



OVARIAN CANCER

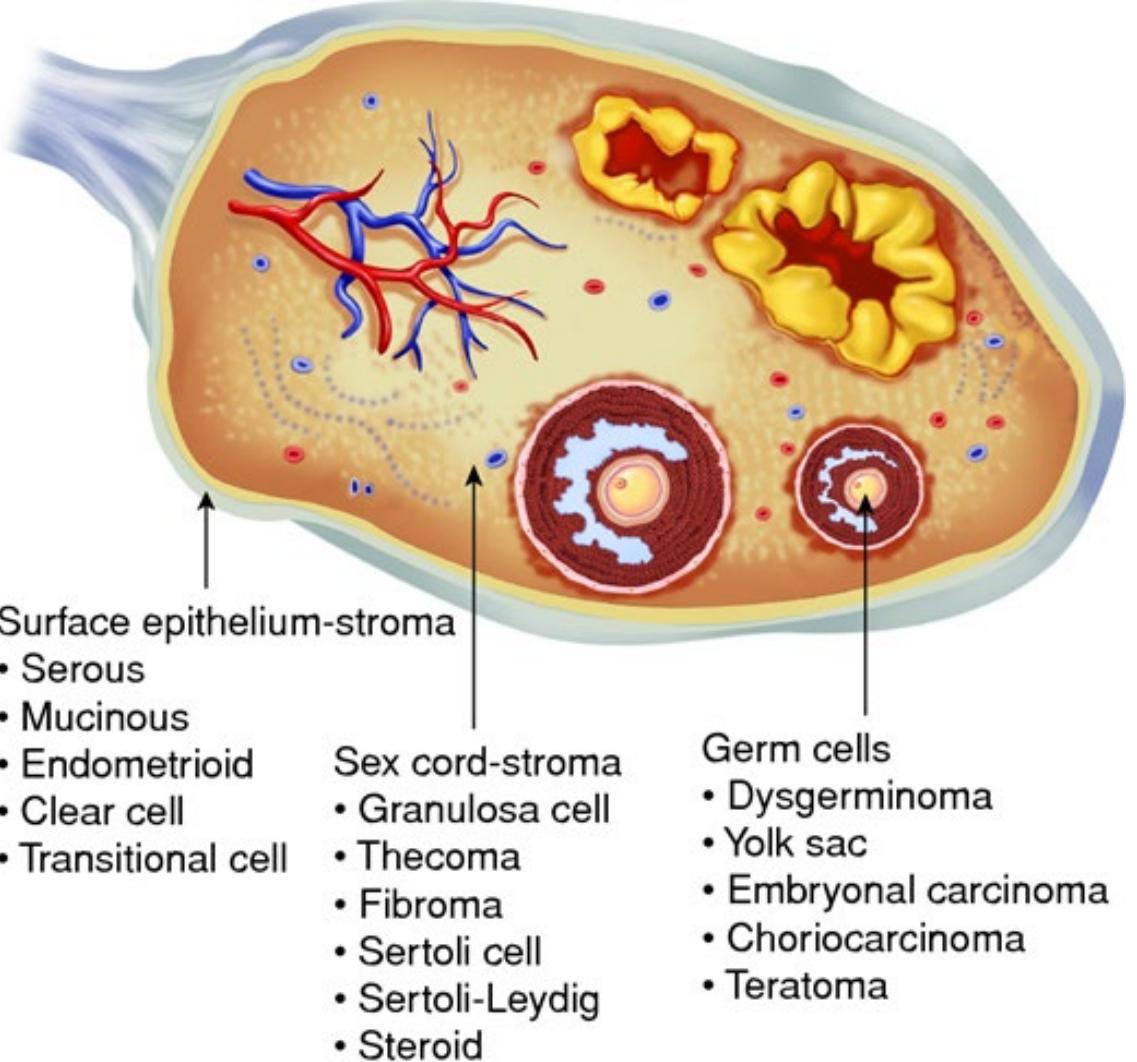
Krishnansu S. Tewari, MD, FACOG, FACS, FRSM

Professor with Tenure

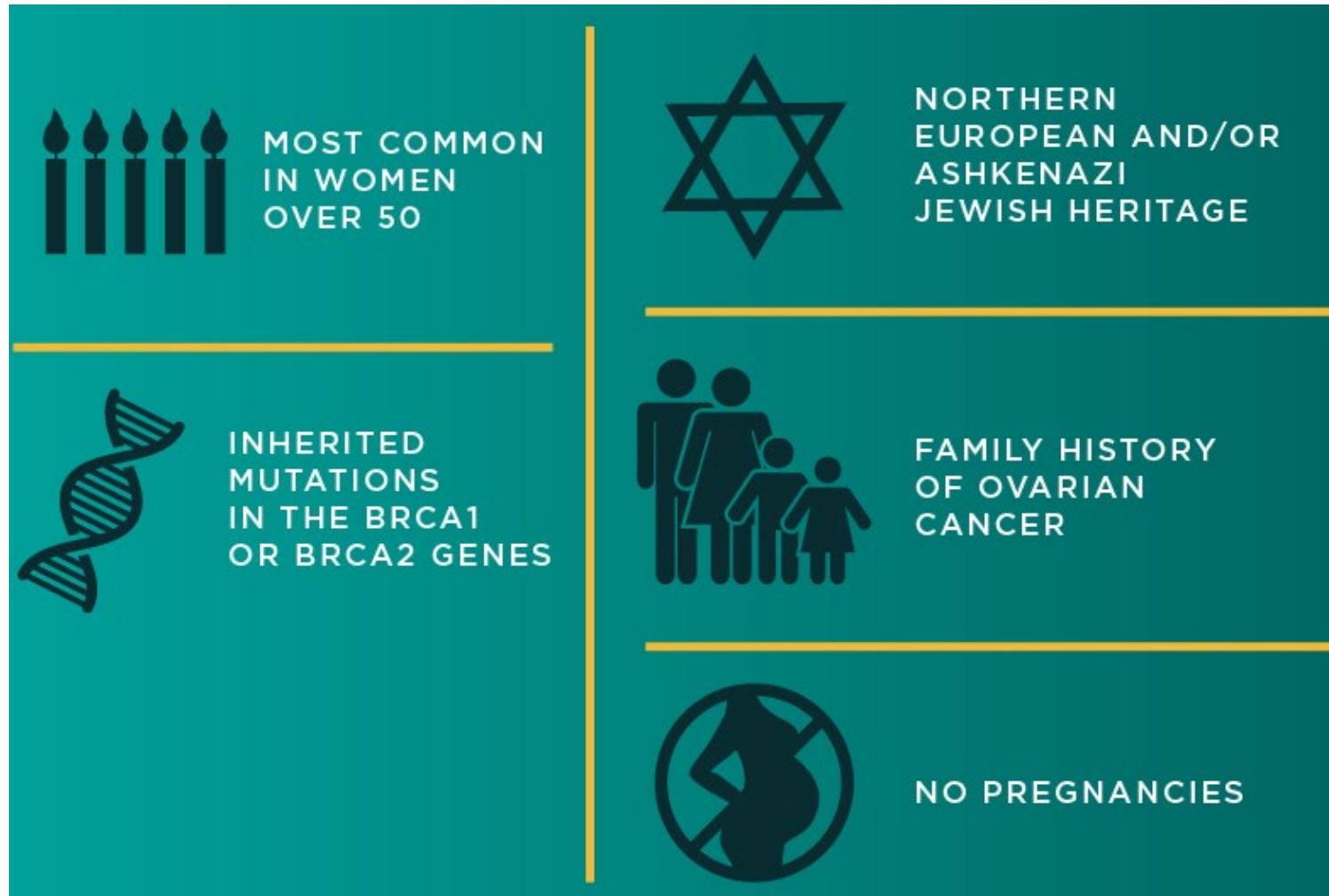
The Philip J. DiSaia, MD Endowed Chair in Gynecologic Oncology

University of California, Irvine

Principle Types of Ovarian Cancer



Risk Factors



FIGO Staging

Prat J. Int J Gynaecol Obstet 2014;123:1-5.

STAGE I: Tumour confined to ovaries

IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings
IB	Tumour involves both ovaries otherwise like IA

IC: Tumour limited to 1 or both ovaries

IC1	Surgical spill
IC2	Capsule rupture before surgery or tumour on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings

STAGE II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues

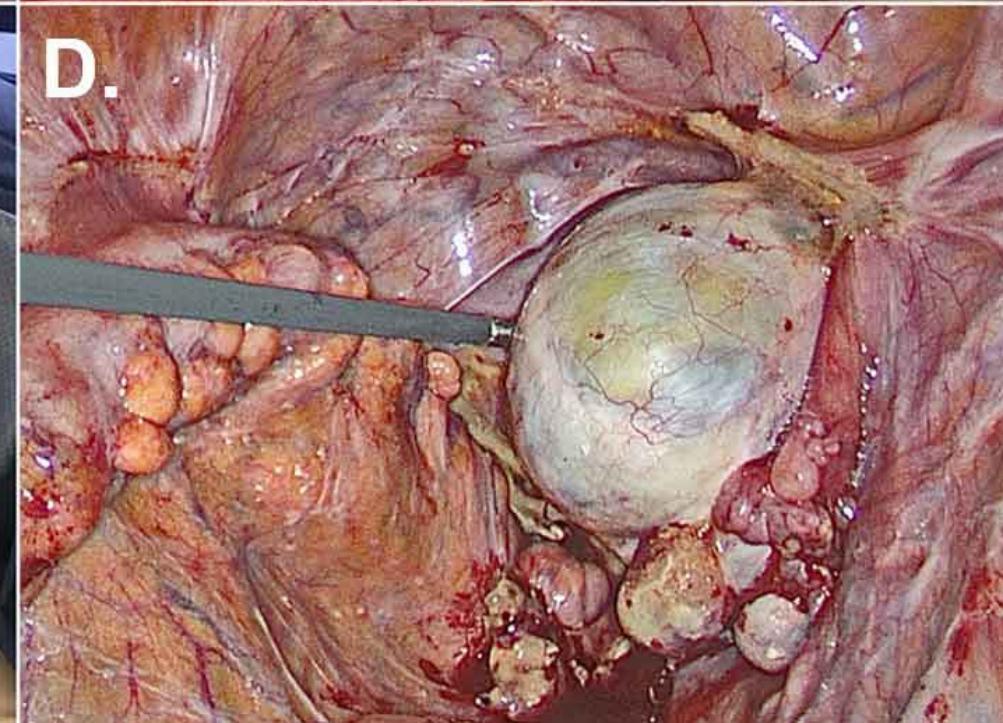
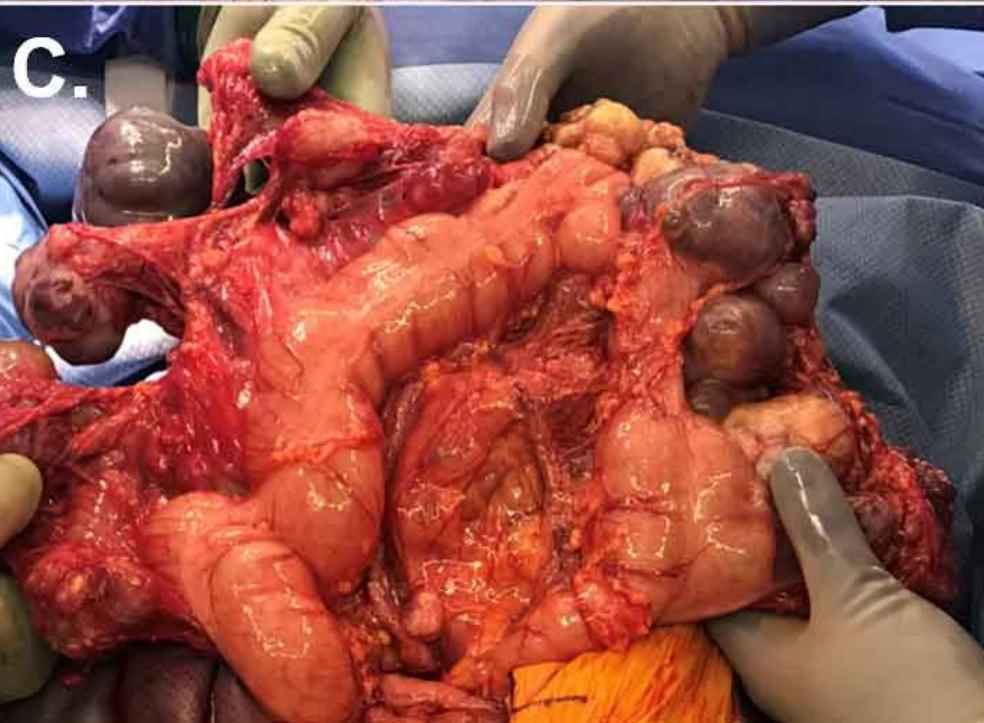
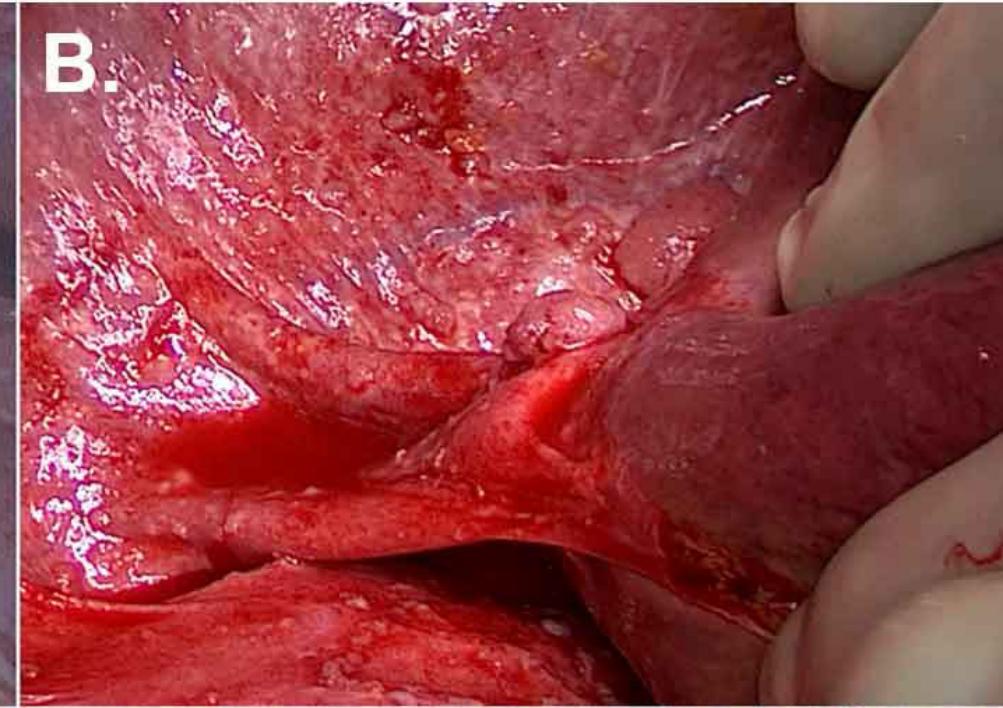
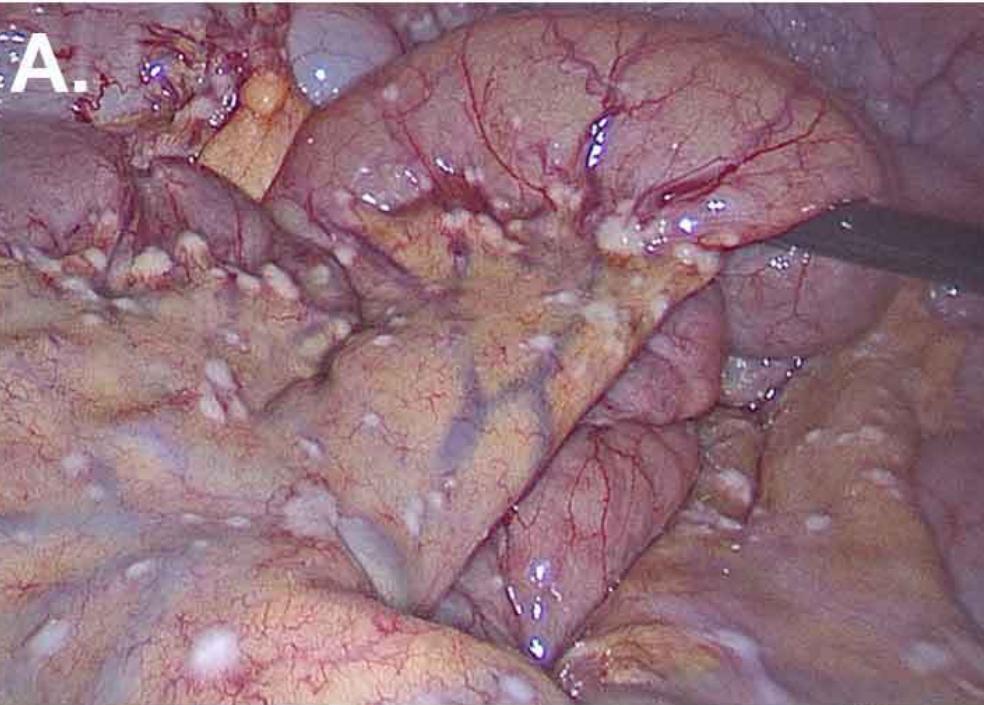
STAGE III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)

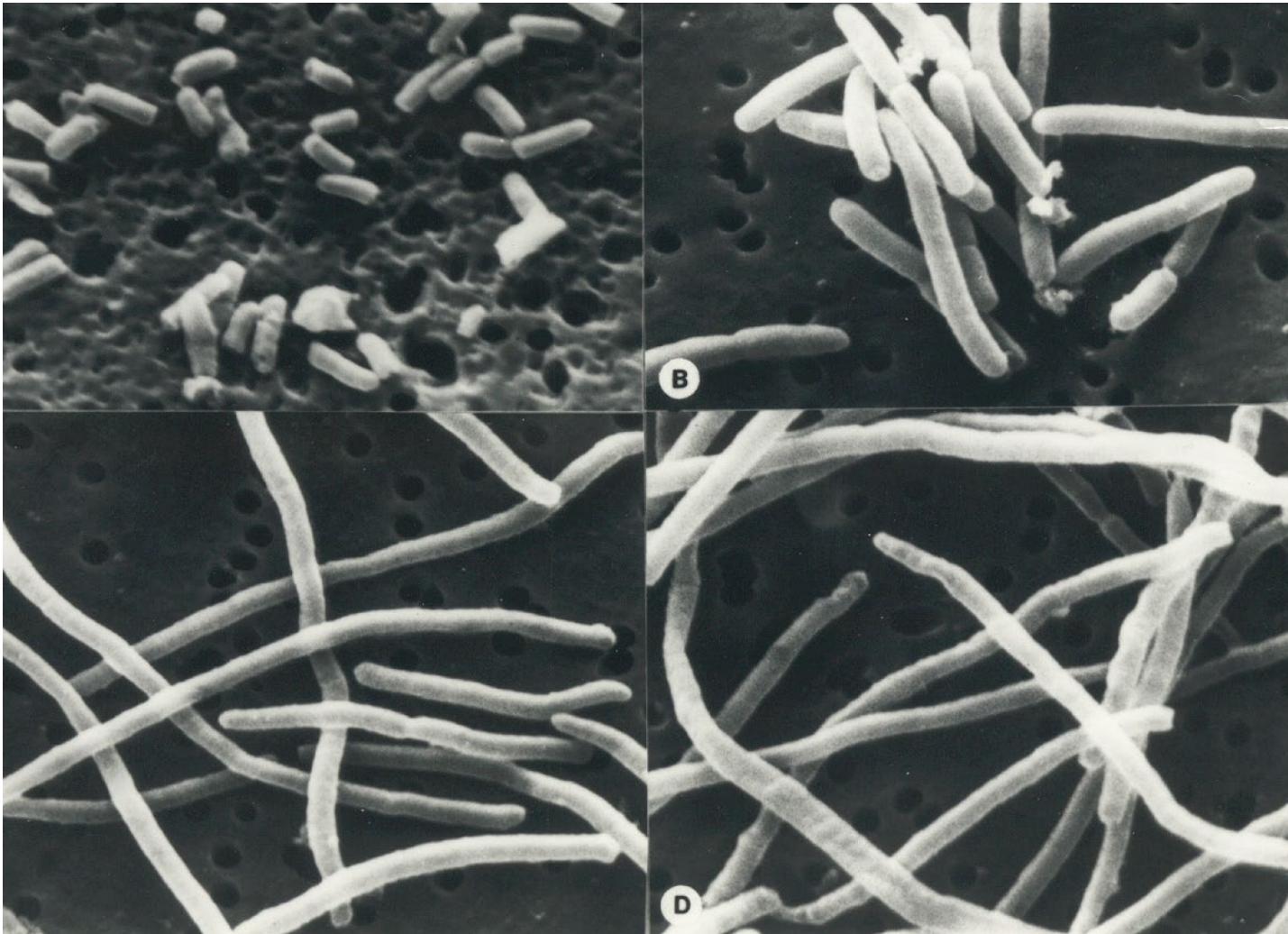
IIIA1	Positive retroperitoneal lymph nodes only	
	IIIA1(i)	Metastasis ≤ 10 mm
IIIA1 (ii)		Metastasis > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	

STAGE IV: Distant metastasis excluding peritoneal metastasis

IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)



Chemotherapy Drug #1: Platinum

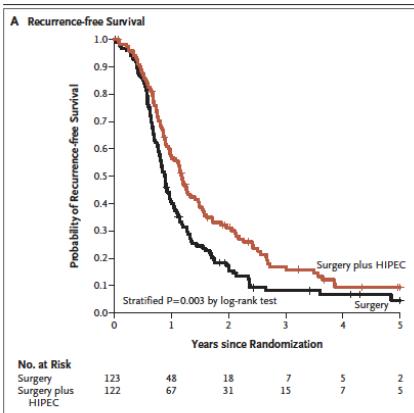


Chemotherapy Drug #2: Paclitaxel



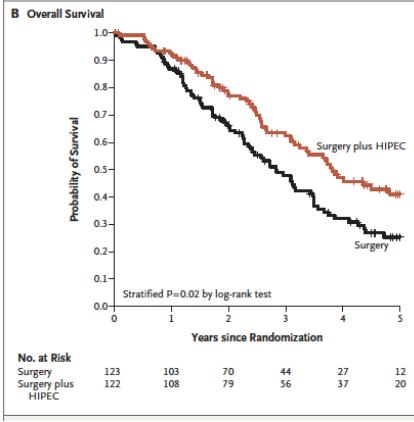
Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Netherlands Study (NCT00426257): van Driel WJ, et al. N Engl J Med 2018;378:230-40.

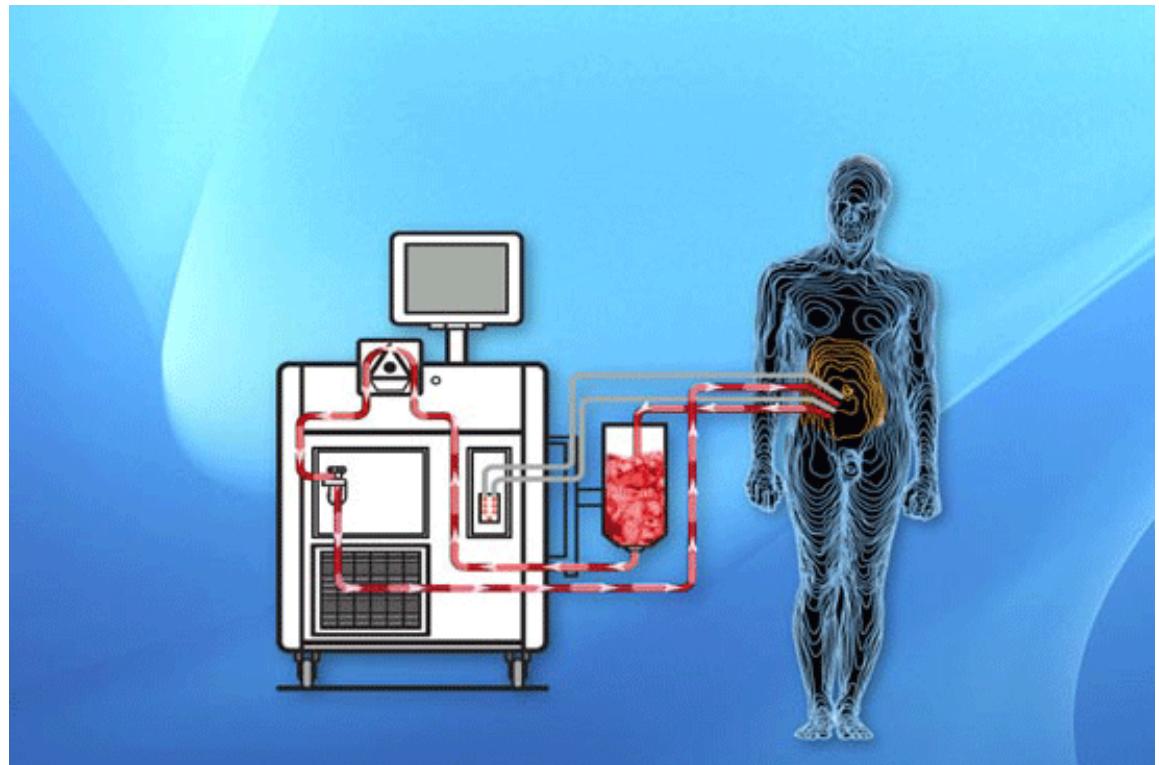


All patients: Neoadjuvant ChemoRx
Randomized at surgery if optimal or complete resection
CDDP 100 mg/m² 40°C (104°F) 1 L/min 90-min infusion
Post-op IV ChemoRx 3 cycles
G3/4 Toxicity similar between groups

