Taxol in the Management of Ovarian Cancer

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NATIONAL CANCER INSTITUTE
Center for Cancer Research

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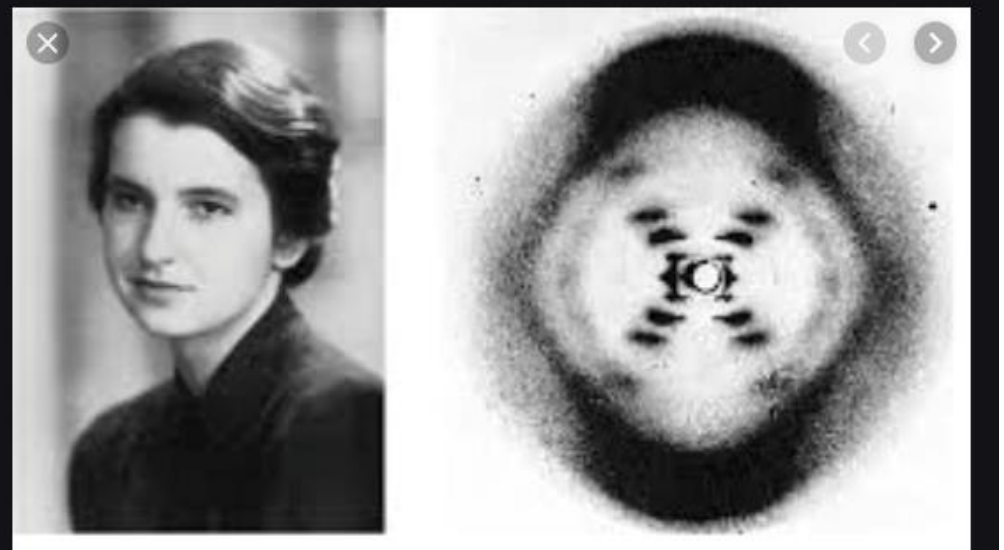
Disclosures

I have no remunerated positions.

I may answer questions with responses indicating investigational use of agents or use of investigational agents.

Rosalind Franklin

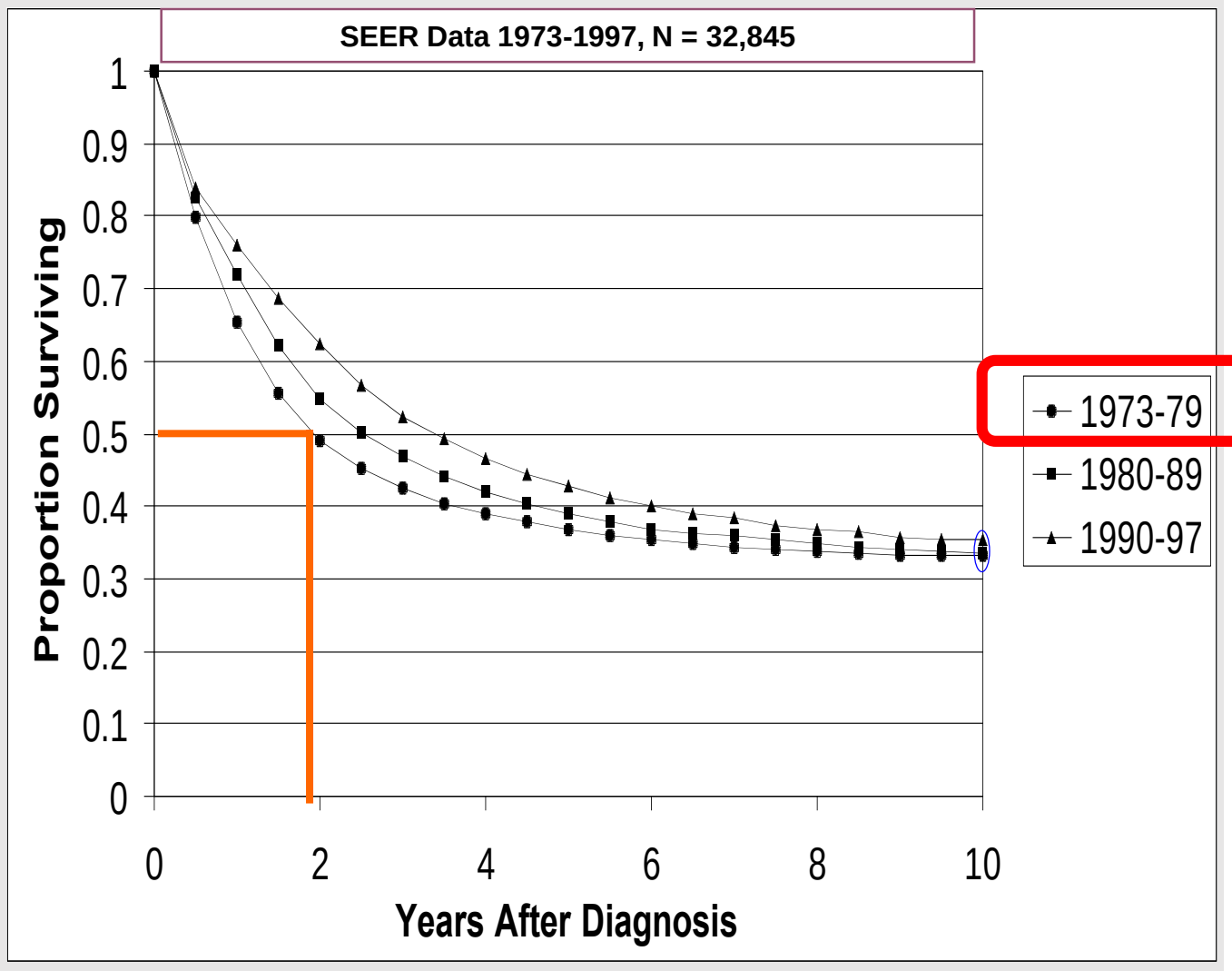
- Received her PhD from Cambridge in 1945
- Early 1950s, discovery of DNA structure
- 1956, diagnosed with ovarian cancer
- 1958, died in London



