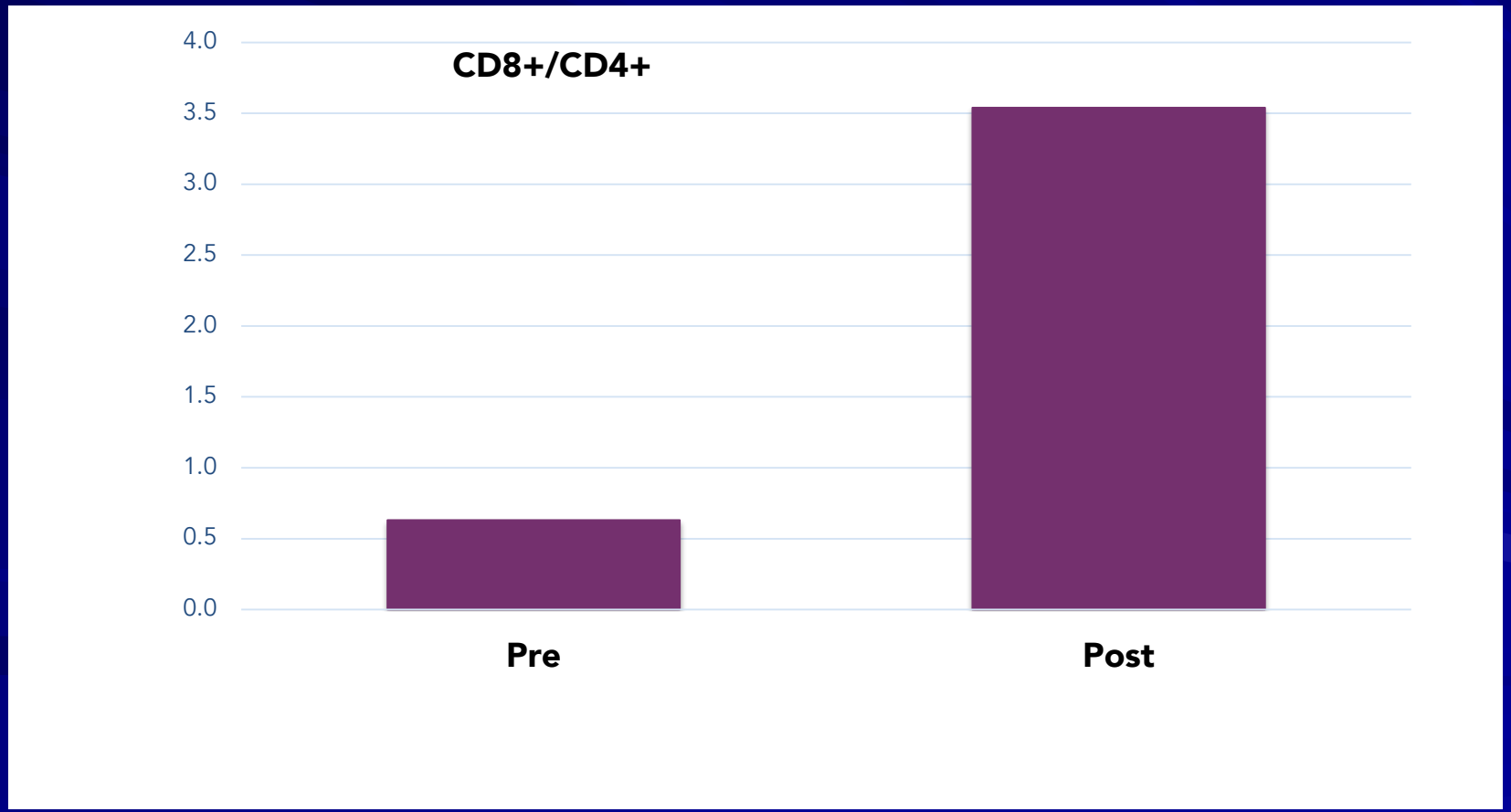


Figure 2. Changes in the ratios of CD4+ and CD8+ T cells to immunosuppressive markers presented as post-treatment ratio to pretreatment ratio (e.g., (post- CD4/PD-1)/(pre- CD4/PD-1).

