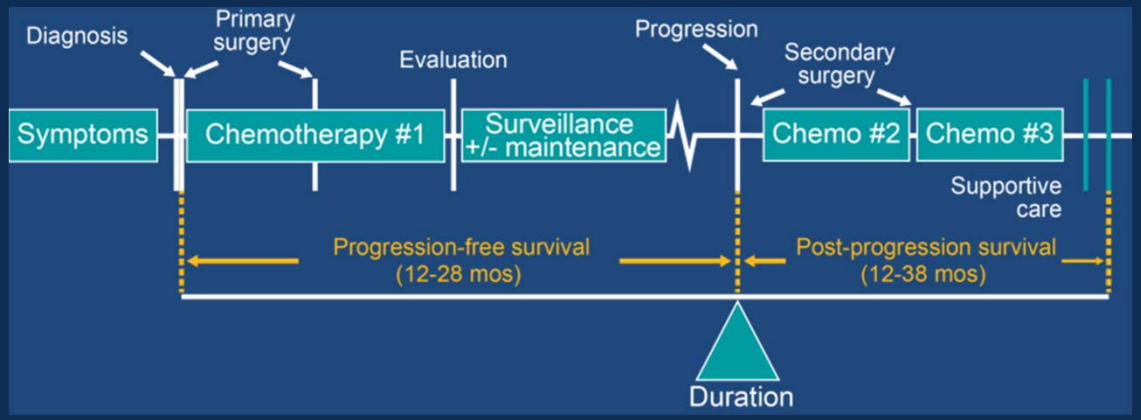
Phase I study of the safety and activity of formulated IL-12 plasmid administered intraperitoneally in combination with neoadjuvant chemotherapy in patients with newly diagnosed advanced stage ovarian cancer

P.H. Thaker, W. Bradley, C. A. Leath III, C. Gunderson,
N. Borys, K. Anwer, L. Musso, R. D. Alvarez

PRESENTED AT: 2019 ASCO-SITC Clinical Immuno-Oncology Symposium | #ImmunoOnc19

Treatment Landscape Overview for Advanced Ovarian Cancer



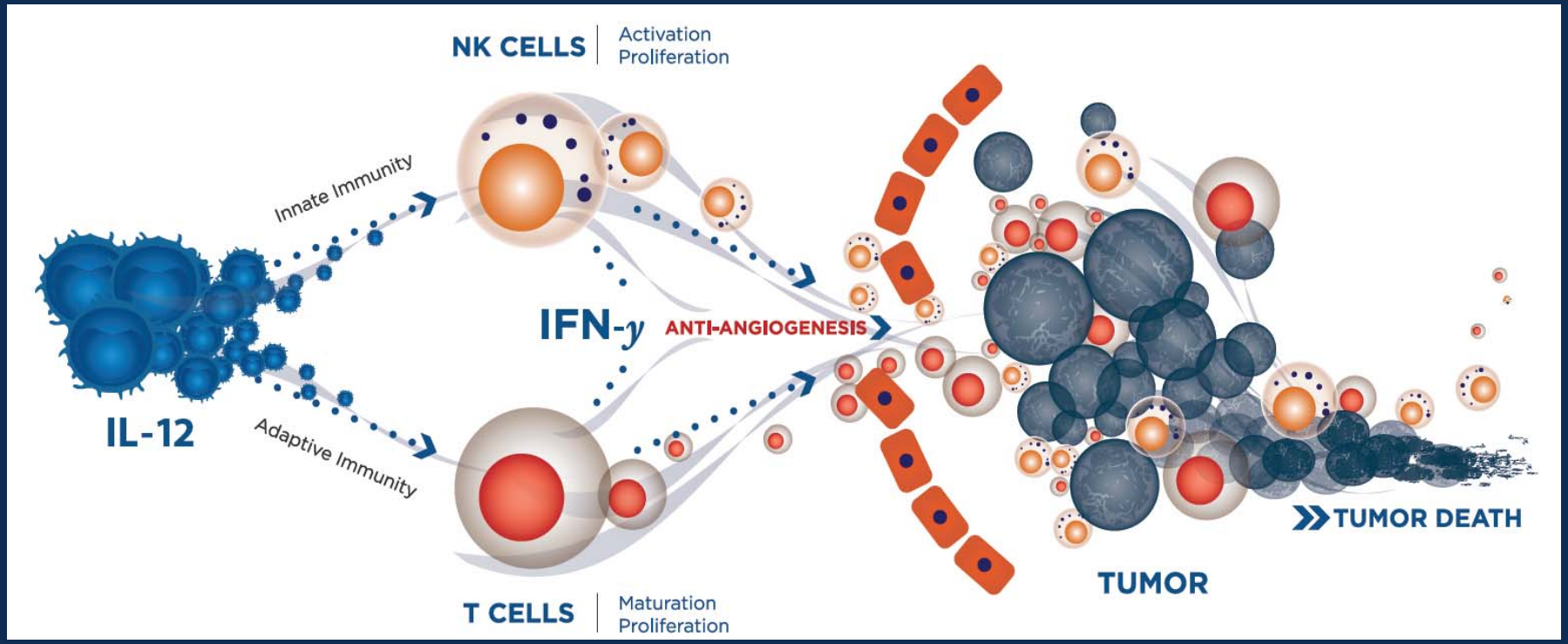
- Surgical goal is complete cytoreduction of all macroscopic visible disease[1]
- Standard adjuvant chemotherapy is an IV or IP taxane/platinum combination[1]
- Despite optimal upfront surgery and adjuvant chemotherapy, approximately 80% of patients will relapse[2]
- Unknowns: maintenance therapy, antiangiogenic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