(a) Rosalind Franklin

(b) Franklin's X-ray diffraction photograph of DNA

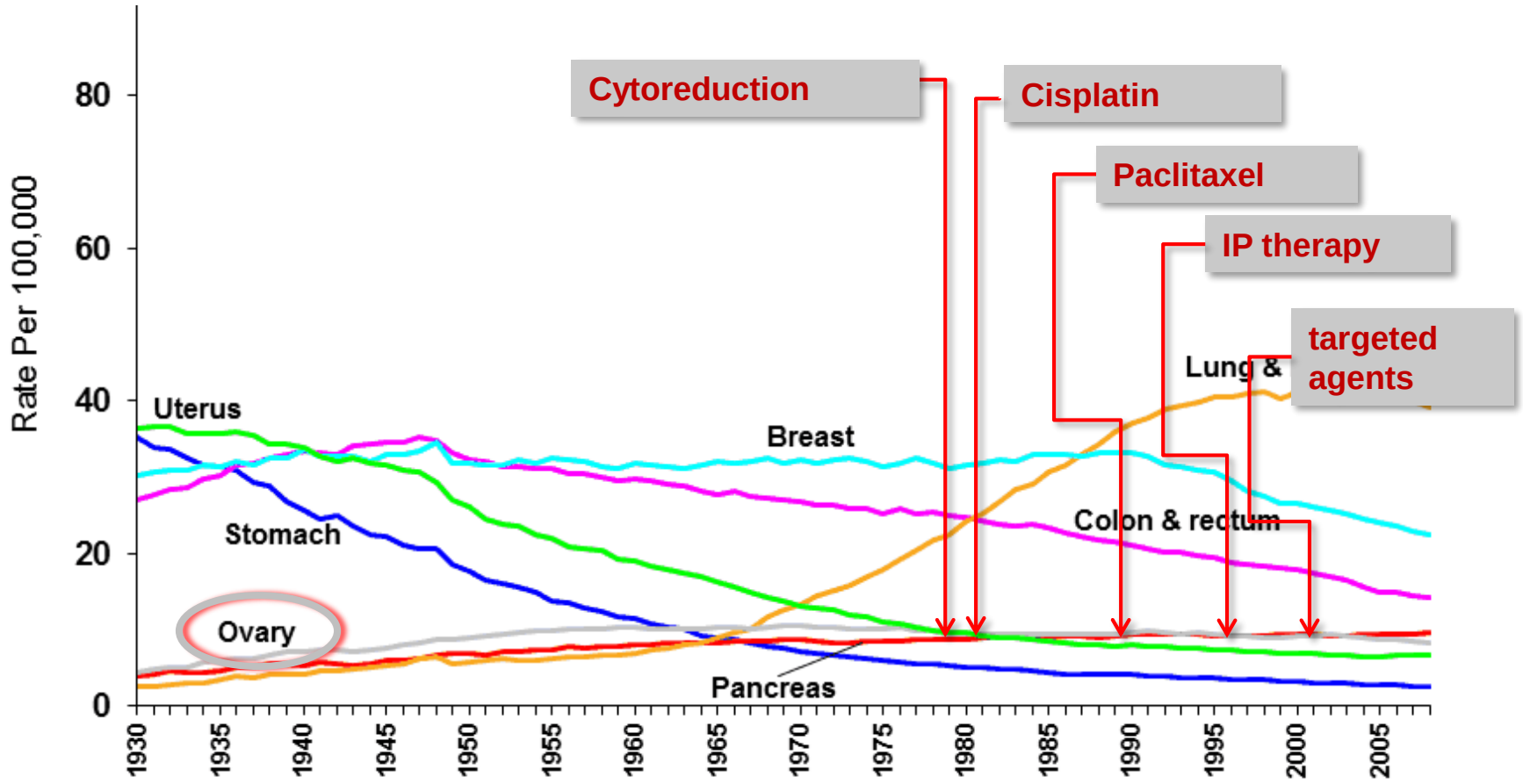
Ovarian cancer survival trends



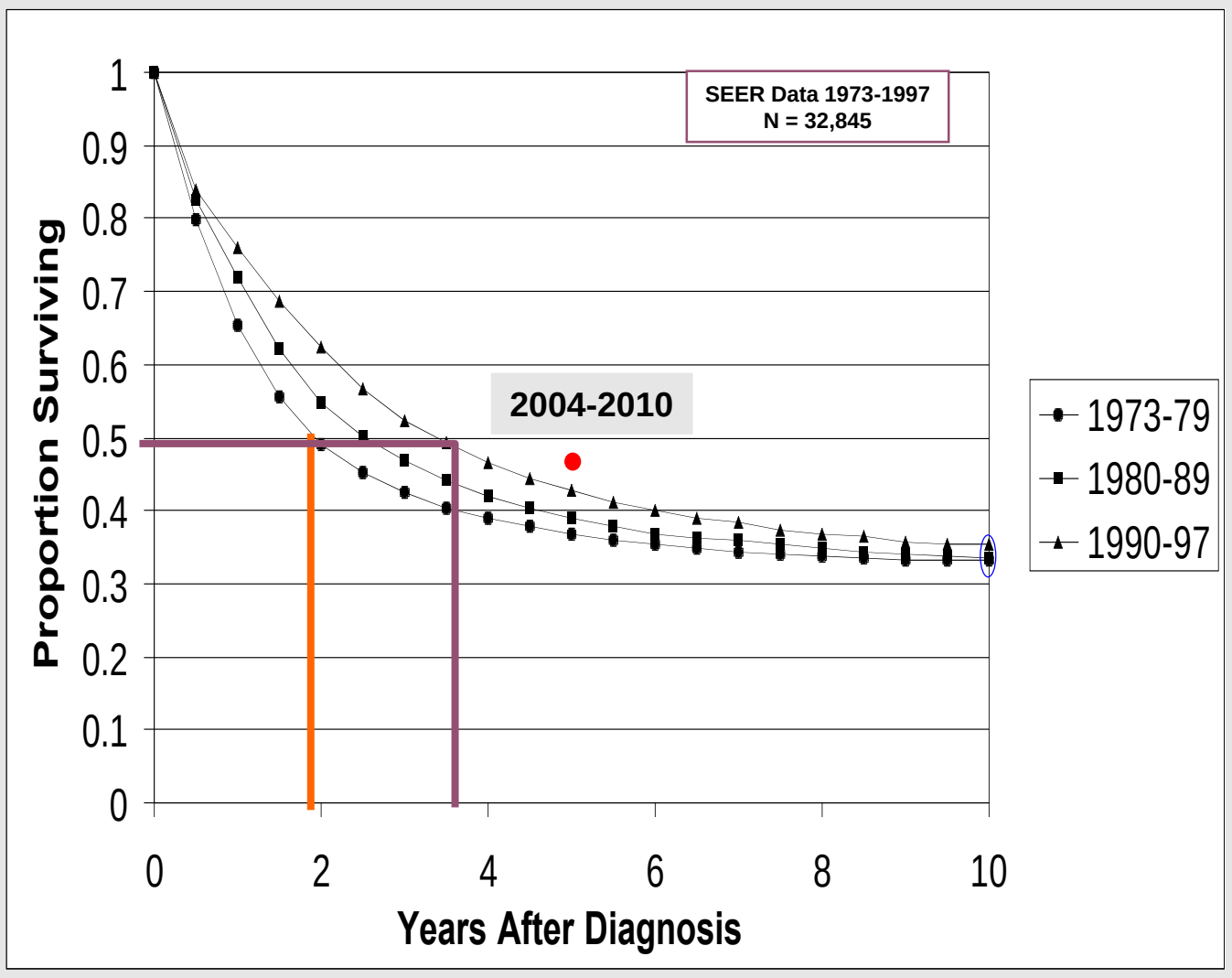
SEER: The Surveillance, Epidemiology, and End Results

Have our interventions been successful?

US Cancer Death Rates 1930-2008



Slowly but surely, we have made a good progress



Ovarian cancer

Rare but most lethal gynecologic cancer in the U.S.

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

Estimated 22,400 new cases (2.6%) in 2017

Estimated Deaths

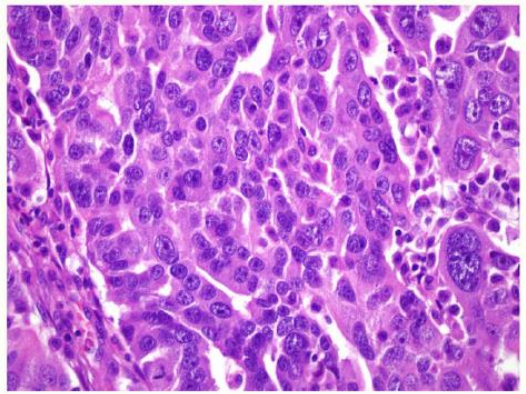
Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