Median recurrence-free survival 10.7 vs 14.2m (HIPEC)
HR 0.66; 95% CI, 0.50-0.87; p=0.03



Median OS: 33.9 vs 45.7m (HIPEC)
HR 0.67; 95% CI, 0.48-0.94; p=0.02
G3/4 Toxicity similar between groups





Primary cytoreduction vs
neoadjuvant chemotherapy



Time from
surgery to
initiation of
systemic
therapy



Intraperitoneal
chemotherapy



Dose-dense
therapy



Heated
intraoperative
chemotherapy
(HIPEC)



Incorporation
of targeted
therapy



VEGF inhibition
Synthetic
lethality
Checkpoint
blockade
Novel
combinations

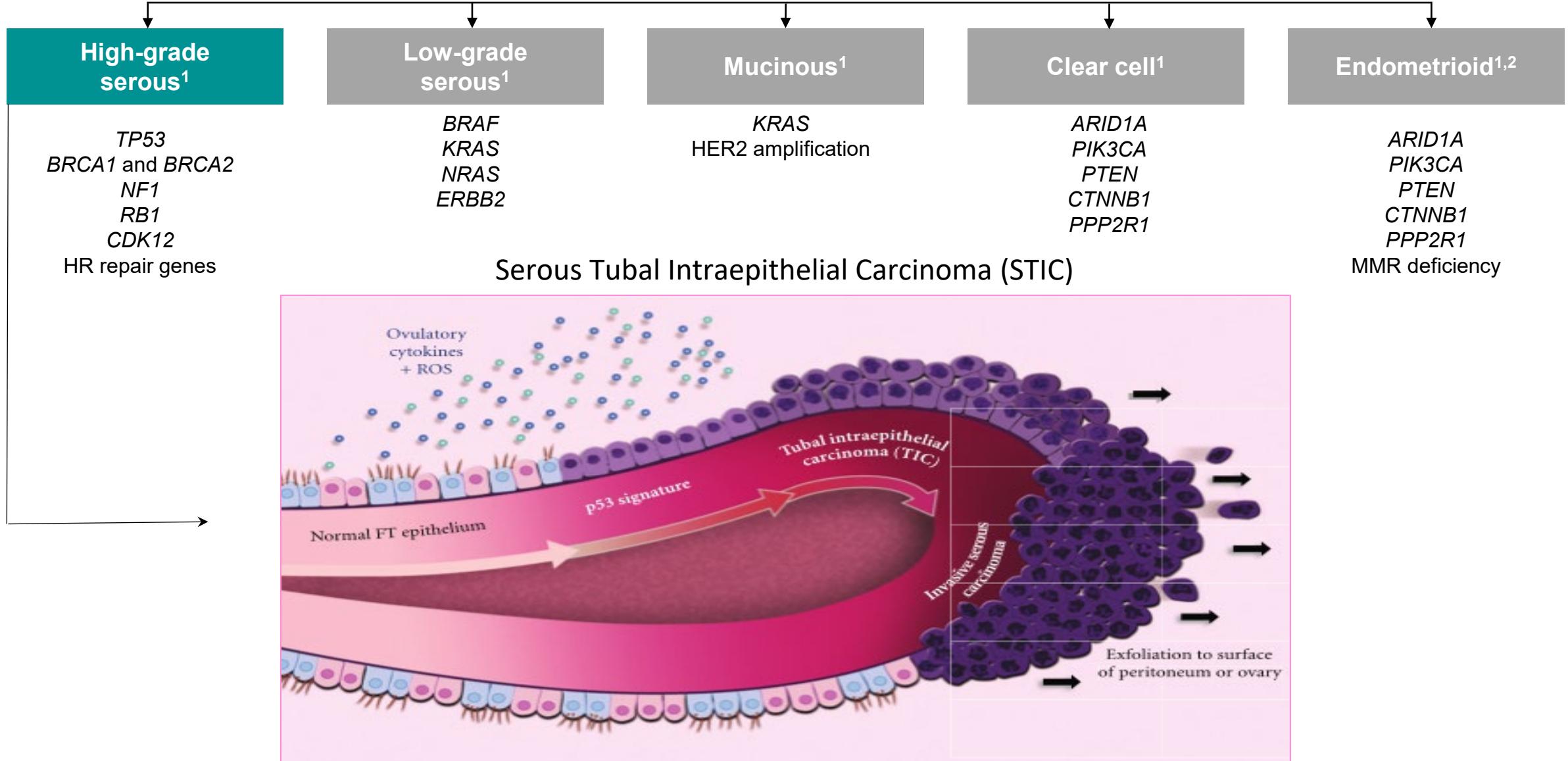
Key Research Questions



Prospectively Validated
PREDICTIVE BIOMARKERS

The Holy Grail

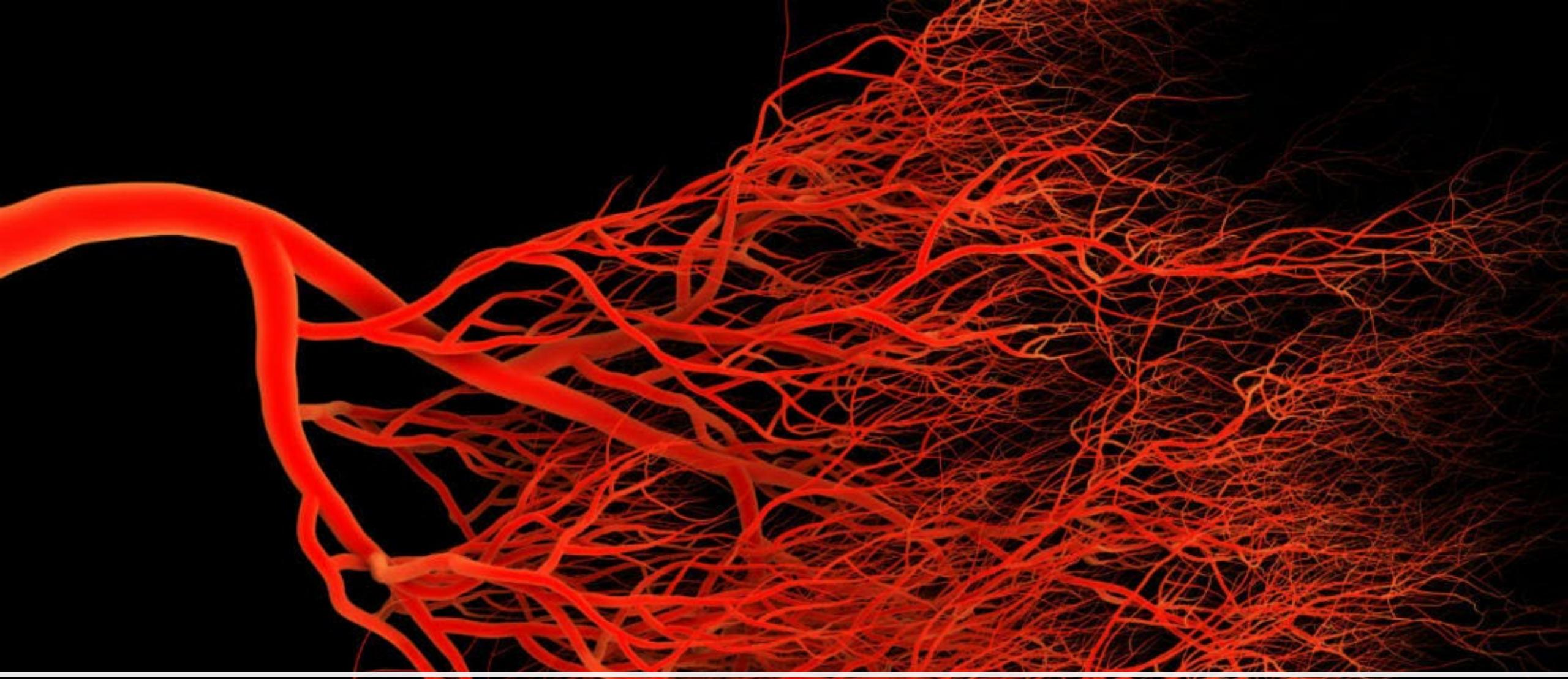
Epithelial Ovarian Cancer





Effective and Tolerable
MAINTENANCE THERAPY

Another Grail Quest

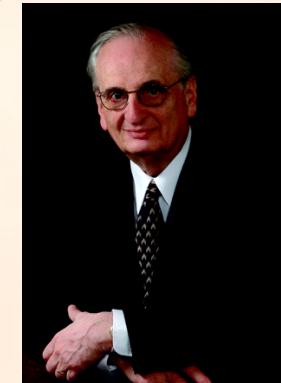


Tumor Angiogenesis



Moses Judah Folkman
Tumor Angiogenesis

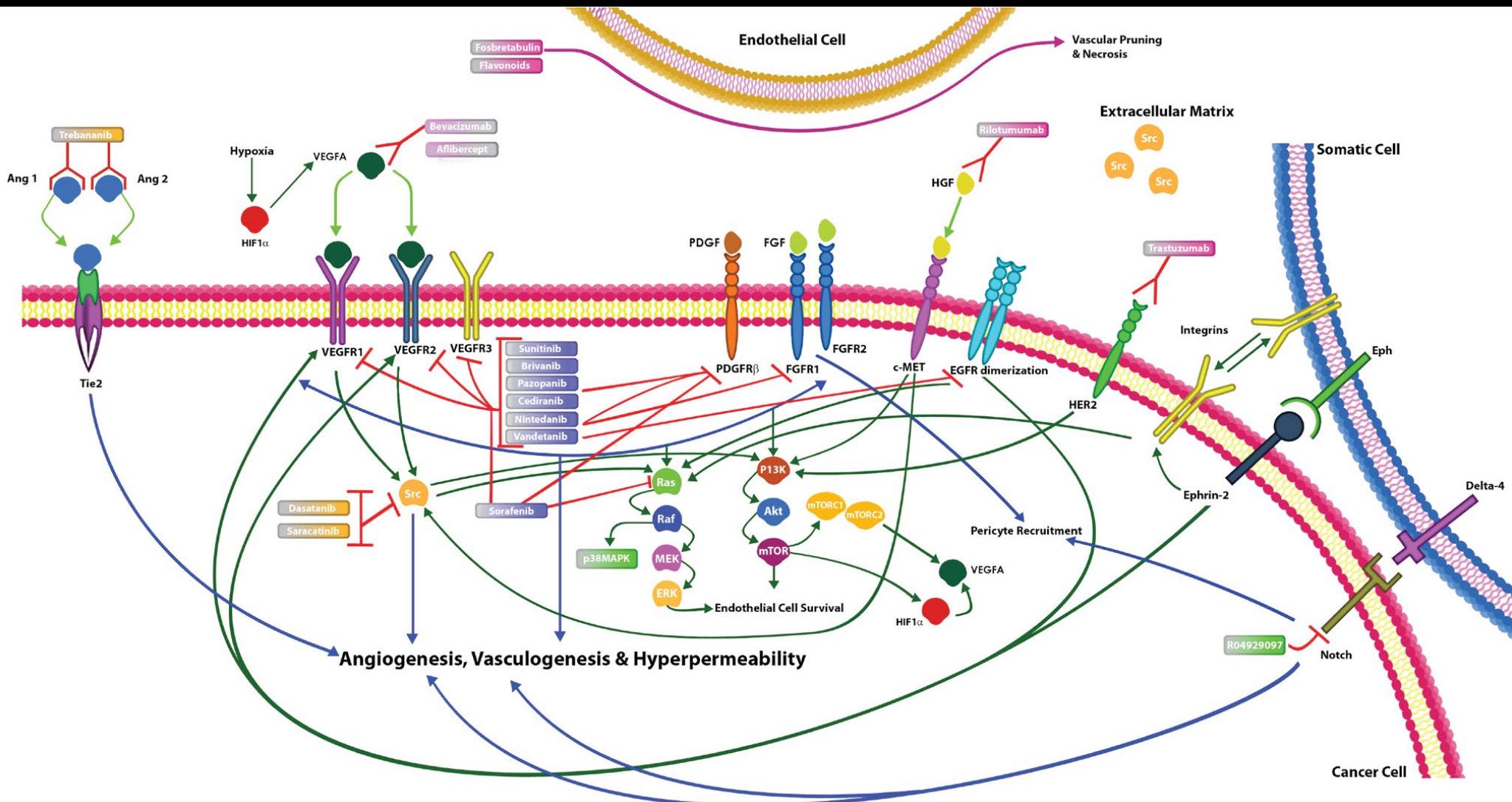
Folkman J. N Engl J Med 1971;285:1182-6.