EOC, epithelial ovarian cancer; IV, intravenous; IP, intraperitoneal.

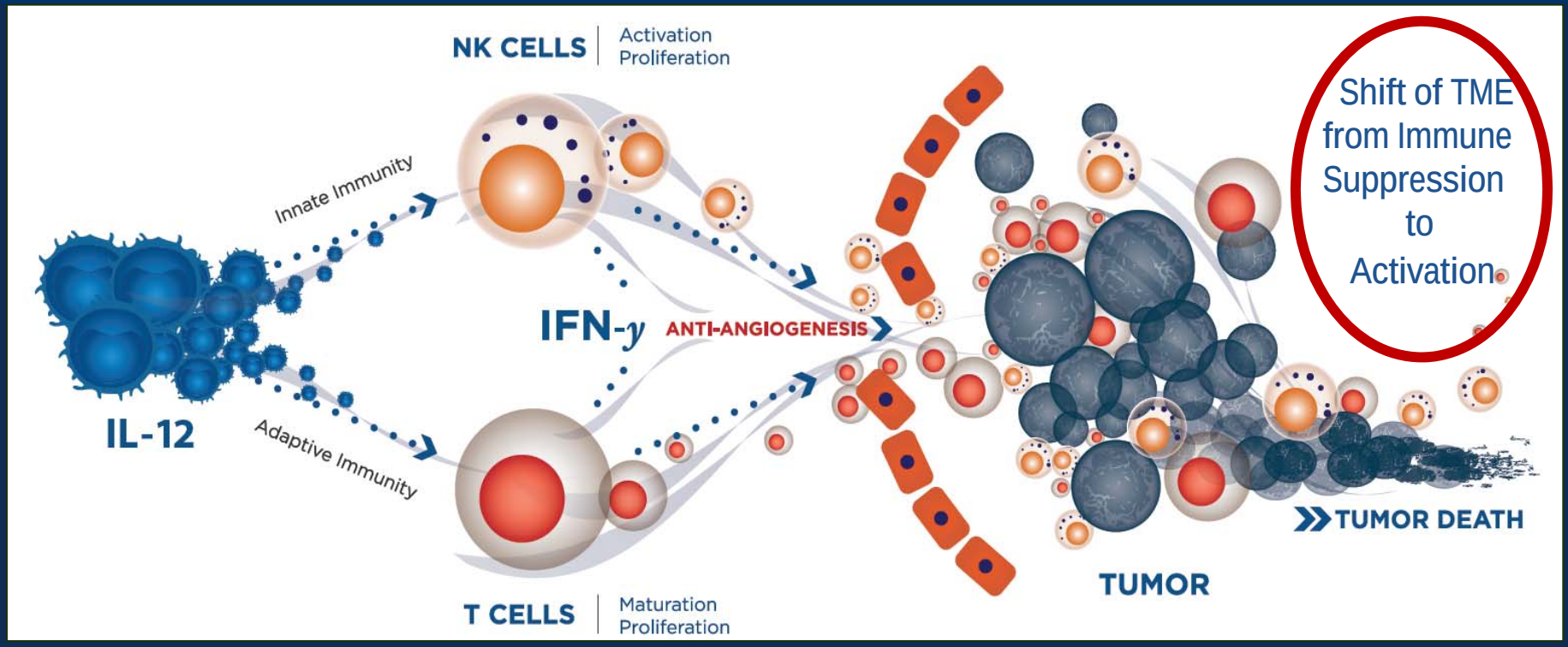
1. Ledermann et al. *Ann Oncol.* 2013;24 Suppl 6:vi24-32.
2. du Bois. *Cancer*. 2009;115(6):1234-44.