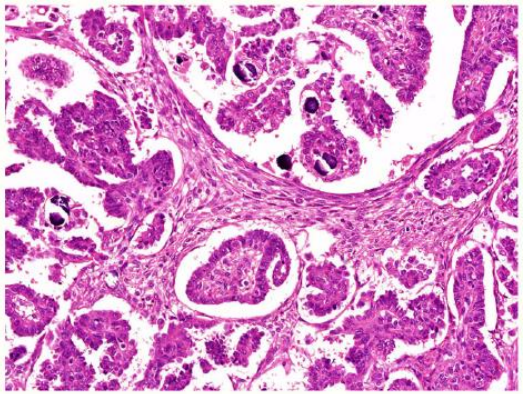
Fractional death rate 63%

Siegel *et al.* *CA Cancer J Clin* 2017

“Ovarian” cancer histology

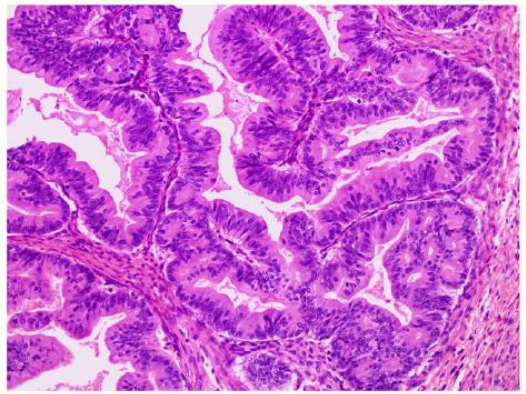
High grade serous

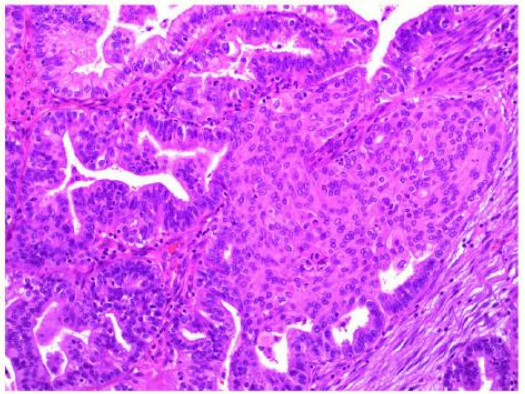




Low grade serous

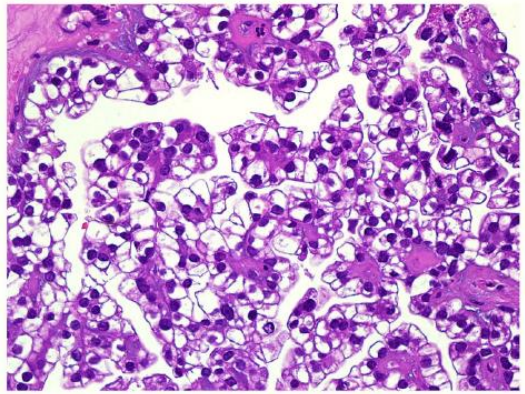
Mucinous





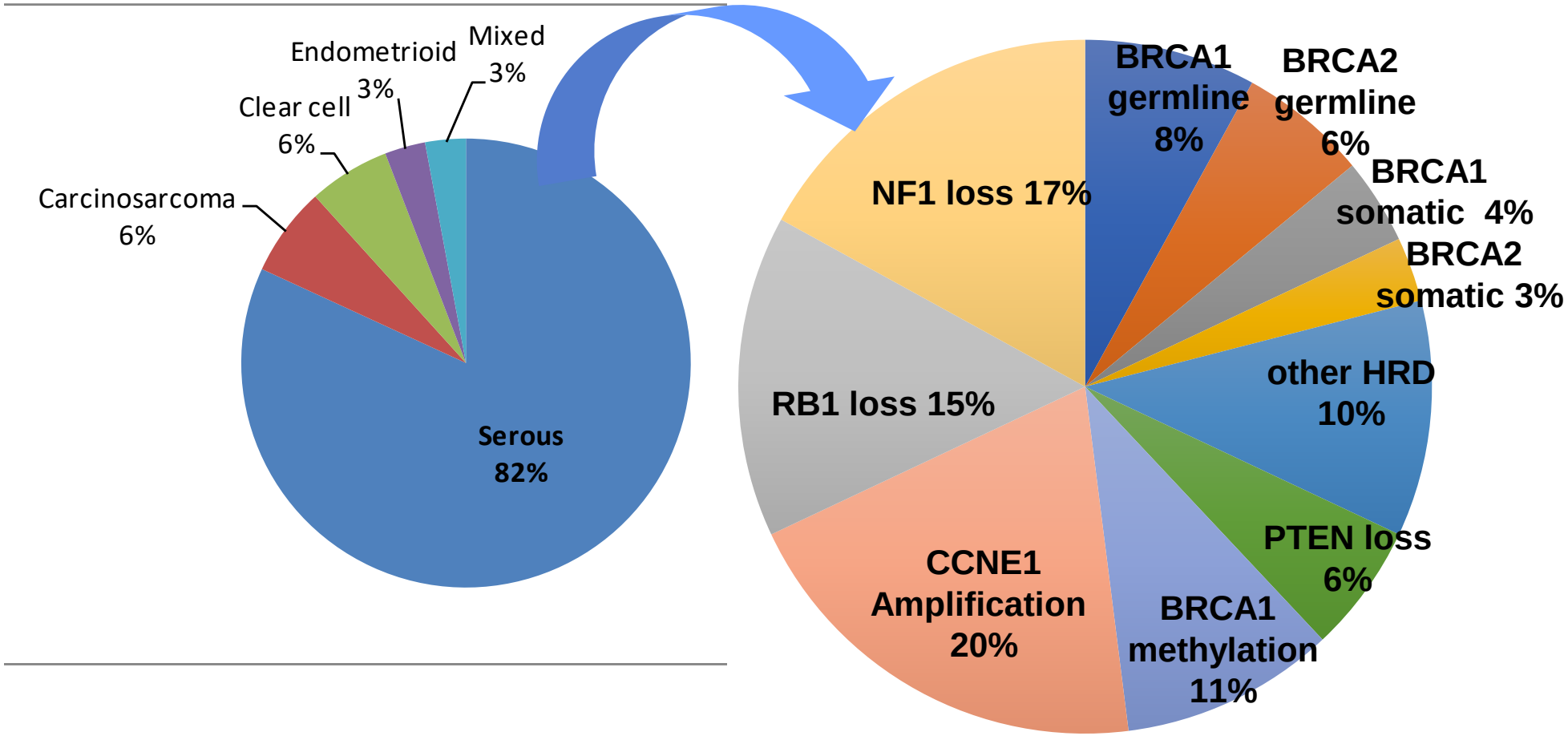
Endometrioid

Clear cell



Genetic sources of genomic instability

Mutually exclusive events



TCGA Consortium, *Nature,* 2011, Patch and Bowtell *et al, Nature,* 2015

Treatment with Taxol still matters for ovarian cancer in this genomic era

Introduction of Taxol to the treatment of ovarian cancer

[CANCER RESEARCH 47, 2486–2493, May 1, 1987]

Phase I Clinical and Pharmacokinetic Study of Taxol[1]

Peter H. Wiernik,[2] Edward L. Schwartz, Janice J. Strauman, Janice P. Dutcher, Richard B. Lipton, and Elisabeth Paietta

Albert Einstein Cancer Center, Montefiore Medical Center, Bronx, New York 10467

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ARTICLES

Taxol: A Unique Antineoplastic Agent with Significant Activity in Advanced Ovarian Epithelial Neoplasms

William P. McGuire, MD; Eric K. Rowinsky, MD; Neil B. Rosenshein, MD; Francis C. Grumbine, MD; David S. Ettinger, MD; Deborah K. Armstrong, MD; and Ross C. Donehower, MD

30% response rate in platinum-resistant ovarian cancer
Annals of Internal Medicine. 1989;111:273-279.

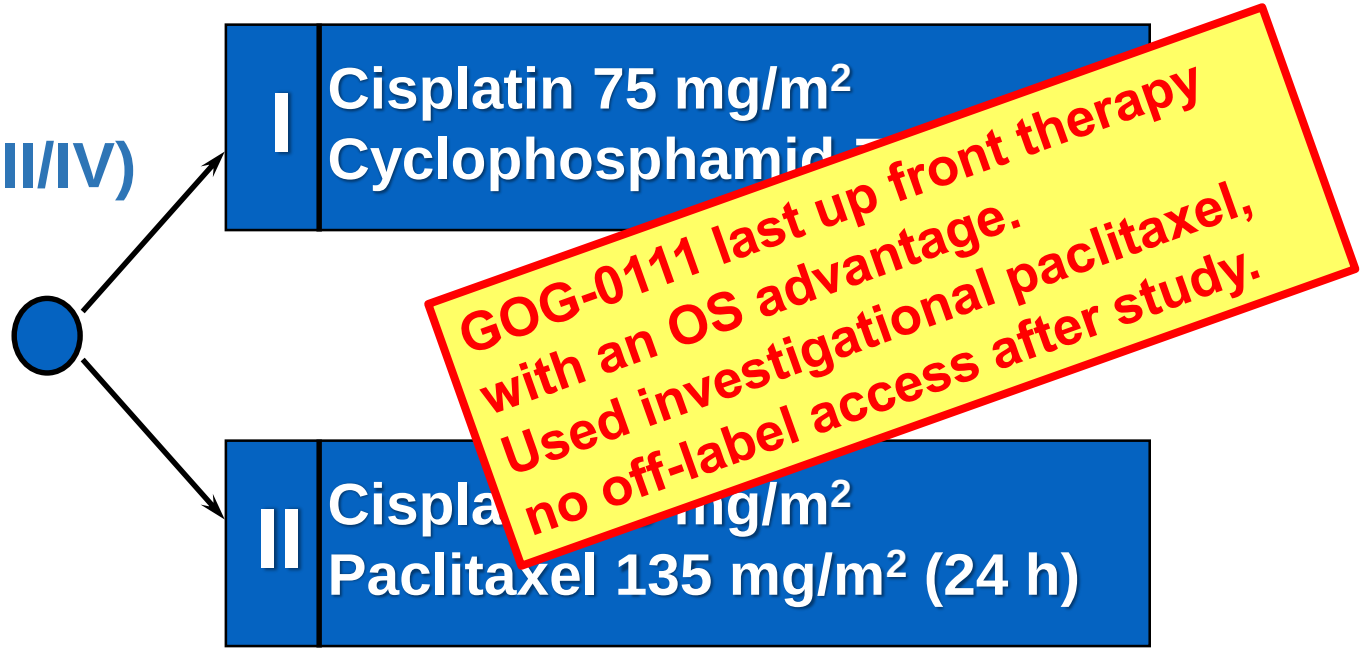
FDA approval of taxol for ovarian cancer in 1992

Changing the treatment paradigm

Taxol plus platinum agent is superior to other combo

GOG111: Ovarian (suboptimal III/IV)

- **Epithelial Ovarian Cancer**
- **Suboptimal Stage III/IV**
- **No prior therapy**