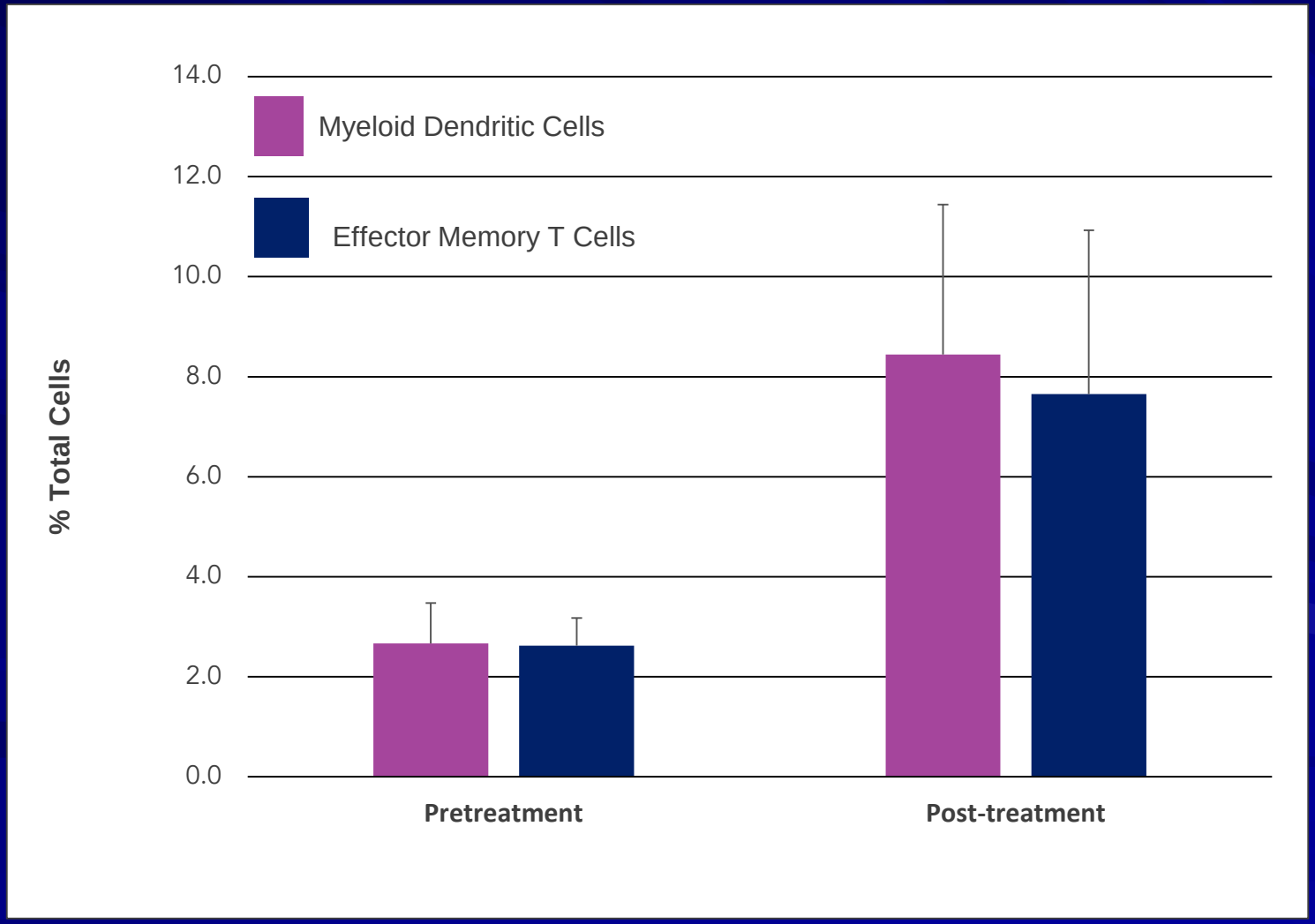
Celsion

Increase in CD8+/CD4+ in Tumor Post GEN-1 / NAC Treatment

Ratio of CD8+/CD4+ T cells increased nearly 500%



Increases in Dendritic and T_{EM} Cells population GEN-1 / NAC



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Summary of TR Findings

- 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 effect.
- The increases in IL-12 and IFN-g follows a dose response.
- Analysis of tumor tissue and ascites for immune cell populations shows a shift in local environment favoring immunostimulatory mechanisms over immunosuppressive mechanisms.
- The immunological changes observed in local tumor environment following GEN-1/NACT are of high prognostic value and favorable to novel combination immune therapies.

Conclusions

- Adding GEN-1 to doublet treatment is safe and appears to be active in EOC patients receiving neoadjuvant chemotherapy.
- Dose limiting toxicity was not reached.
- GEN-1 appears to change the tumor microenvironment.
- OVATION 2 is extending the results of the phase I OVATION trial.