1933-2008

The Angiogenesis Map

Liu FW, Cripe J, Tewari KS. Oncology 2015;29: 350-60.



9 Positive Phase 3 Randomized Trials Anti-Angiogenesis Therapy for Ovarian Carcinoma

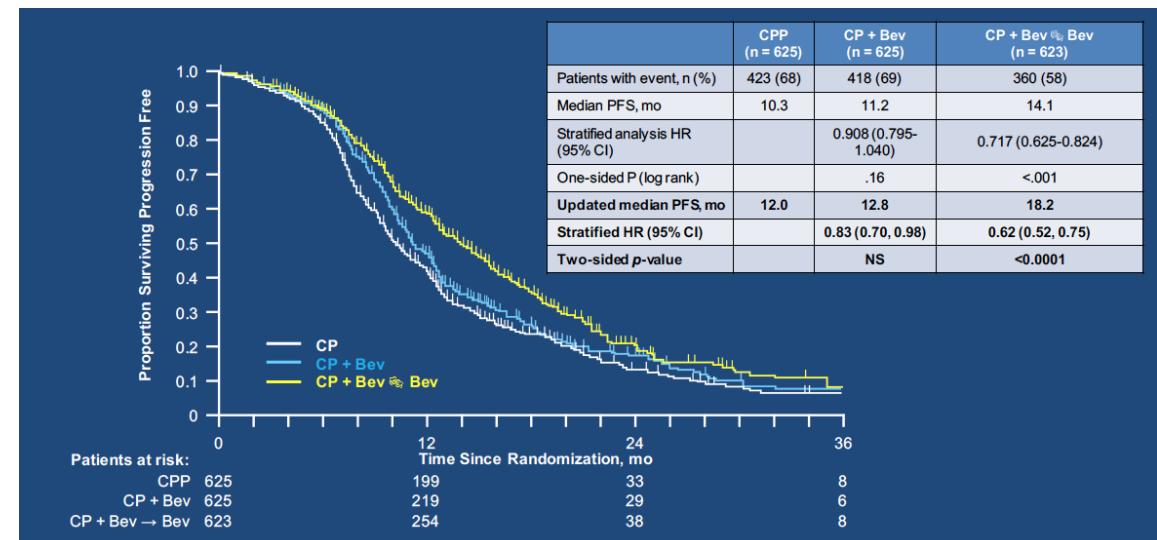
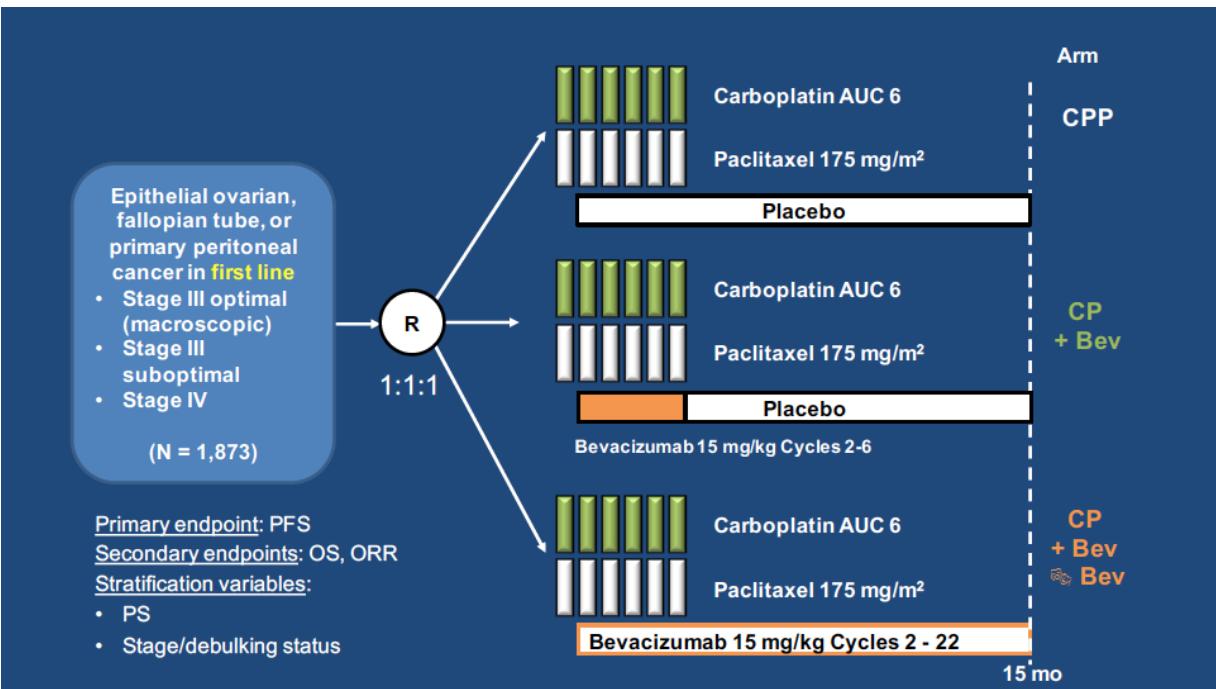
Eskander RN, Tewari KS. Gynecol Oncol 2014;132:496-505.

Study	Agent	Target	HR-PFS (95% CI)	HR-OS (95% CI)
GOG-0218	Bevacizumab	VEGF Ligand	0.72 (0.63-0.82)	0.89 (0.75-1.04)
ICON-7			0.81 (0.70-0.94)	0.99 (0.85-1.14)
AURELIA			0.48 (0.38-0.60)	0.85 (0.66-1.08)
OCEANS			0.53 (0.41-0.70)	0.96 (0.76-1.21)
GOG-0213			0.61 (0.52-0.72)	0.82 (0.68-0.99)
AGO-OVAR-12	Nintedanib	VEGFR, FGFR, PDGFR	0.84 (0.72-0.98)	NR
AGO-OVAR-16	Pazopanib		0.77 (0.64-0.91)	0.99 (0.75-1.32)
ICON-6	Cediranib	VEGFR	0.57 (0.44-0.74)	0.70 (0.51-0.99)
TRINOVA-1	Trebananib	Ang ligand	0.66 (0.57-0.77)	0.86 (0.69-1.08)

GOG-0218

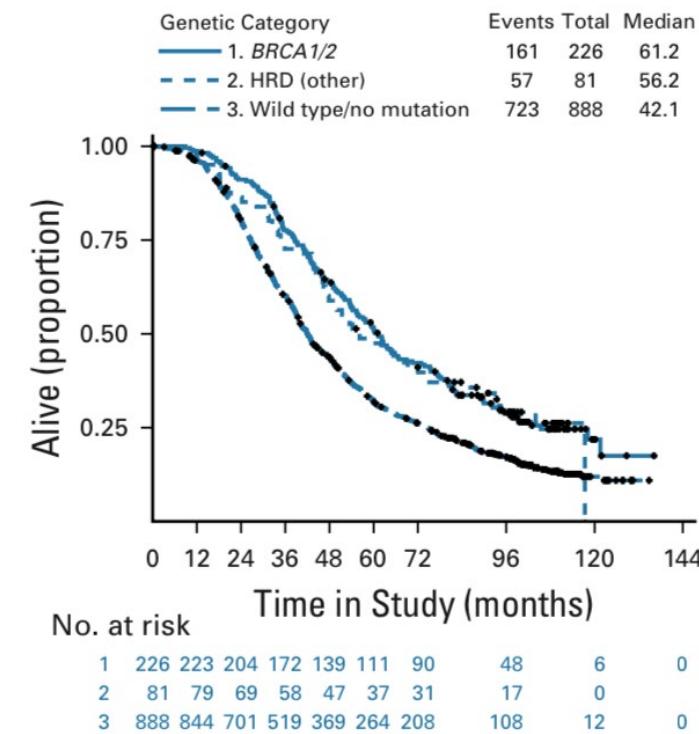
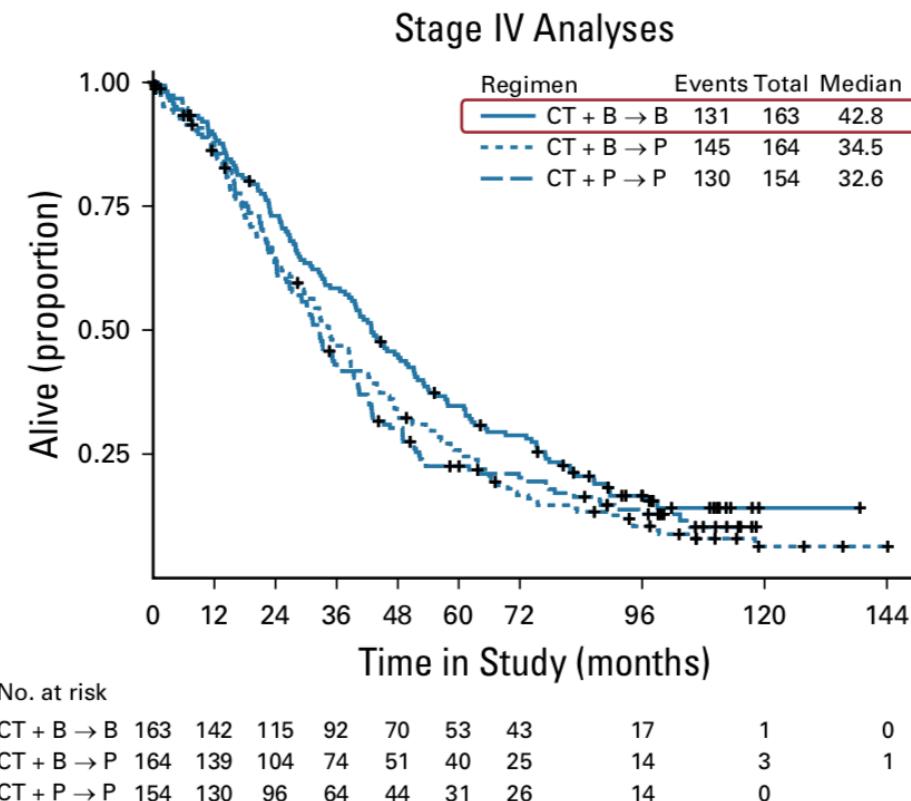
Newly Diagnosed Advanced Ovarian Cancer

Burger RA, et al. N Engl J Med 2011;365:2473-83.



GOG-0218 – Stage IV and BRCA/HRD

Tewari KS, et al. J Clin Oncol 2019;37:2317-28.



FDA approves bevacizumab in combination with chemotherapy for ovarian cancer

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On June 13, 2018, the Food and Drug Administration approved bevacizumab (Avastin, Genentech, Inc.) for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for stage III or IV disease after initial surgical resection.

Content current
06/13/2018

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Drug Products with
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Approval was based on GOG-0218 (NCT00262847), a multicenter, randomized, double-blind, placebo-controlled, three-arm study evaluating the addition of bevacizumab to carboplatin and paclitaxel for patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection. Patients (n=1,873) were randomized (1:1:1) to carboplatin plus paclitaxel without bevacizumab, carboplatin plus paclitaxel with bevacizumab for up to six cycles, or carboplatin plus paclitaxel with bevacizumab for six cycles followed by single-agent bevacizumab for up to 16 additional doses. Bevacizumab was administered at 15 mg/kg intravenously every three weeks. On this trial, 1,215 patients received at least one bevacizumab dose.

Bevacizumab Adverse Events of Interest

- **Black Box Warnings**
 - Gastrointestinal wall disruption/perforation: 0.3-3% incidence
 - Surgery and wound healing:
 - d/c > 28 days prior to surgery;
 - resume > 28 days after surgery and when wound fully healed
 - Hemorrhage – hemoptysis, epistaxis, GI, CNS, vaginal
- **Also:**
 - Hypertension
 - Proteinuria
 - Venous thromboembolism



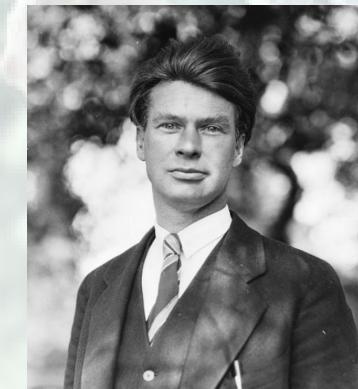
Synthetic Lethality & PARP Inhibition



Calvin Blackman Bridges

Synthetic Lethality

Bridges CB. American Naturalist 1922;56:51-63.