Open: 13-Apr-90
Closed: 02-Mar-92
Accrual: 410 pts

McGuire, et al. NEJM 334:1-6, 1996

GOG 182: less is better

FIGO III-IV
All residuum
EOC or PPC
IDS ok
GCIG study
>4000 pts

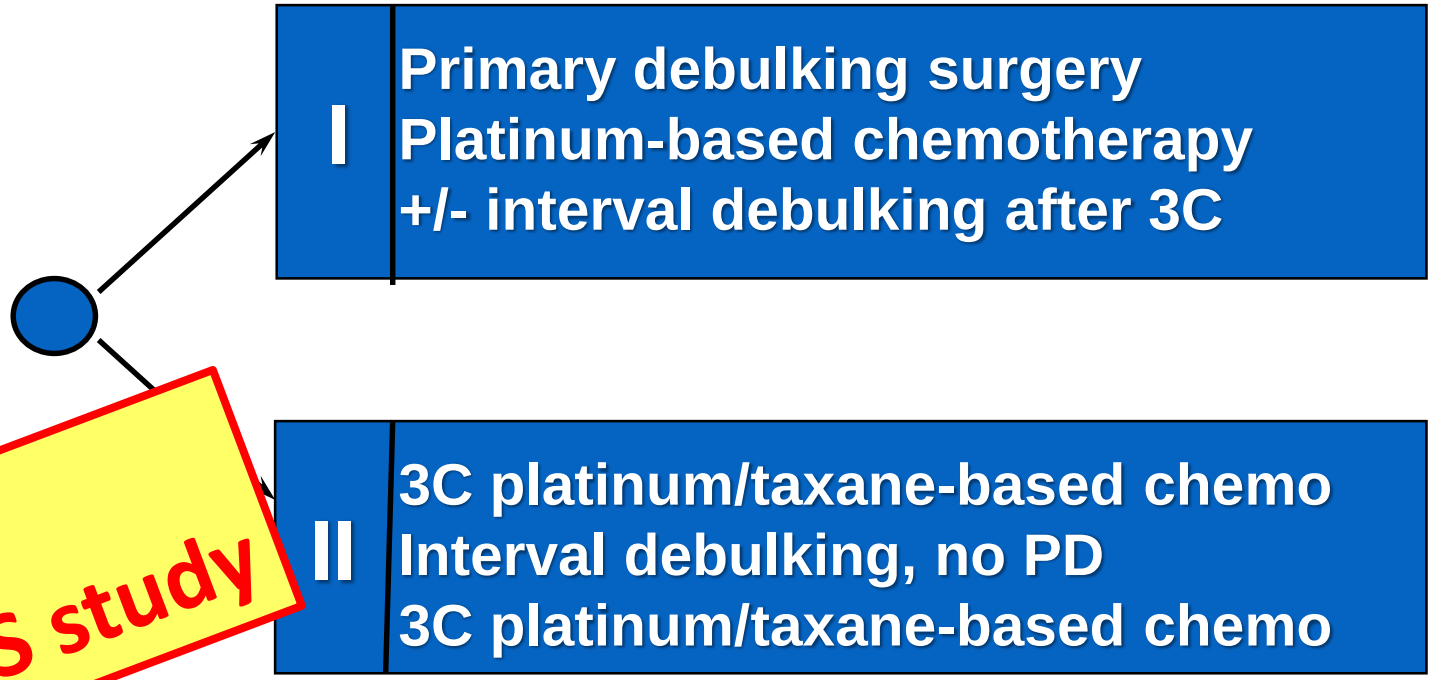
- Paclitaxel 175 mg/m^2 3 hrs
  Carboplatin AUC 6 — x8
- Paclitaxel 175 mg/m^2 3 hrs
  Carboplatin AUC 5
  Gemcitabine 800 mg/m^2 d 1, 8 — x8
- Paclitaxel 175 mg/m^2 3 hrs
  Carboplatin AUC 5 — ALTERNATING COURSES → Paclitaxel 175 mg/m^2 3 hours
  Carboplatin AUC 5
  DOXIL30 mg/m^2
- Topotecan 1.5 mg/m^2 d1 - 3
  Carboplatin AUC 5
  x4 cycles → Paclitaxel 175 mg/m^2 3 hours
  Carboplatin AUC 6
  x4 cycles
- Gemcitabine 1,000mg/m^2 d1, 8
  Carboplatin AUC 6
  x4 cycles → Paclitaxel 175 mg/m^2 3 hours
  Carboplatin AUC 6 x4 cycles

NO DIFFERENCE

Bookman et al, J Clin Oncol 2009

It does not matter whether you give before or after surgery

Ovarian, tubal, peritoneal
IIIC/IV suboptimal
Physician's choice platinum-based therapy

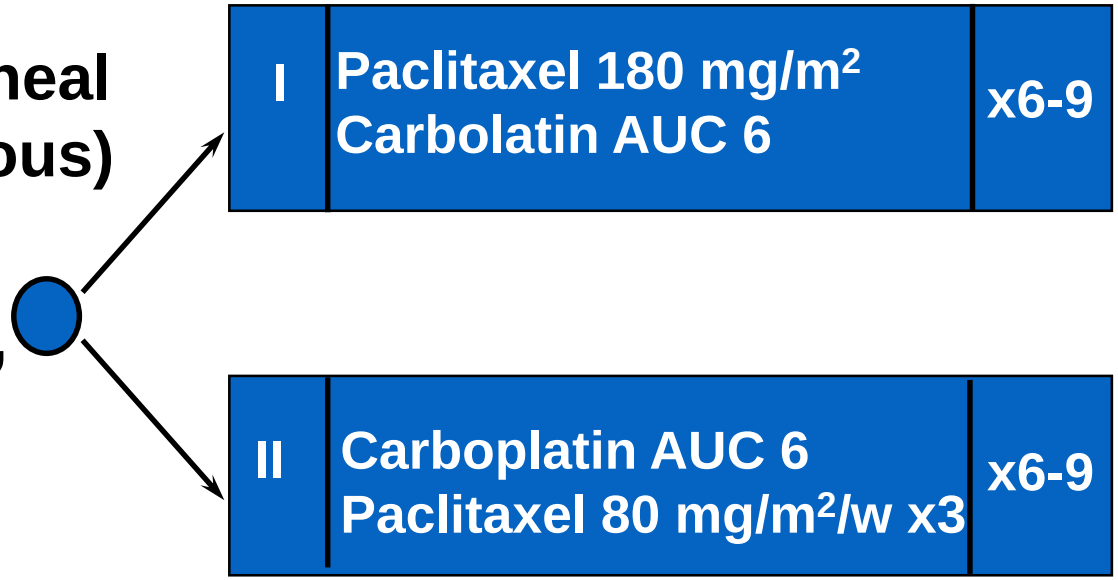


NO DIFFERENCE
Confirmed by CHORUS study

Vergote I et al, NEJM, 2010
CONFIRMED: Kehoe S et al, Lancet Oncol 2015
Pooled analysis EORTC55971 and CHORUS Vergote et al. Lancet Oncol 2018

JGOG: dose-dense weekly Paclitaxel

- Epithelial ovarian or peritoneal (including clear cell/mucinous)
- Stage II – IV
- Stratified: residual disease, stage, histology
- Primary endpoint: PFS
- Secondary: OS



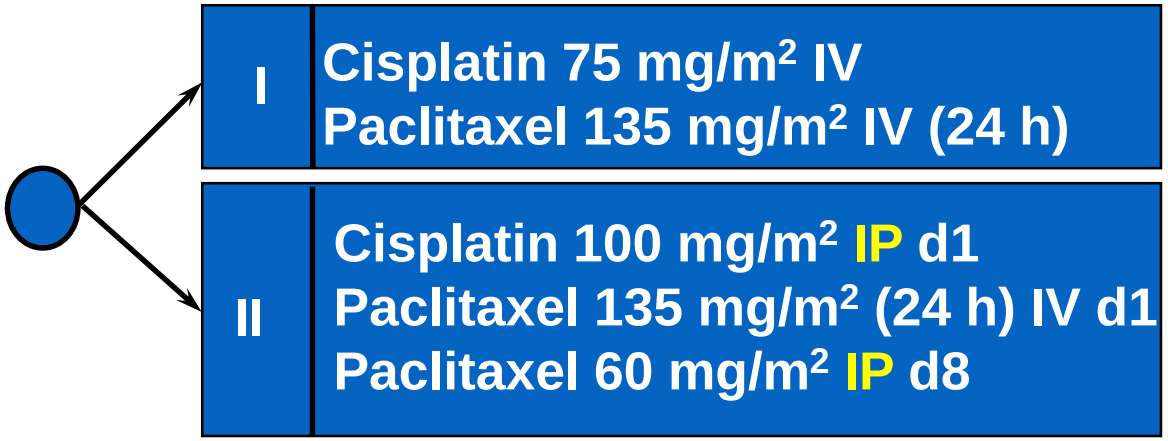
- Dose-dense paclitaxel hematologic toxicity, fewer pts completed protocol therapy
- Improved PFS and OS in Japanese patients with dose-dense weekly paclitaxel