Presented by:

IL-12: Four Distinct Mechanisms of Action



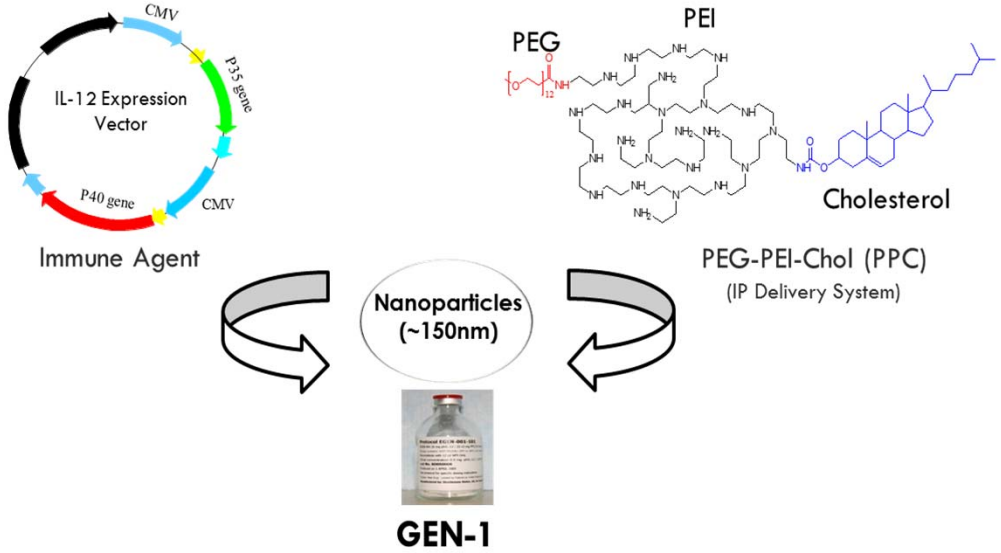
IL-12: Four Distinct Mechanisms of Action



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

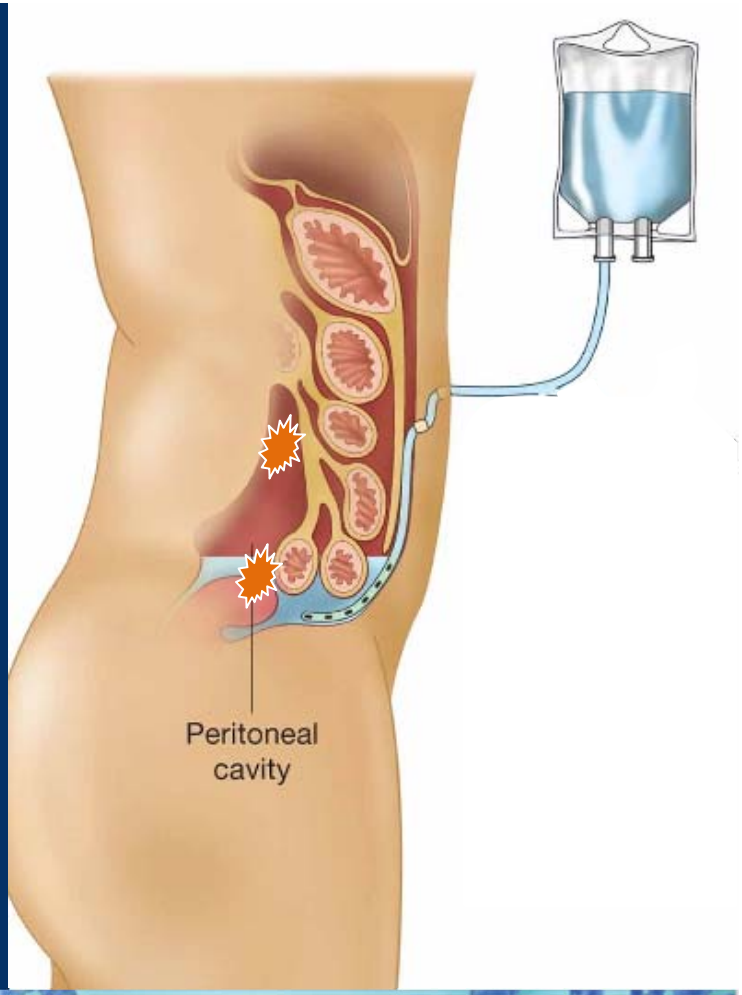


GEN-1 intraperitoneally (IP) produces durable local levels of IL-12 and related cytokines after a single injection and is delivered safely for several weeks for modulation of TME