1889-1938



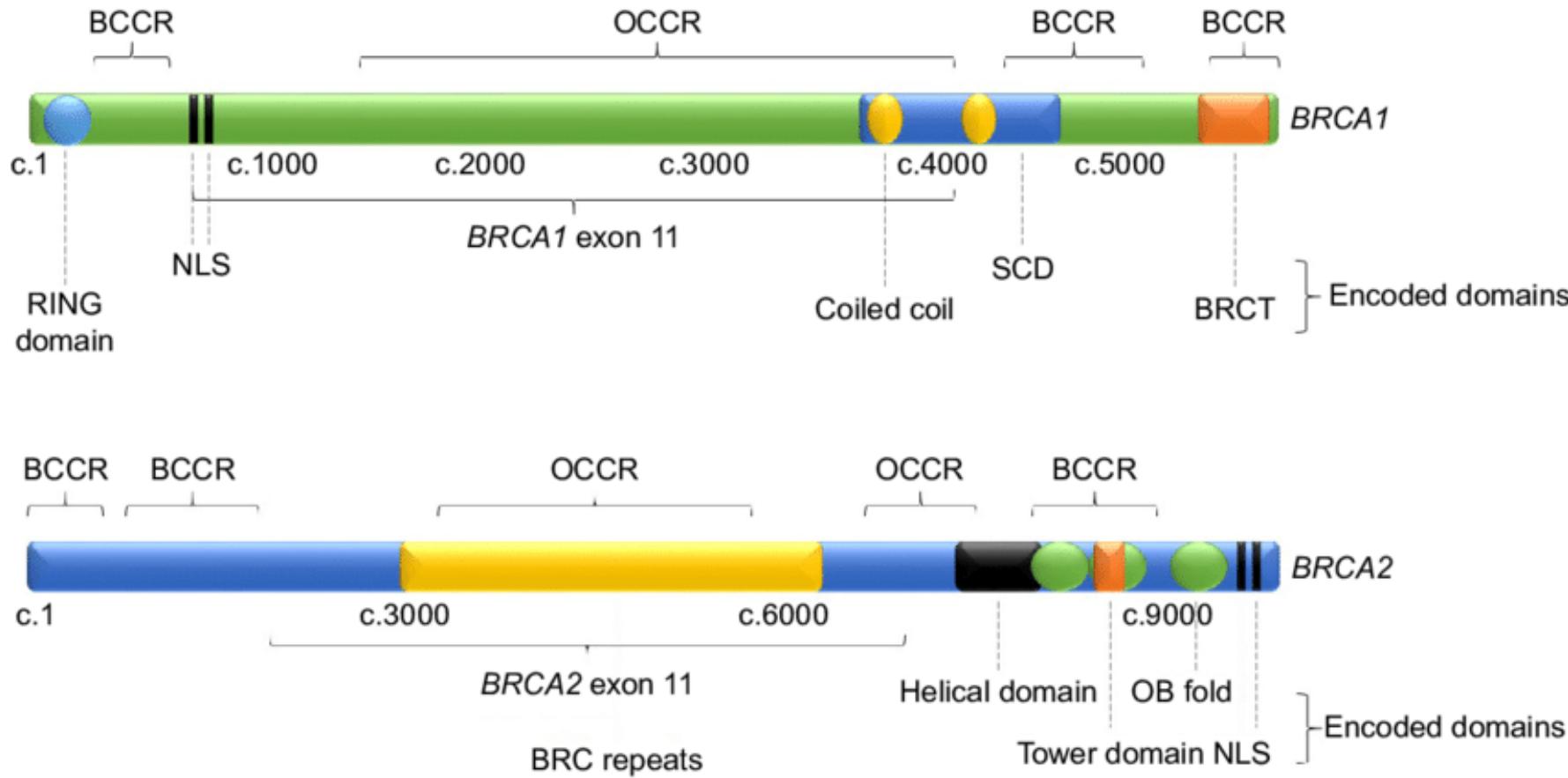
Mary-Claire King
Discovery of *BRCA1*

Hall JM, et al. Science 1990;250:1684-9.



b. 1946

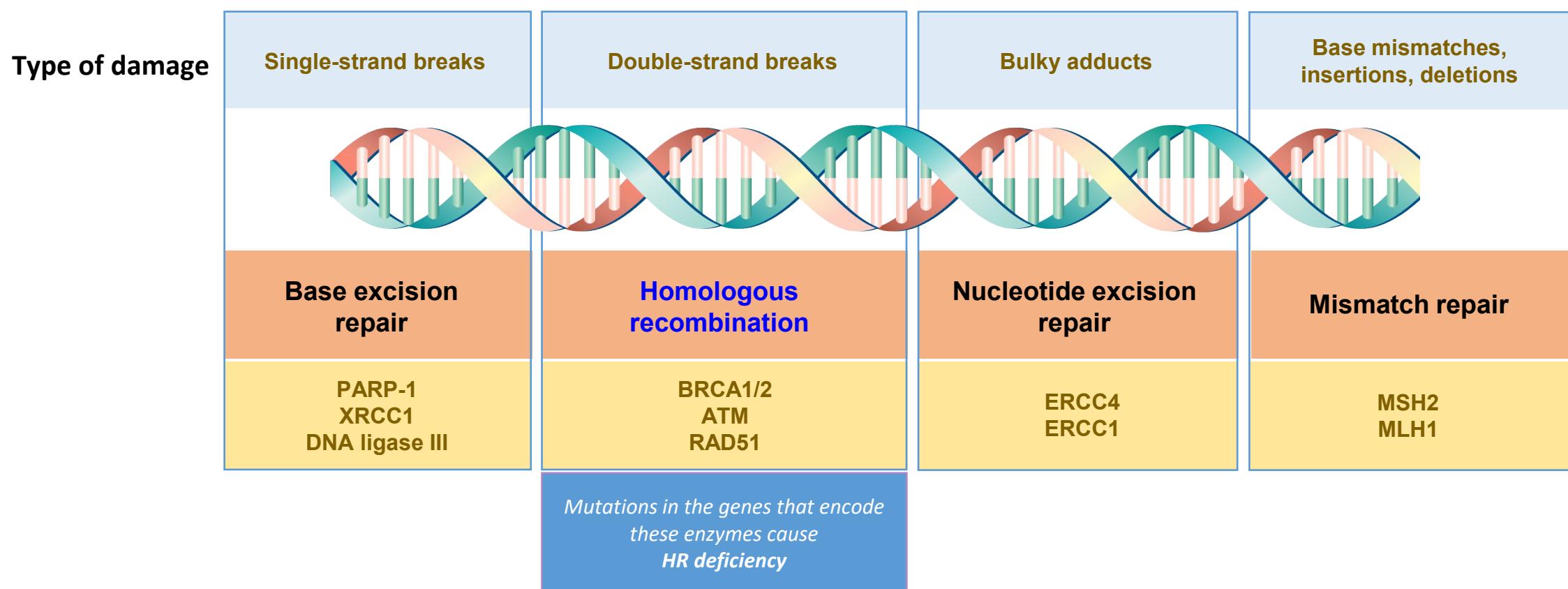
BRCA1
BRCA2



DNA Repair Mechanisms

Lord CJ, et al. Nature 2012;481:287-94.

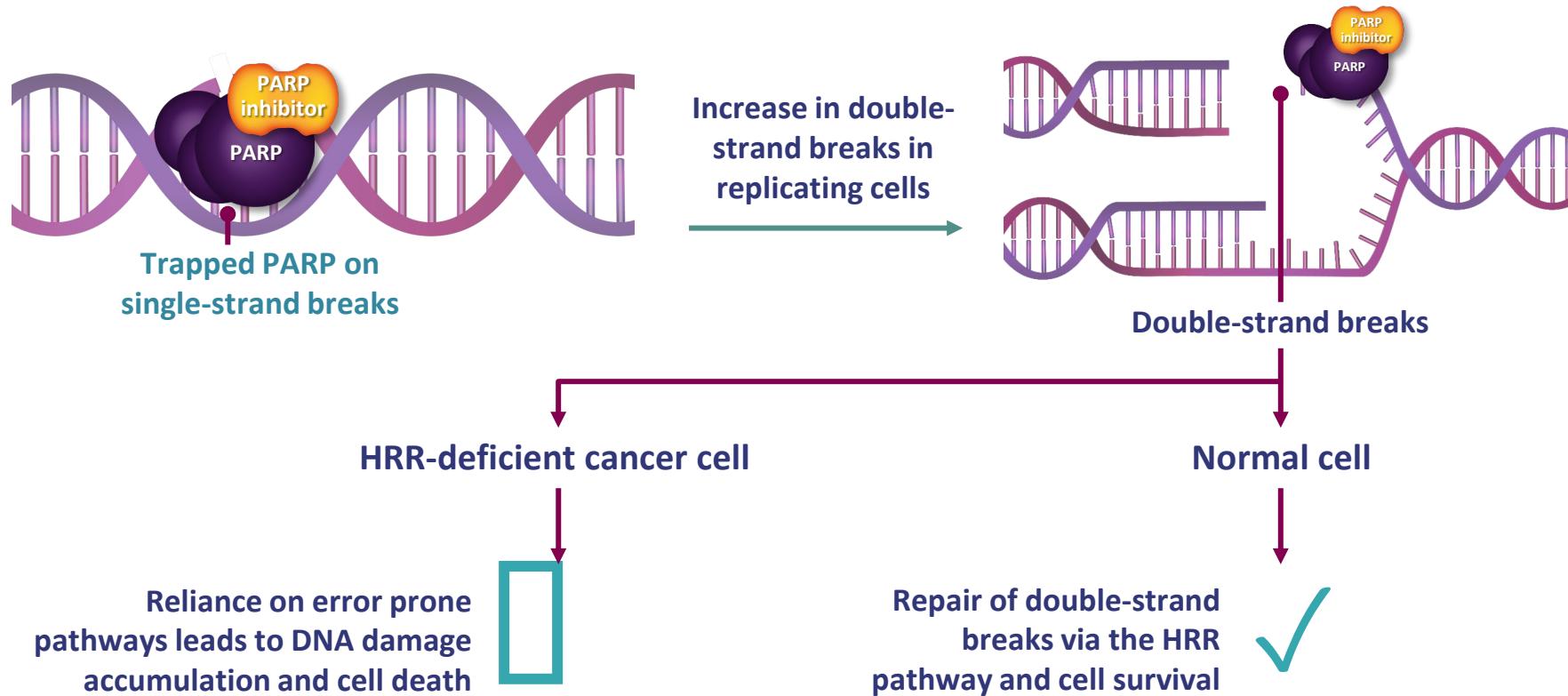
Sehl ME, et al. Clin Cancer Res 2009;15:2192-203.



PARP Inhibitors Induce Synthetic Lethality in Patients with HRD

Sonnenblick A, et al. Nat Rev Clin Oncol 2015;12:27-41.

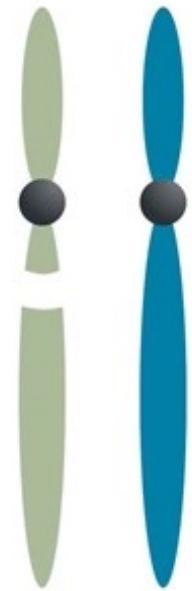
O'Connor MJ. Mol Cell 2015 2015;60:547-60.



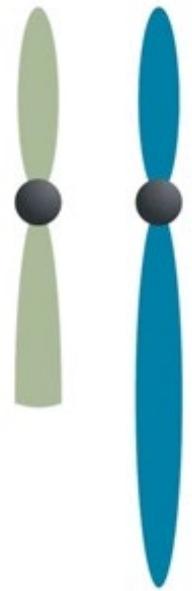
Genomic Scars

Biomarkers for Homologous Recombination Deficiency

Watkins JA, et al. Breast Cancer Res 2014;16:211. doi:10.1186/bcr3670.