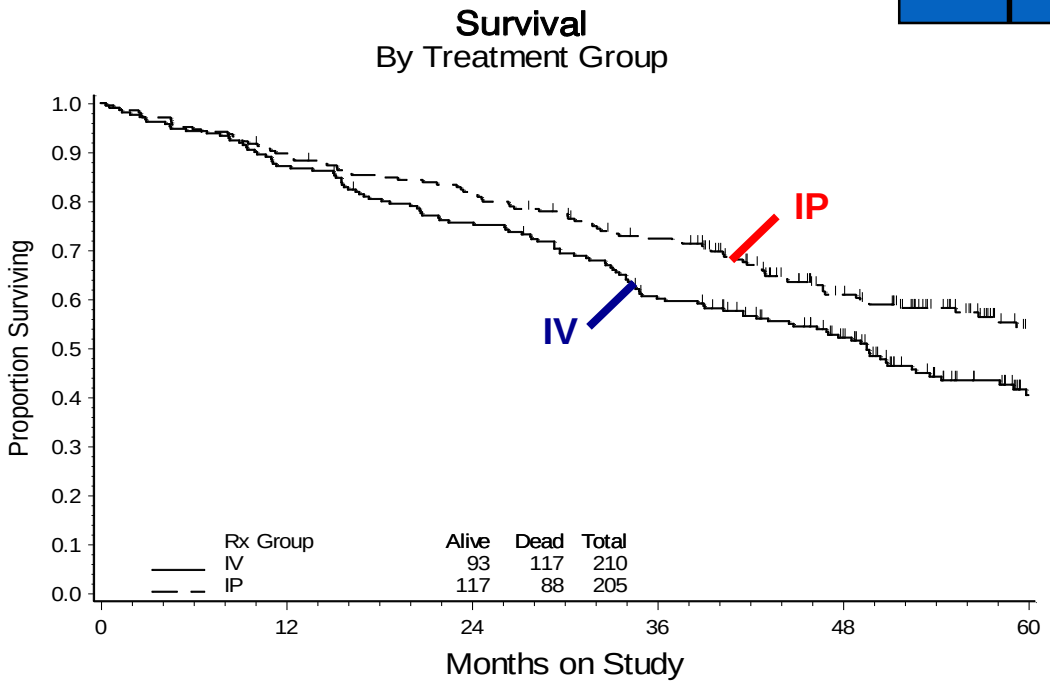
Accrual: 637 pts (intent-to-treat)

Katsumata N, et al Lancet, 2009
Katsumata N, et al Lancet Oncol, 2013

GOG172: IP vs. IV
The way of delivery of carboplatin and taxol may matter

- EOC
- Optimal stage III
- Elective SLO





	Median	HR	95% CI	p-value
PFS		0.79	0.63-0.99	0.027
OS	49.7 v 65.6 mo	0.71	0.54-0.94	0.0076

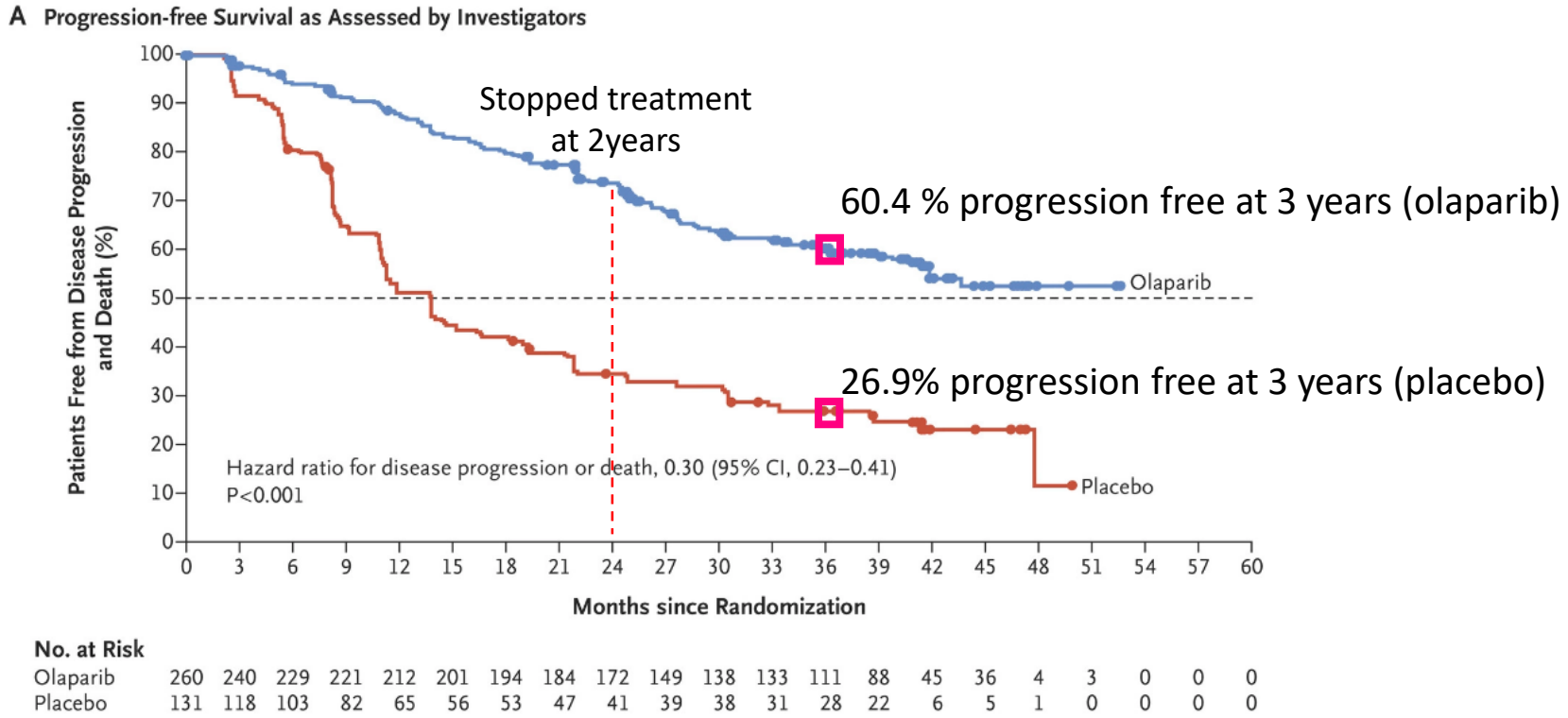
Armstrong, et al. NEJM, 2006

Upfront treatment summary

- **Surgery followed by taxane/platinum-based chemotherapy is standard treatment for newly diagnosed ovarian cancer patients**
- **Taxol plus platinum-based chemotherapy combination is active in ovarian cancer, independent of histology**
- **IP chemotherapy would benefit the selected population**

Taking to the next level

PARP inhibitor maintenance following chemotherapy



SOLO1: olaparib maintenance in *BRCA mutant patients*
FDA approval 2018

	Olaparib (n=260)	Placebo (n=131)
Events (%)[50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
	HR 0.30	