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

GEN-1 Design Concepts

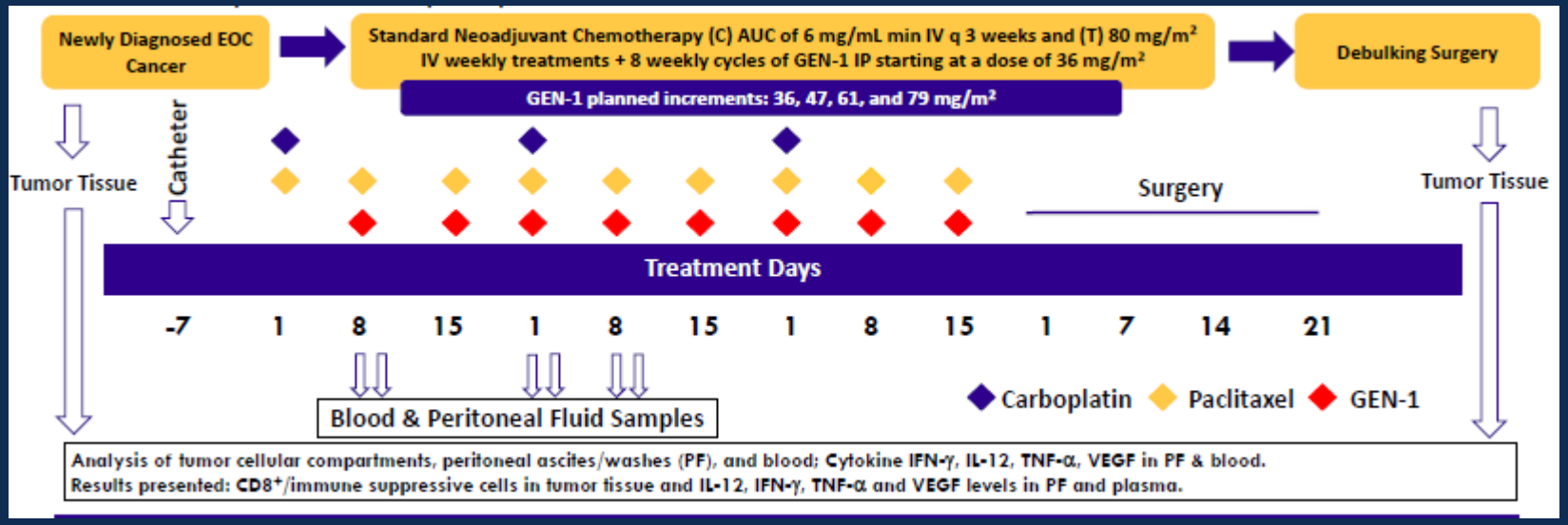
- PEI condenses DNA into nanoparticle to escape endosomes
- Cholesterol is designed to facilitate uptake by cellular membrane
- PEG improves *in vivo* stability (weekly dosing)



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



Study Endpoints

- To determine safety, feasibility and dose in targeted patient population
- Secondary Objective: pathological CR, PFS
- Translational Objectives: IFN-γ, 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)