OVATION 2

Ovarian Cancer Patients
(FIGO IIIC & IV)

Up to 130 patients
12 patients in Phase I Run-in (100 mg/m²);
Up to 118 patients in Phase II

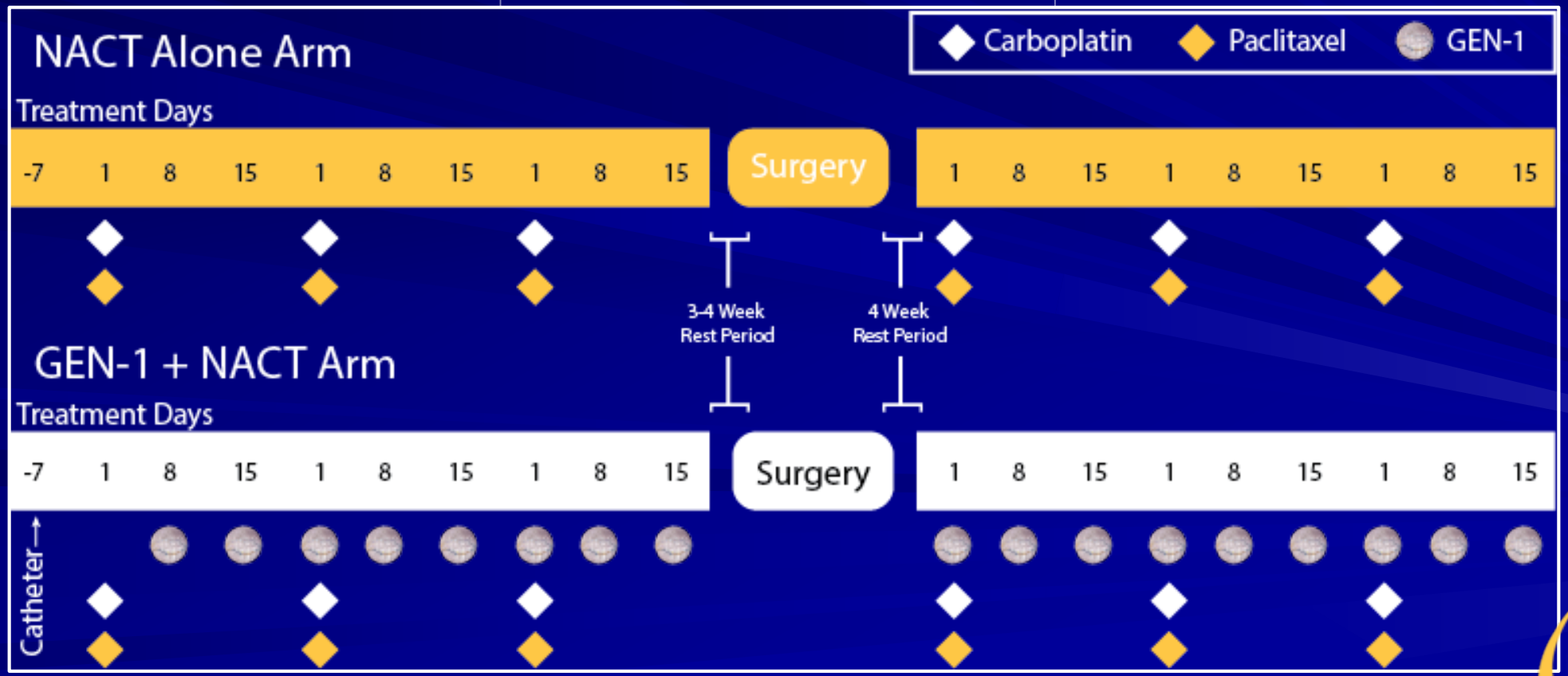
Randomized 1:1
NAC +/- GEN-1

Primary Endpoint

Progression
Free Survival

Secondary Endpoint

Clinical Response, Pathological Response,
Surgical Response, Safety, Biological



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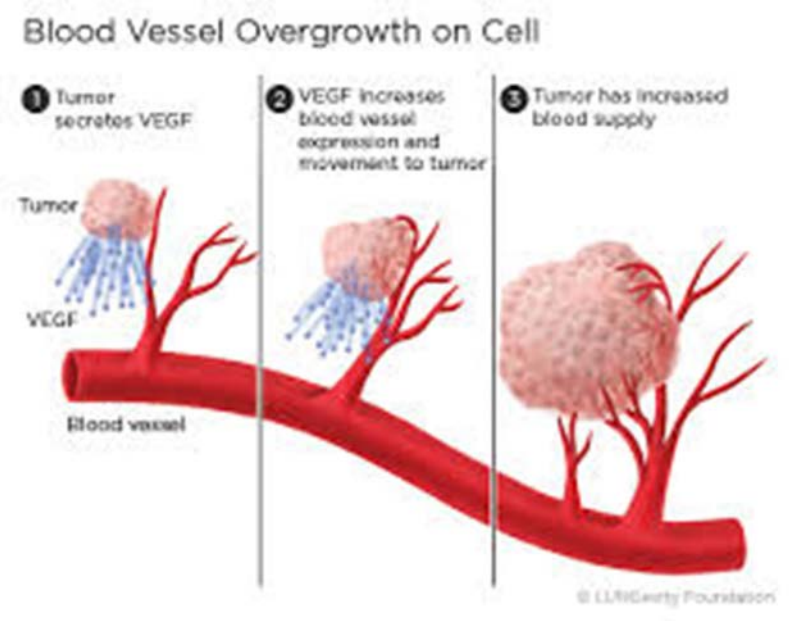
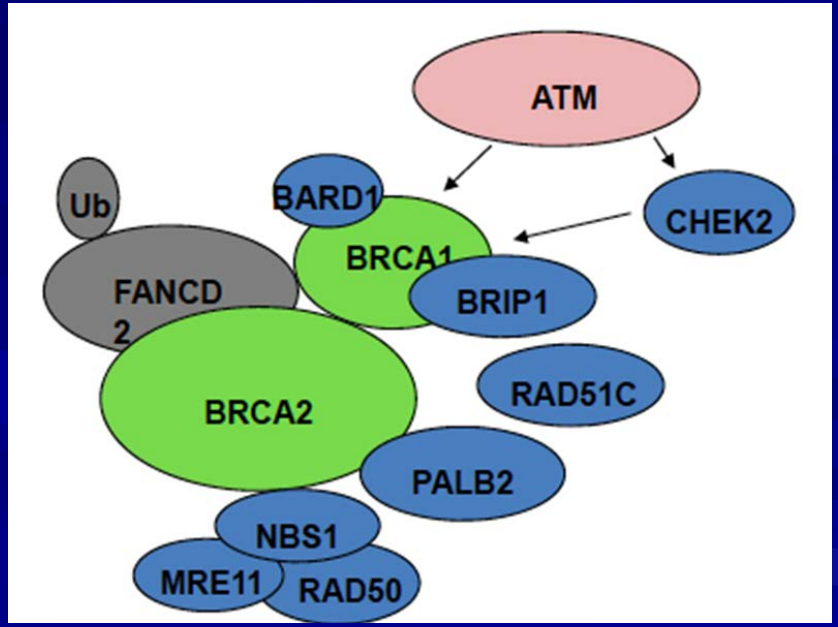
MAINTENANCE THERAPY





FDA-Approved Options for 1L Maintenance Therapy: Bevacizumab and Olaparib

Registrational Clinical Trial(s)	Drug	Indication	Biomarker Testing Required?	Recommended Dosing
GOG-0218	Bevacizumab[1]	Bevacizumab in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent for treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection	No	15 mg/kg IV q3w in combination with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg q3w as a single agent, for a total of up to 22 cycles or until disease progression, whichever occurs earlier
SOLO-1	Olaparib[2]	Olaparib maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*^{mut} or s*BRCA*^{mut} advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to 1L platinum-based chemotherapy	Yes, FDA-approved companion diagnostic to select patients with g*BRCA*^{mut} disease	300 mg (two 150-mg tablets) bid

bid, twice daily; BRCA, breast cancer susceptibility gene; CR, complete response; FDA, US Food and Drug Administration; IV, intravenous; g, germline; L, line; mut, mutation; PR, partial response; q3w, every 3 weeks; s, somatic.

1. Bevacizumab package insert. Genentech, Inc; June 2018. **2.** Olaparib package insert. AstraZeneca Pharmaceuticals LP; December 2018.