**Loss of
heterozygosity
(LOH)**

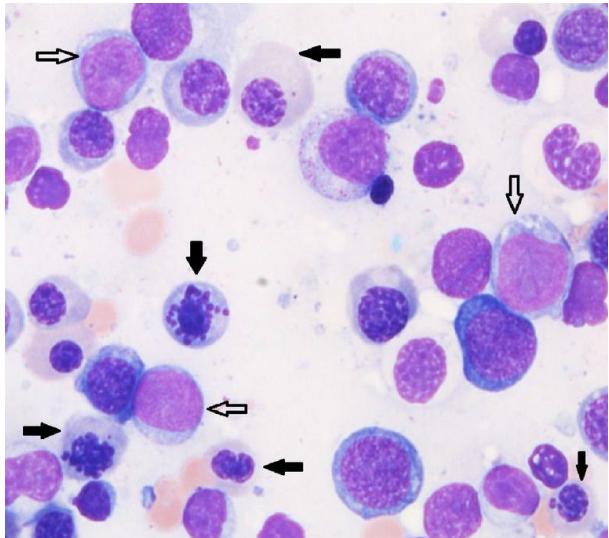


**Telomeric allelic
imbalance (TAI)**



**Large-scale state
transitions (LST)**

PARP Inhibitors *Adverse Events of Interest*



Myelodysplastic syndrome (MDS)/
Acute myeloid leukemia (AML)
0.5-2% incidence



Hematologic

Anemia

Thrombocytopenia



Gastrointestinal

Dyspepsia

Nausea

Diarrhea



Other

Fatigue

Asthenia

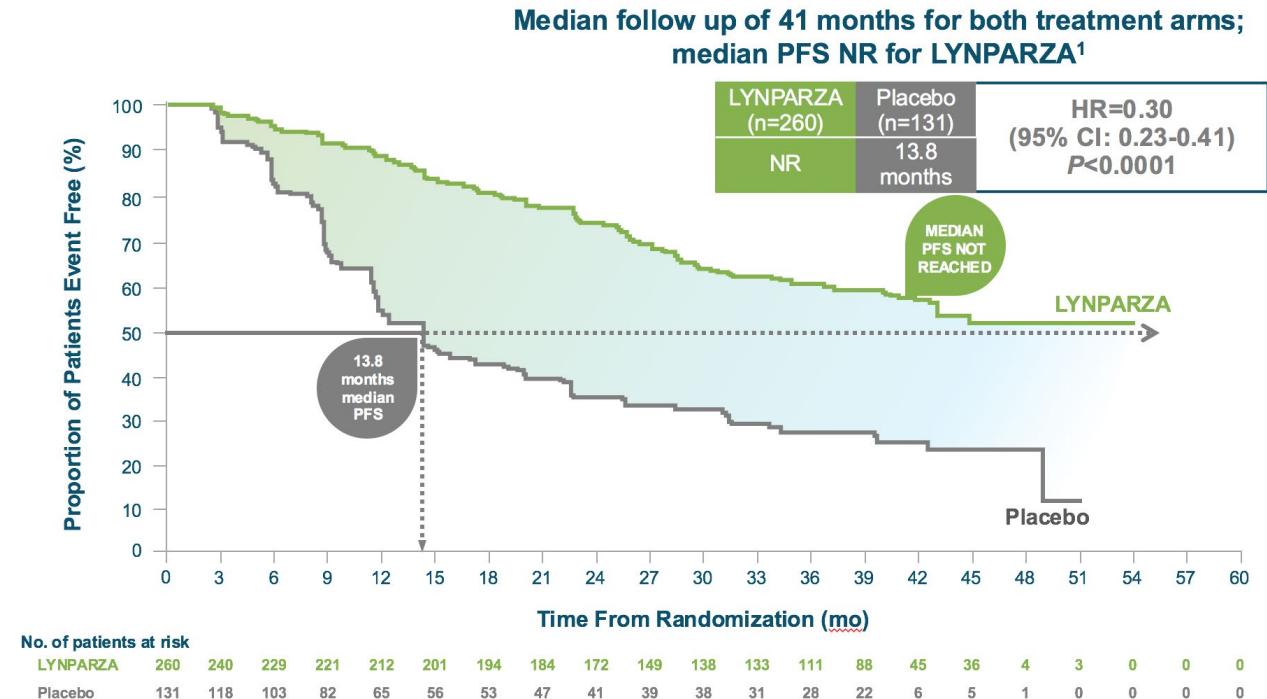
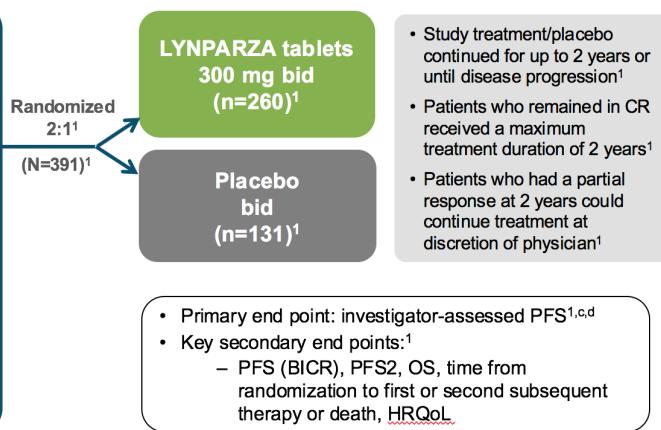
Elevation serum
creatinine

SOLO-1

Frontline Maintenance Therapy

Moore K, et al. N Engl J Med 2018;379:2495-505.

Eligibility criteria:	
• A <i>BRCA1</i> or <i>BRCA2</i> mutation, germline or somatic ¹	
– <i>gBRCA</i> mutation was determined by an FDA-approved companion diagnostic ³	
– <i>sBRCA</i> mutation was determined by an investigational tissue assay ³	
• FIGO stage III or IV, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer ¹	
• CR or PR after first-line platinum-based regimen ^{1,a}	
• ECOG PS 0 or 1 ¹	
• Cytoreductive surgery ^{1,b}	



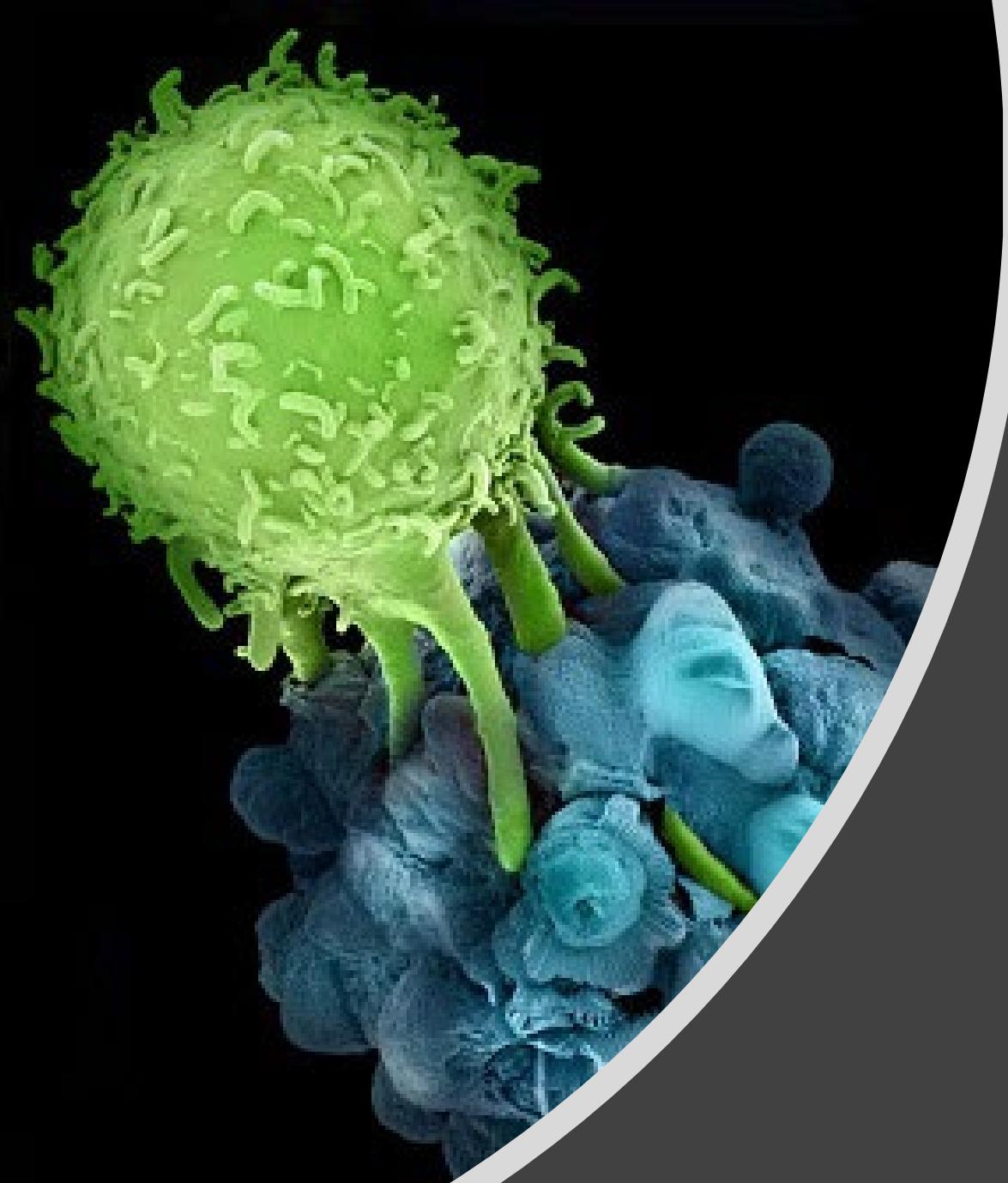
[Learn Here's how you know](#) ▾

AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based

FDA approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based



On December 19, 2018, the Food and Drug Administration approved olaparib

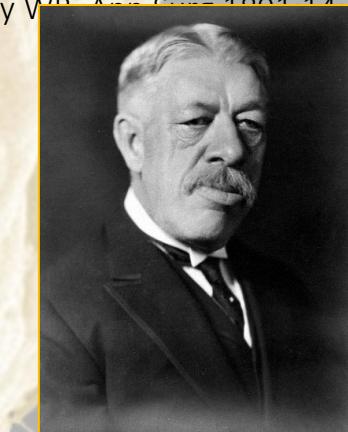


Immunotherapy

A scanning electron micrograph showing several cancer cells. One large, central cell is yellowish-green with a porous, sponge-like surface. It is surrounded by several smaller, pinkish-red cells with irregular, spiky surfaces. A thin, yellowish filament extends from the bottom left towards the center cell.

William Bradley Coley Coley's Toxins

Coley W.B. Ann Surg - 1901; 14:199-220.

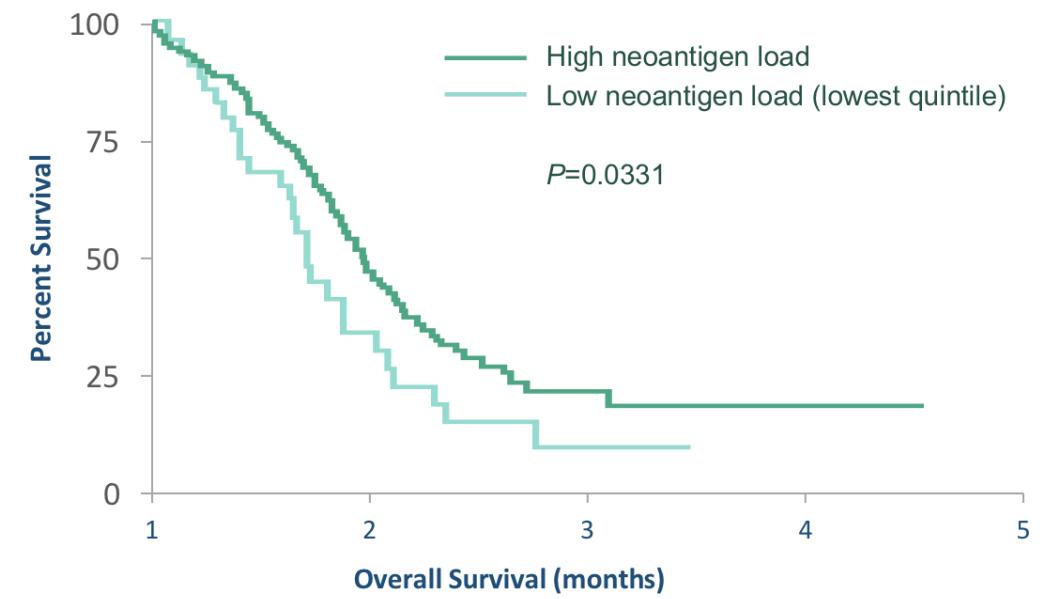
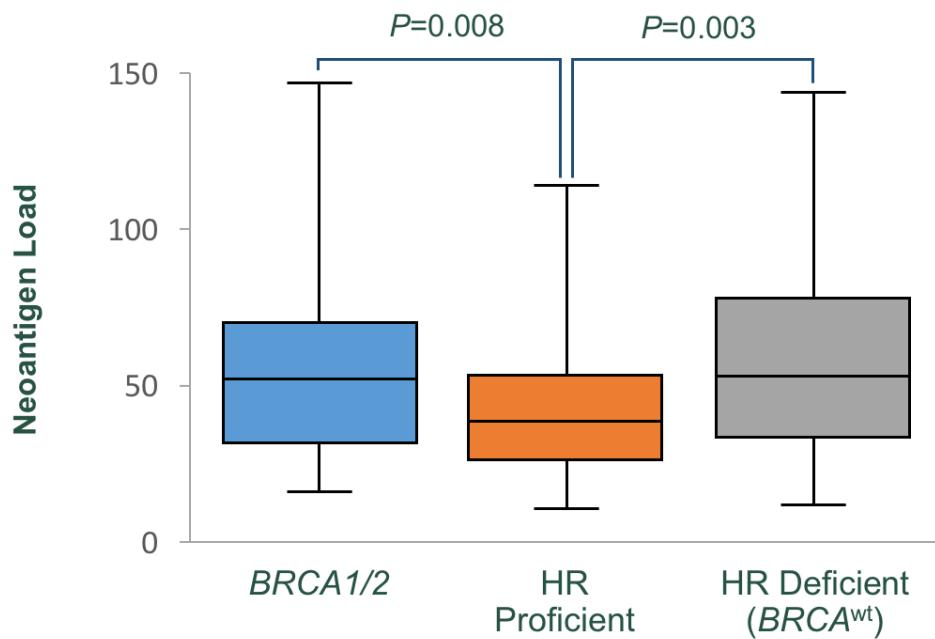


1862-1936

Neoantigen Load

Prognostic Biomarker for Survival

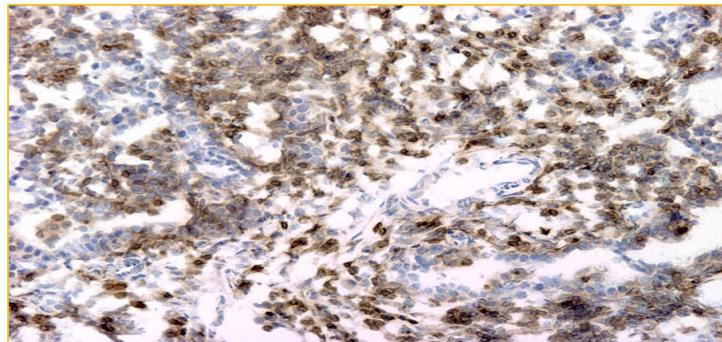
Strickland KC, et al. Oncotarget 2016;7:13587-98.