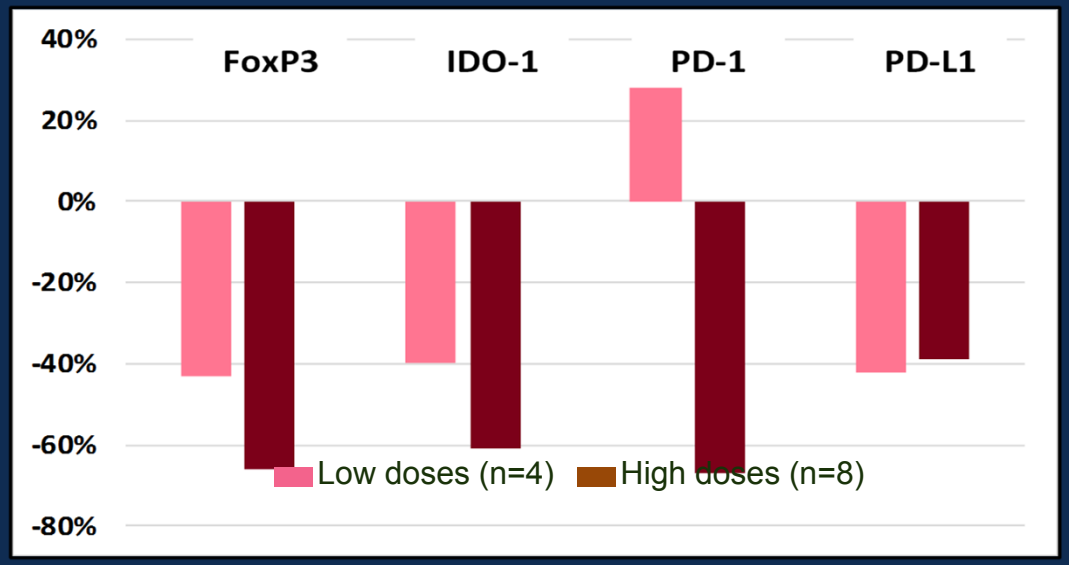
Response Data

Response		Total n	36 mg/m^2	47 mg/m^2	61 mg/m^2	79 mg/m^2
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 (n = 14)	cPR	1	1	0	0	0
	Micro	8	1	2	1	4
	Macro	5	1	1	2	1

Follow-up Data: PFS

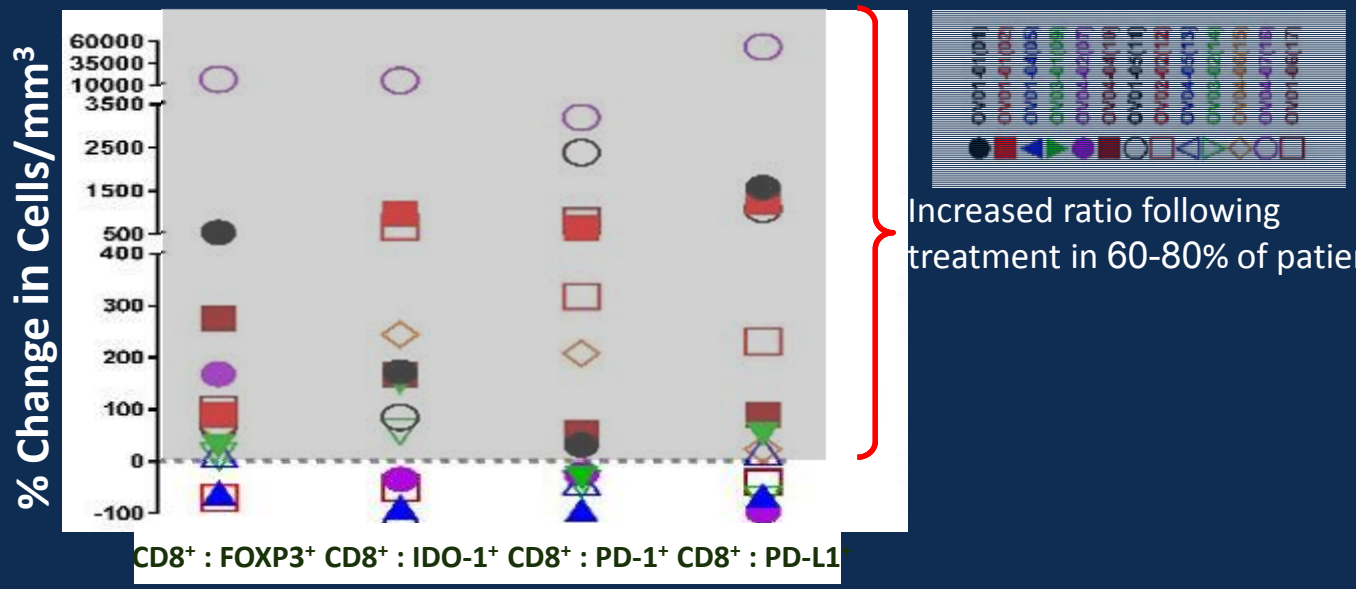
Patients	Stage	Largest tumor	PFS (months)
18 (ITT)	IIIC: 67% IV: 33%	150 mm	Median: 17.1 Range: .1 – 26.9
14 (Per Protocol)	IIIC: 71% IV: 29%	150 mm	Median: 21 Range: 9.3 – 26.9