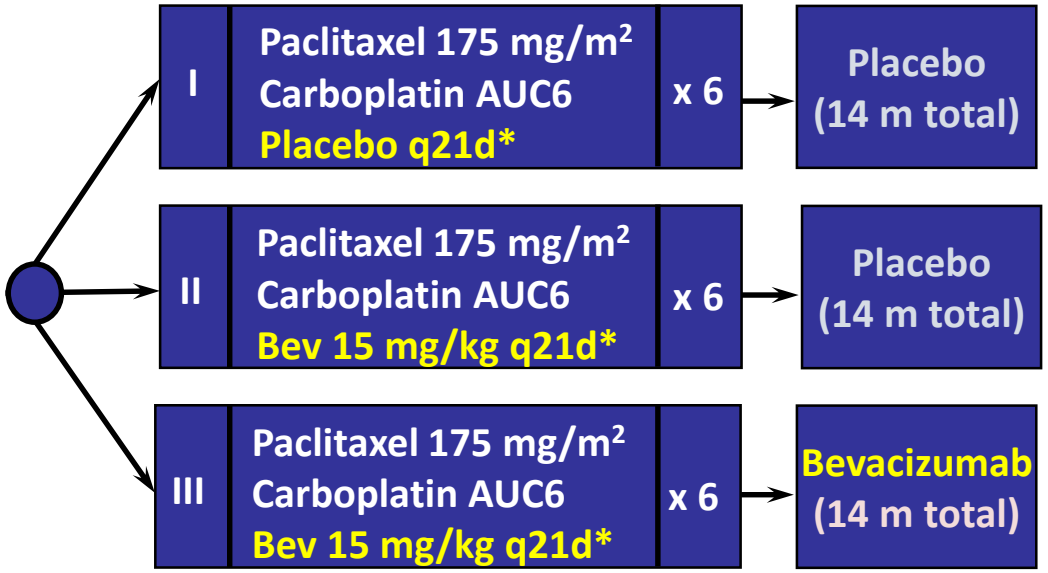
95% CI 0.23 to 0.41 *P*<0.0001

Moore et al. NEJM 2018

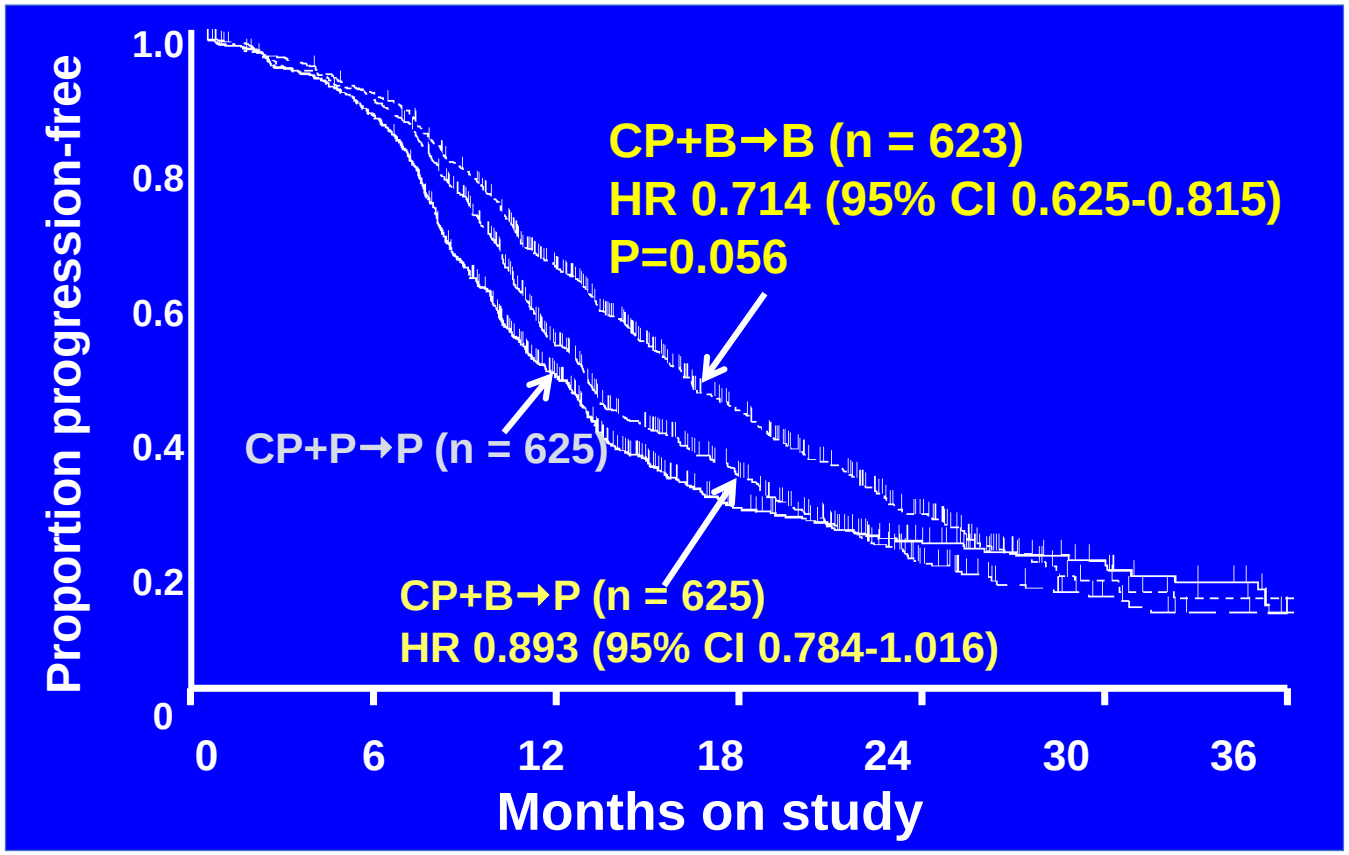
Taking to the next level

Bevacizumab maintenance following chemotherapy

- **EOC**
- **III/IV**



*starting with C2



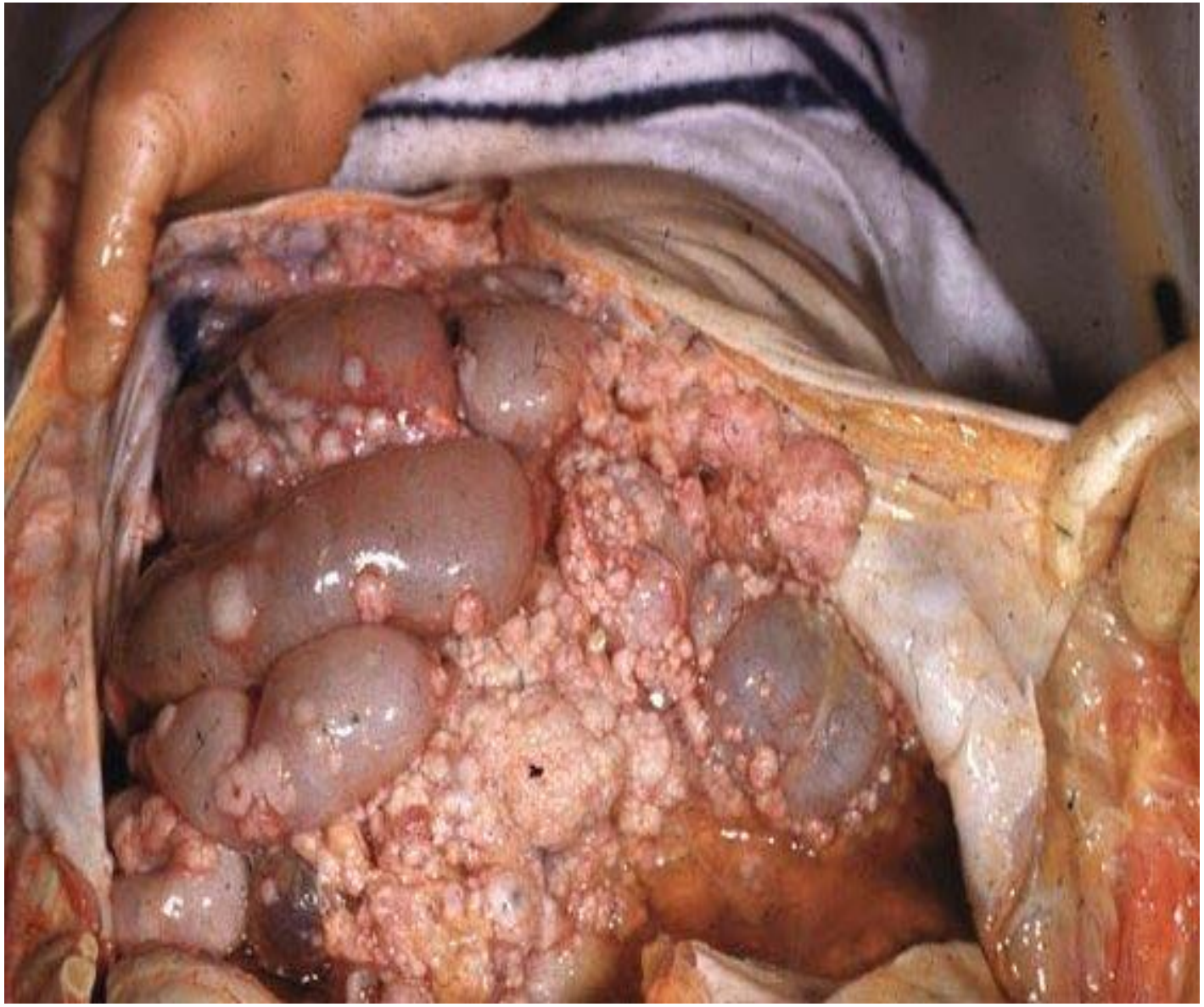
GOG218: bevacizumab maintenance

FDA approval 2018

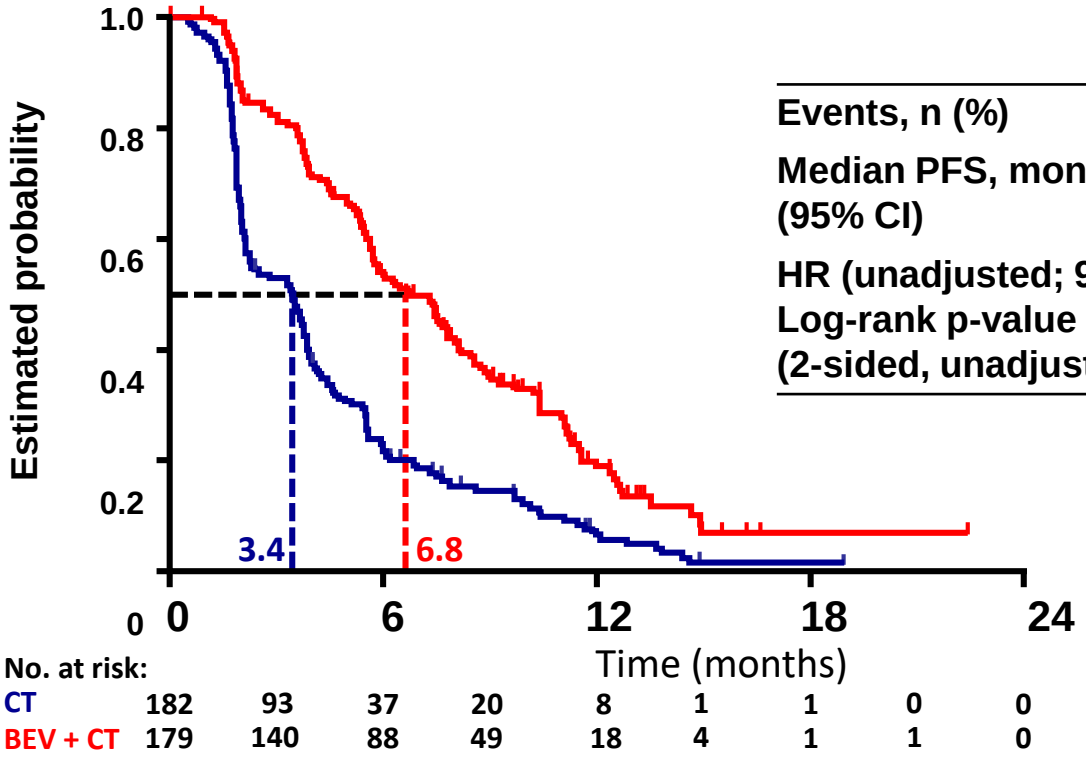
FDA approval June 2018

Burger RA, et al. NEJM, 2011

Unfortunately, recurrence is common in ovarian cancer



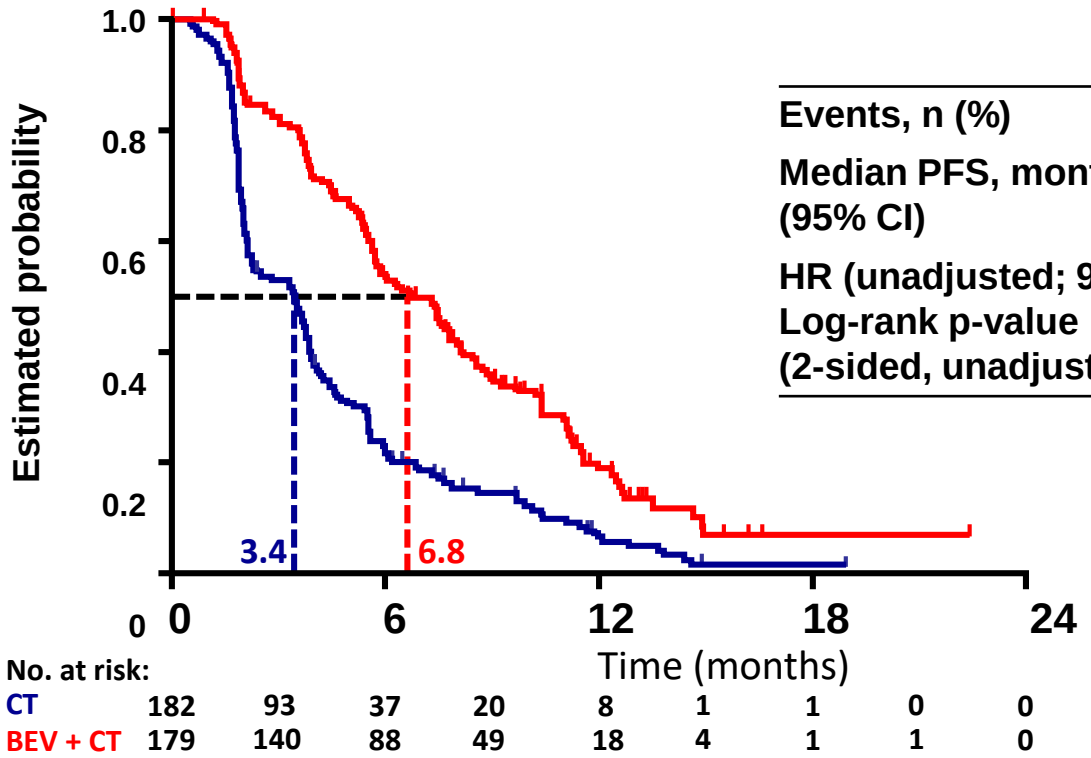
AURELIA: Chemo + bevacizumab vs chemo
Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	3.4 (2.1–3.8)	6.8 (5.6–7.8)
HR (unadjusted; 95% CI)	0.38 (0.30–0.49)	
Log-rank p-value (2-sided, unadjusted)	<0.0001	

Pujade-Lauraine E et al, *JCO* 2014, 2015

AURELIA: weekly paclitaxel drove results



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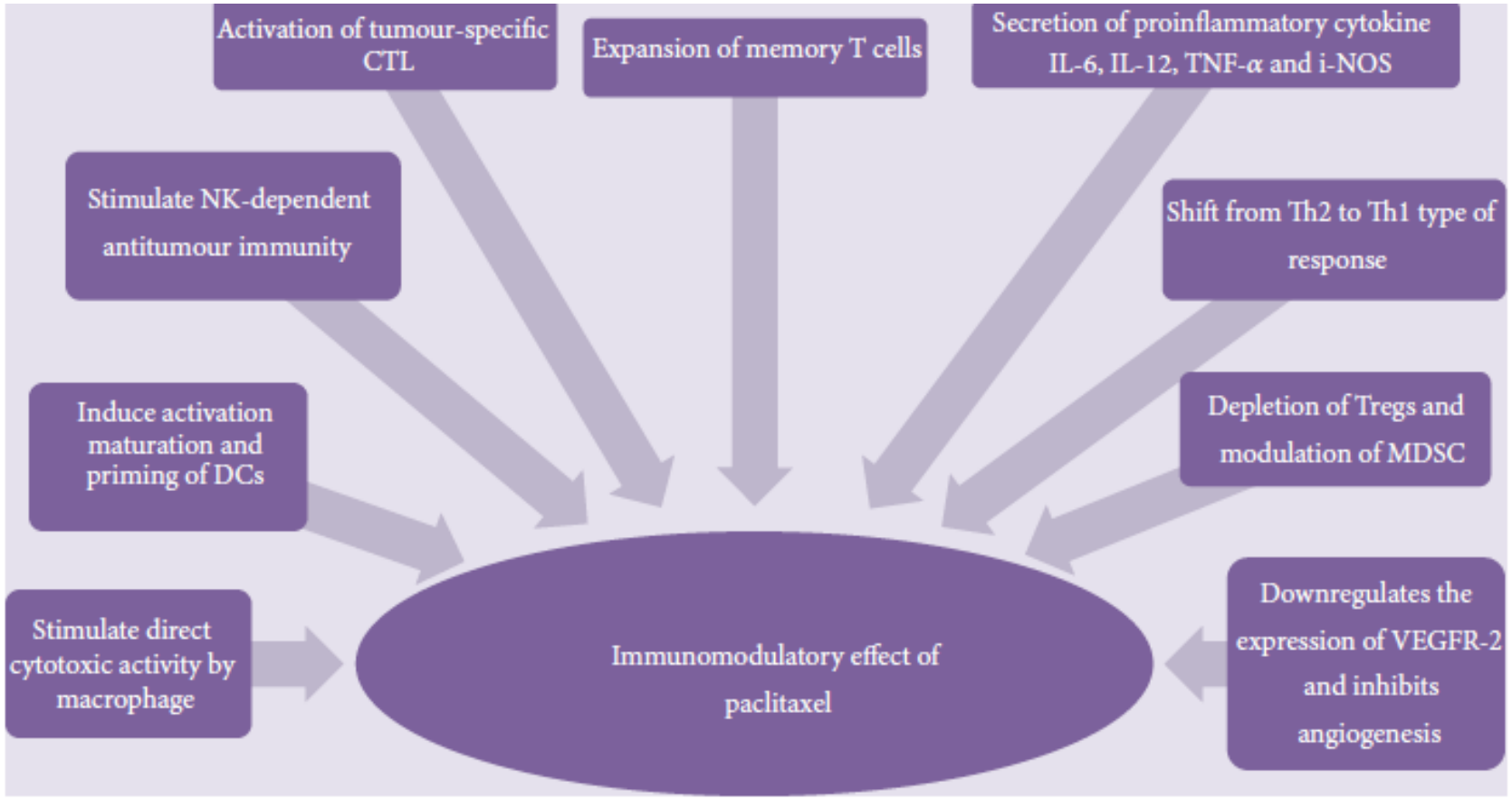
Chemo arm*	ORR (bev/no bev)	PFS HR (bev/no bev)	OS HR (bev/no bev)
Paclitaxel	53.3 v 30.2%	0.46 (10.4 v 3.9 mo)	0.65 (22.4 v 13.2 mo)
PLD	17.0 v 0%	0.57 (5.4 v 3.5 mo)	0.91 (13.7/14.1 mo)
topotecan	13.7 v 7.8%	0.32 (5.8 v 2.1 mo)	1.09 (13.8/13.3 mo)