Tumor-Infiltrating Lymphocytes Within Tumor-Cell Islets Correlation with Improved Clinical Outcome

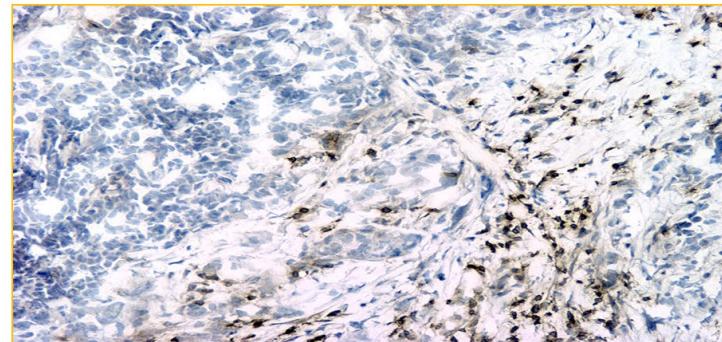
Zhang L, et al. N Engl J Med 2003;348:203-13.

TIL present in 55% of tumors^a

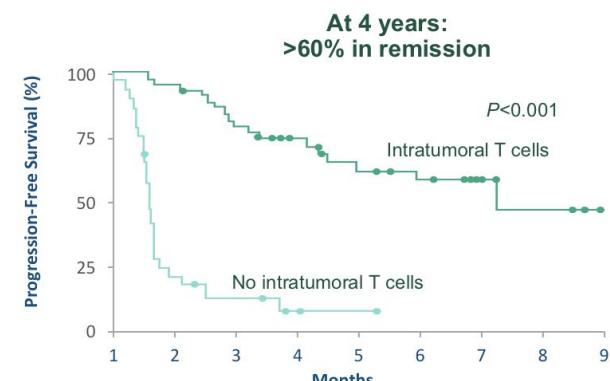
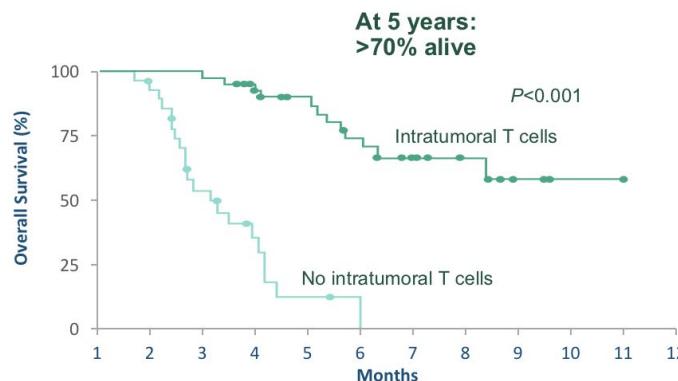