Translational Data: Changes in TME



- Changes in immunosuppressive markers in response to low and high dose GEN-1
- Density of markers measured in tissue sections via immunohistochemistry staining

Ratio of CD8+ Cells to Immunosuppressive Cell Signals

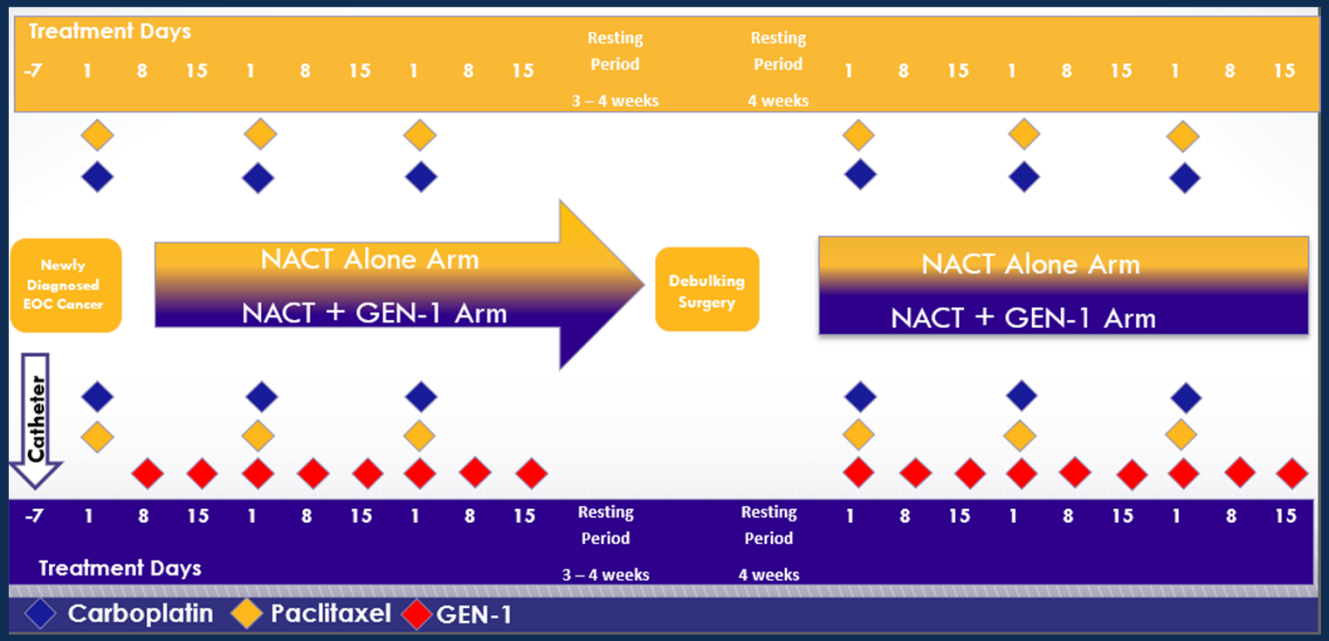


- Ratio of $CD8^+$ cells to FoxP3, IDO-1, PD-1 or PD-L1 T-cells in tumor sections counted
- % change in the ratio between pre- & post-treatment plotted

Conclusions

- Adding GEN-1 to doublet treatment is safe and appears to be active in EOC patients receiving NAC.
- Dose limiting toxicity was not reached.
- GEN-1 appears to change the tumor microenvironment.

OVATION 2



- Phase I/II randomized clinical trial for neoadjuvant stage III/IV ovarian cancer patients
- Primary Endpoint: PFS

OVATION Study Group

P.H. Thaker, Washington University School of Medicine
W. Bradley, Medical College of Wisconsin
C. A. Leath III, University of Alabama at Birmingham Hospital
C. Gunderson, Stephenson Cancer Center The University of Oklahoma
N. Borys, Celsion Corporation
K. Anwer, Celsion Corporation
L. Musso, Celsion Corporation
R. D. Alvarez, Vanderbilt University Medical Center

MEDICAL COLLEGE OF WISCONSIN

Washington University in St. Louis
SCHOOL OF MEDICINE

PRESENTED AT: 2019 ASCO-SITC Clinical Immuno-Oncology Symposium | #ImmunoOnc19