Select Phase 2/3 Studies on 1L Maintenance Therapy in Ovarian Cancer

Study Name	NCT Identifier	Ph	Description	Specific Biomarker Status Required?	Primary Endpoint(s)	Est. Primary Completion Date
VELIA / GOG-3005	NCT02470585	3	Carboplatin/paclitaxel + veliparib Followed by maintenance veliparib	No	PFS	Apr 2019
PRIMA	NCT02655016	3	Maintenance niraparib following response on platinum-based chemotherapy	No	PFS	Feb 2020
OVARIO	NCT03326193	2	Maintenance niraparib + bevacizumab following response to platinum-based chemotherapy with bevacizumab	No	PFS rate at 18 mo	Dec 2020
JAVELIN OVARIAN PARP 100	NCT03642132	3	Platinum-based chemotherapy + avelumab Followed by maintenance avelumab + talazoparib	No	PFS	Feb 2022
DUO-O	NCT03737643	3	Chemotherapy + durvalumab + bevacizumab Followed by maintenance durvalumab + bevacizumab + olaparib	No	PFS in non-t*BRCA*^{mut} patients	May 2022
PAOLA-1	NCT02477644	3	Platinum/taxane chemotherapy + bevacizumab Followed by maintenance bevacizumab plus olaparib	No	PFS	Jun 2022
ATHENA	NCT03522246	3	Maintenance rucaparib + nivolumab following response to platinum-based chemotherapy	No	PFS	Dec 2024
ENGOT-ov43 / KEYLYNK-001	NCT03740165	3	Chemotherapy + pembrolizumab Followed by maintenance olaparib[a]	Yes: non-*BRCA*^{mut}	PFS, OS	Aug 2025

[a] Carboplatin/paclitaxel for 5 cycles, plus pembrolizumab for up to 35 cycles, plus olaparib starting cycle 7.

BRCA, breast cancer susceptibility gene; est., estimated; L, line; mut, mutation; OS, overall survival; PFS, progression-free survival; Ph, phase; t, tumor.

ClinicalTrials.gov: NCT02470585, NCT02655016, NCT03326193, NCT03642132, NCT03737643, NCT02477644, NCT03522246, NCT03740165. Accessed January 17, 2019.

Study Designs of Key PARPi Maintenance Therapy Trials in Recurrent Ovarian Cancer

	NOVA[1,2] (NCT01847274)	Study 19[3,4] (NCT00753545)	SOLO-2[5,6] (NCT01874353)	ARIEL3[7,8] (NCT01968213)
N	553	265	295	564
Phase	3	2	3	3
Design	Randomized, placebo-controlled, and with patients who have received ≥2 previous courses of platinum-containing therapy			
Patient population	Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; both g*BRCA*^{mut} and non-g*BRCA*^{mut} cohorts	Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	Platinum-sensitive relapsed high-grade serous ovarian, fallopian tube, or primary peritoneal cancer, or high-grade endometrioid cancer, with *BRCA1*^{mut} or *BRCA2*^{mut}	Platinum-sensitive relapsed high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancers
Dosage	Niraparib oral 300 mg daily until disease progression	Olaparib oral 400 mg bid until disease progression	Olaparib oral 300 mg (tablets) bid until disease progression	Rucaparib oral 600 mg bid until disease progression
1˚ Endpoint	PFS by RECIST			
Assessor of PFS	BICR or central clinical assessment	Investigator radiography assessment		
2˚ Endpoint	PRO, PFS2, time to subsequent therapy, OS, safety	OS, ORR, DCR, DOR, % change tumor size wk 24, best % change CA-125 levels, response, TTP, QoL	OS, TTP, PFS2, QoL, TFST, TSST, TDT, PFS patients with deleterious *BRCA* variant, PK	PFS by RECIST (BICR), QoL, OS, safety, PK
Stratification factors	TTP after completion of penultimate platinum regimen, prior treatment with BEV, best response during last platinum regimen	TTP on penultimate platinum therapy, objective response to last platinum regimen, ethnic descent	Response to previous platinum therapy, PFI	Response to previous platinum therapy, PFI, HR repair gene mutation status

BEV, bevacizumab; BICR, blinded independent central review; bid, twice daily; DCR, disease control rate; DOR, duration of response; g, germline; HR, homologous recombination; mut, mutation; ORR, objective response rate; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization to second progression; PK, pharmacokinetics; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TDT, time from randomization to treatment discontinuation or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death; TTP, time to progression.

1. ClinicalTrials.gov. NCT01847274. Accessed January 18, 2019. **2.** Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.
3. ClinicalTrials.gov. NCT00753545. Accessed January 18, 2019. **4.** Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92.
5. ClinicalTrials.gov. NCT01874353. Accessed January 18, 2019. **6.** Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84.
7. ClincialTrials.gov. NCT01968213. Accessed January 18, 2019. **8.** Coleman RJ, et al. *Lancet.* 2017;390(10106):1949-61.

Conclusion

- Molecular and immunotherapeutic targeted therapies in combination with chemotherapy for upfront treatment