T cells in tumor islets and stroma

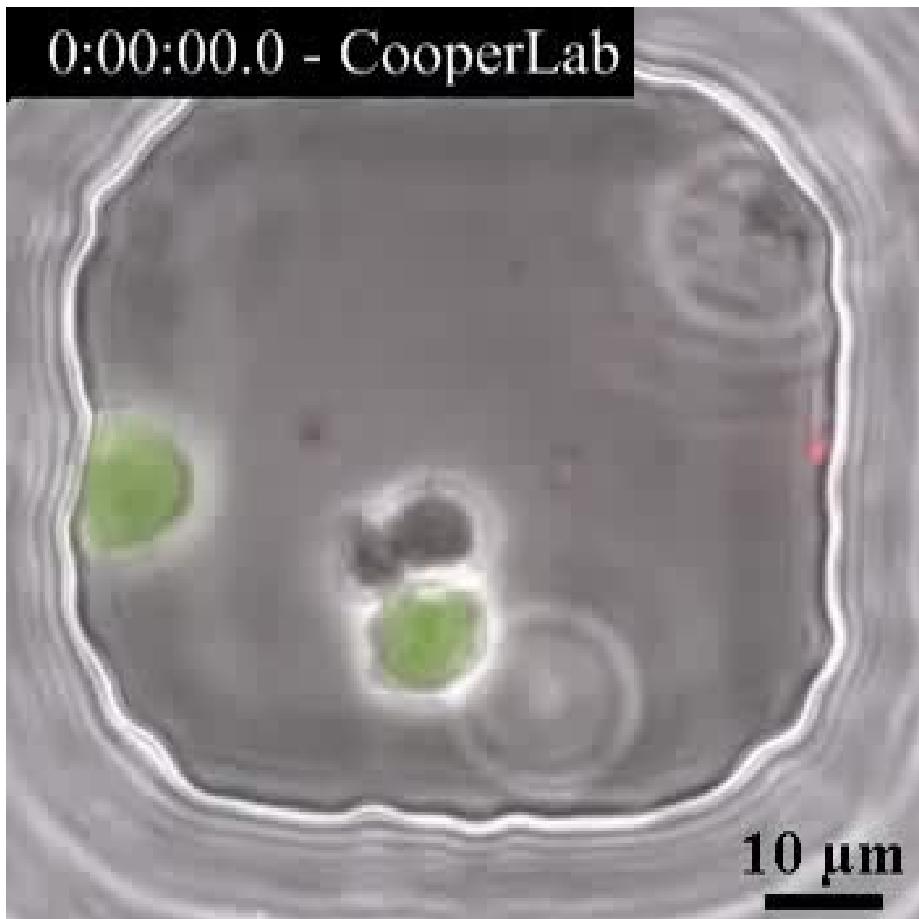
TIL absent in 39% of tumors^a



T cells restricted to peritumoral stroma



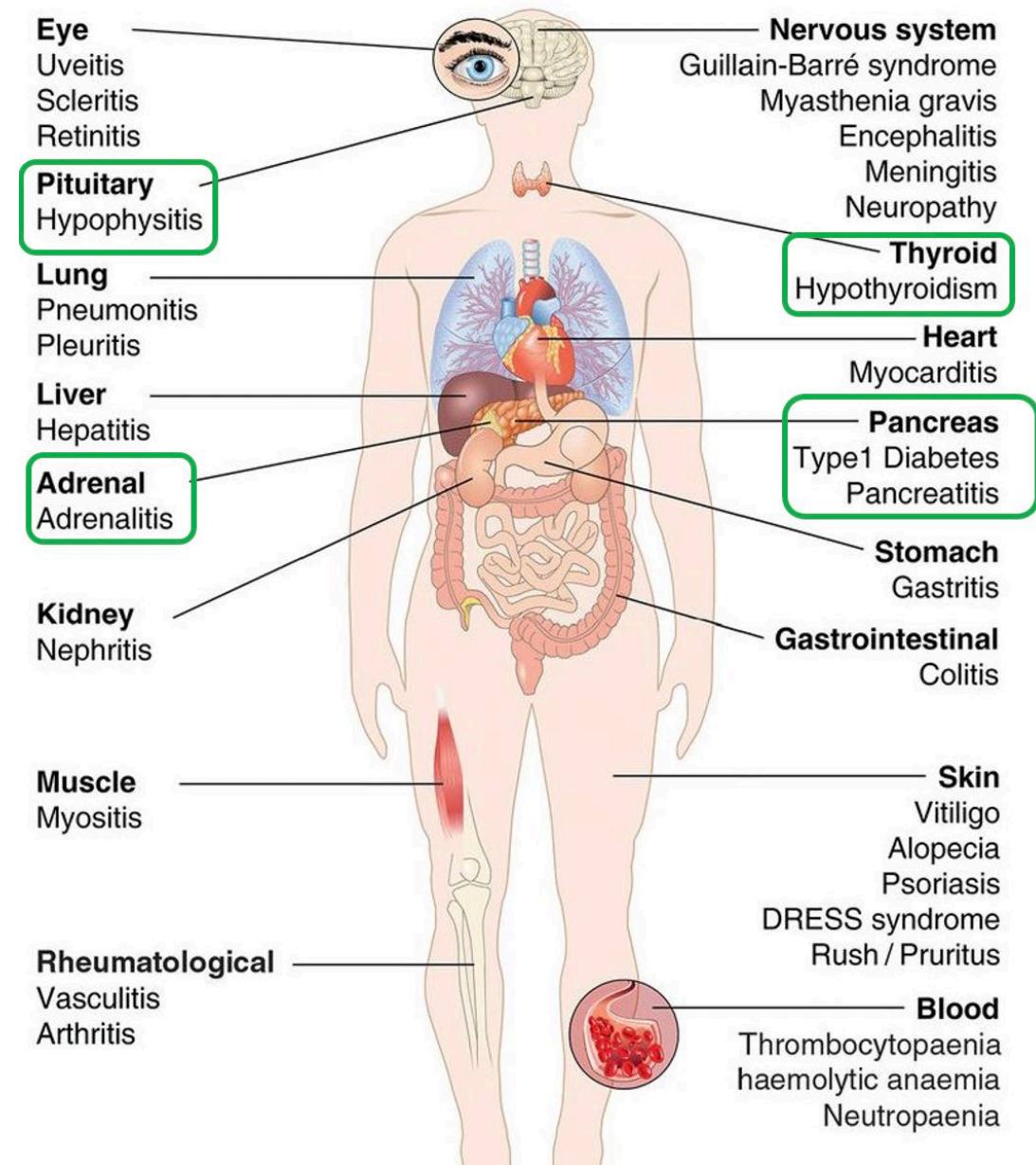
Cold & Inflamed Tumors

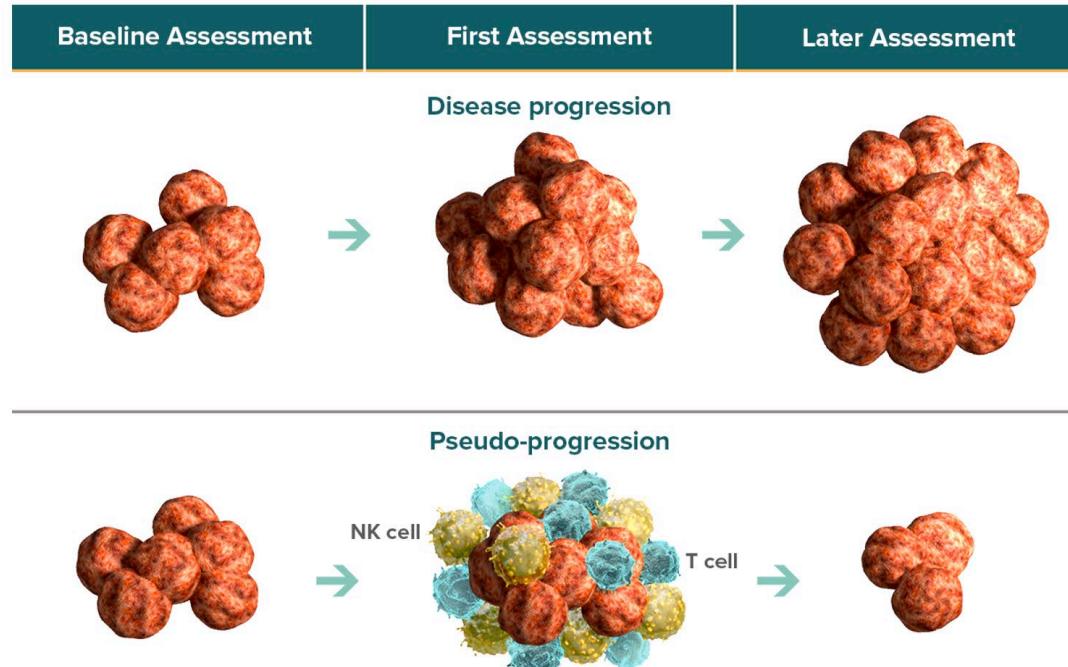


Green = 2 tumor cells
Red = cell death
Unlabeled = T lymphocyte

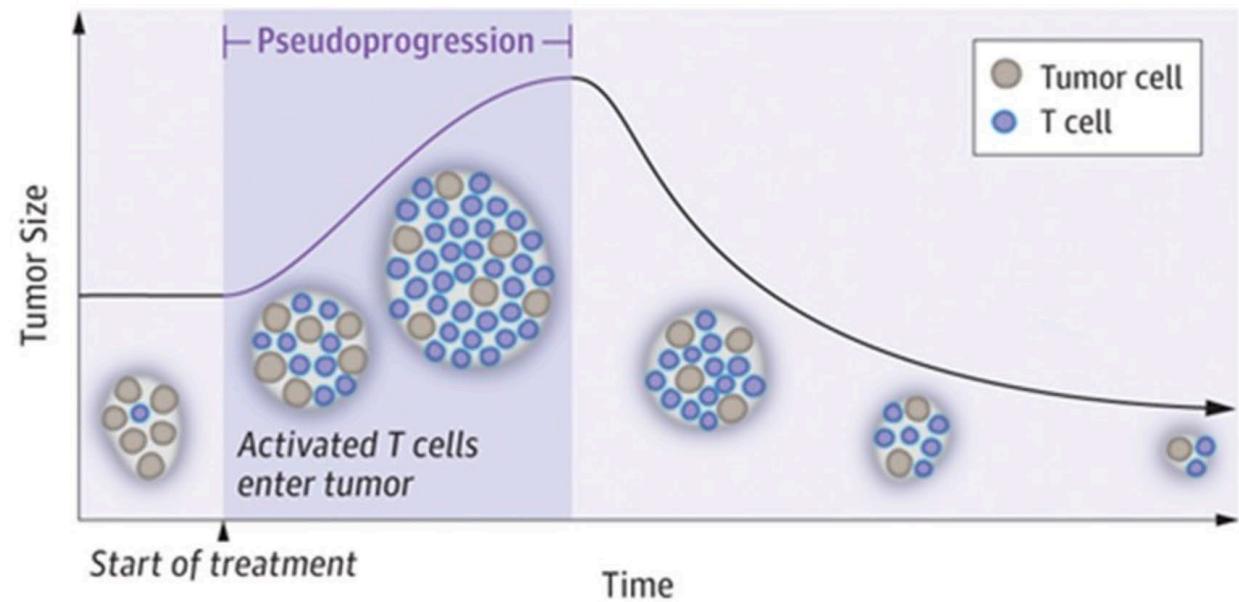
Endocrinopathies

Brahmer JR, et al. J Clin Oncol 2018;36:1714-68.





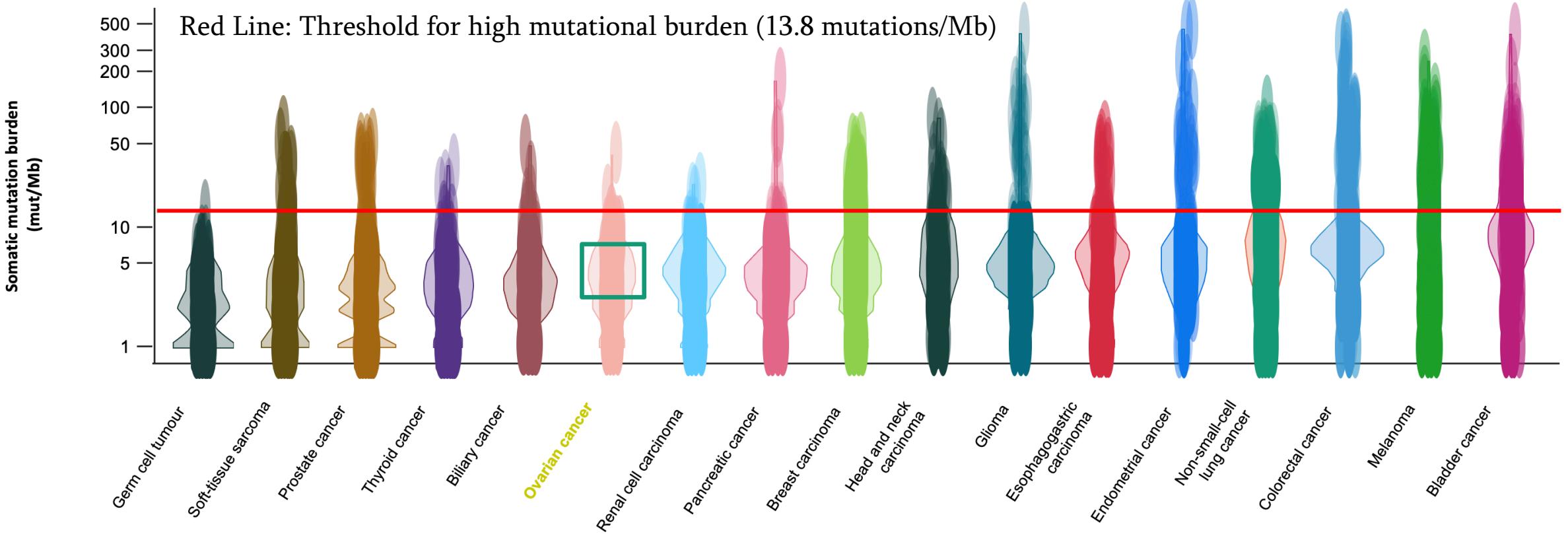
Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)



Pseudoprogression

Beer L, et al. Clin Nucl Med 2019;44:535-43.

Immune-Related RECIST

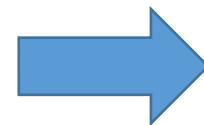
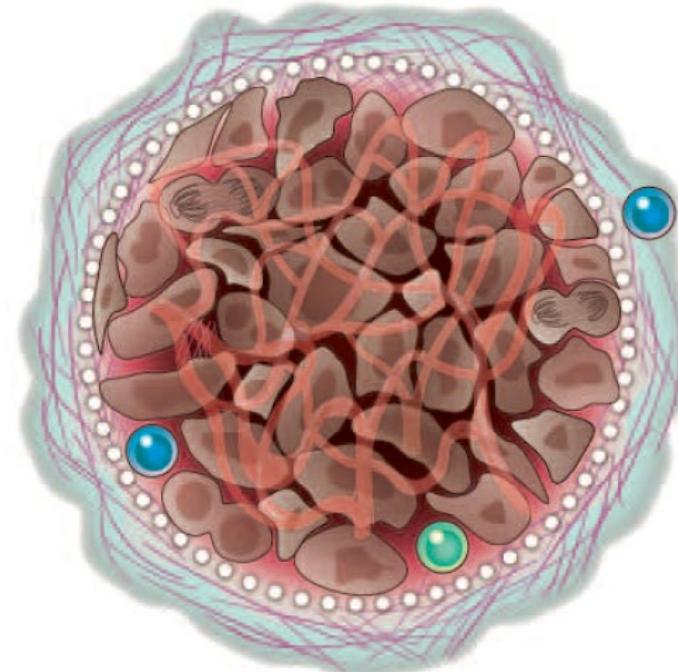


Marginal Mutational Load

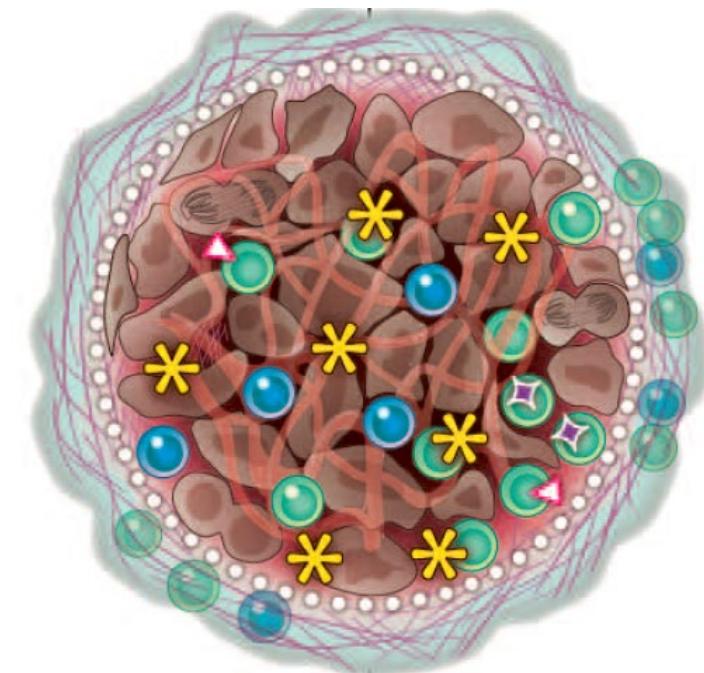
Zehir A, et al. Nat Med 2017;23:703-13.

Sensitizing
“Cold”
Tumors

Nonimmunogenic/“Cold”

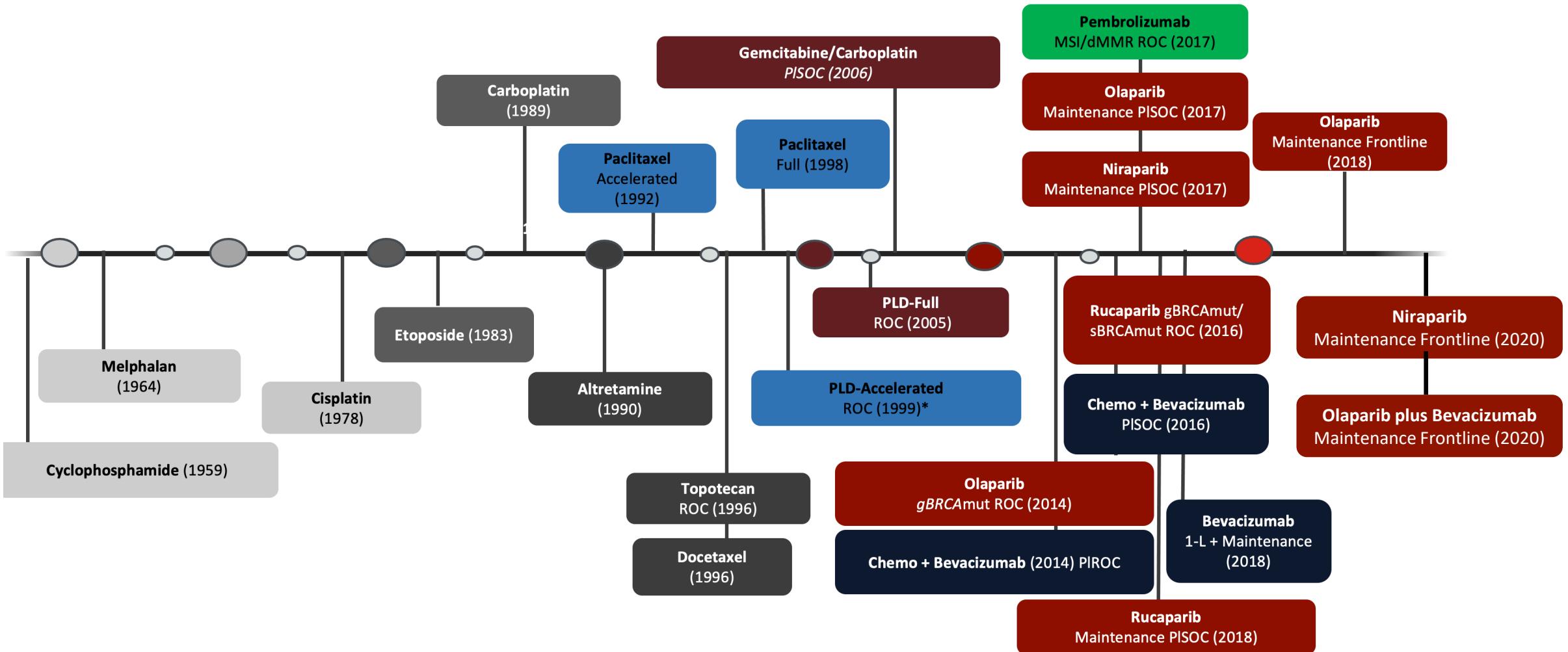


Immunogenic /“Hot”



★ = PD-L1

United States FDA-Approved Drugs for Ovarian Cancer



THANK YOU!

ktewari@uci.edu

@Dr.Tewari