Pujade-Lauraine E et al, *JCO* 2014, 2015

Making another history

- **Immunomodulatory effect of Taxol**



Kampan et al. BMRI 2015

Making another history

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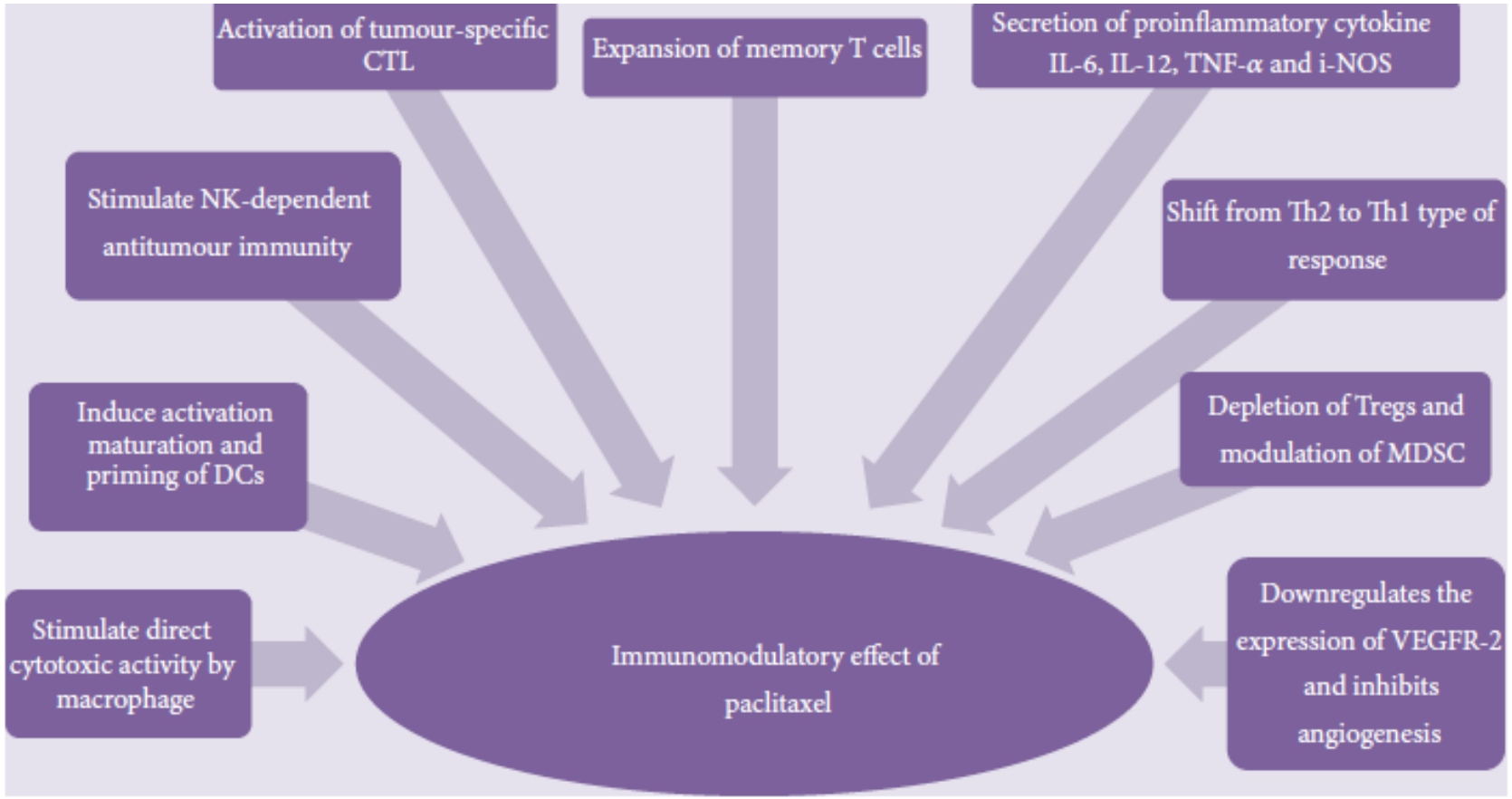


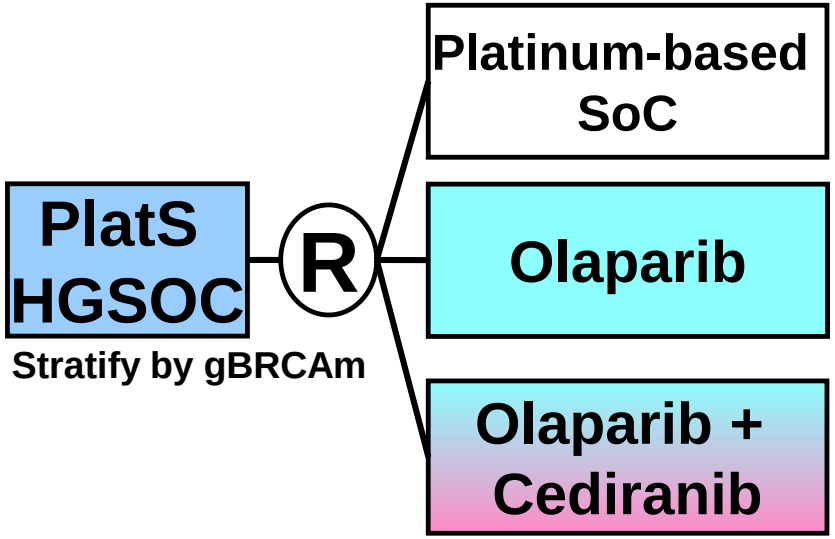
- **Ongoing phase 3 clinical trials in the upfront treatment setting using Taxol/Carboplatin + immune checkpoint inhibitor +/- anti-angiogenic drug**

Other new directions in the treatment of ovarian cancer

Targeted agents combination
PARP inhibitor olaparib and VEGF receptor inhibitor cediranib in Phase III Registration Trials

Platinum-sensitive Ovarian cancer

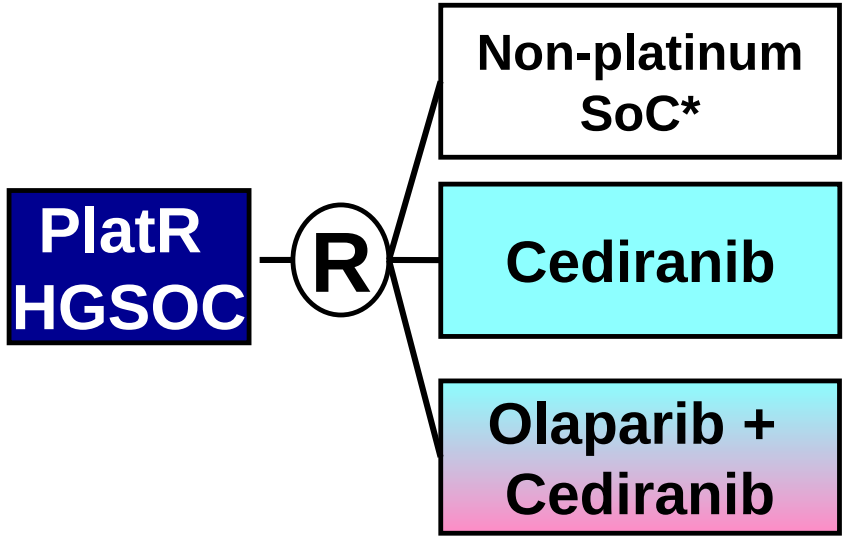
NRG GY-004



Platinum-refractory/resistant Ovarian Cancer

NRG GY-005 (PI: J Lee)

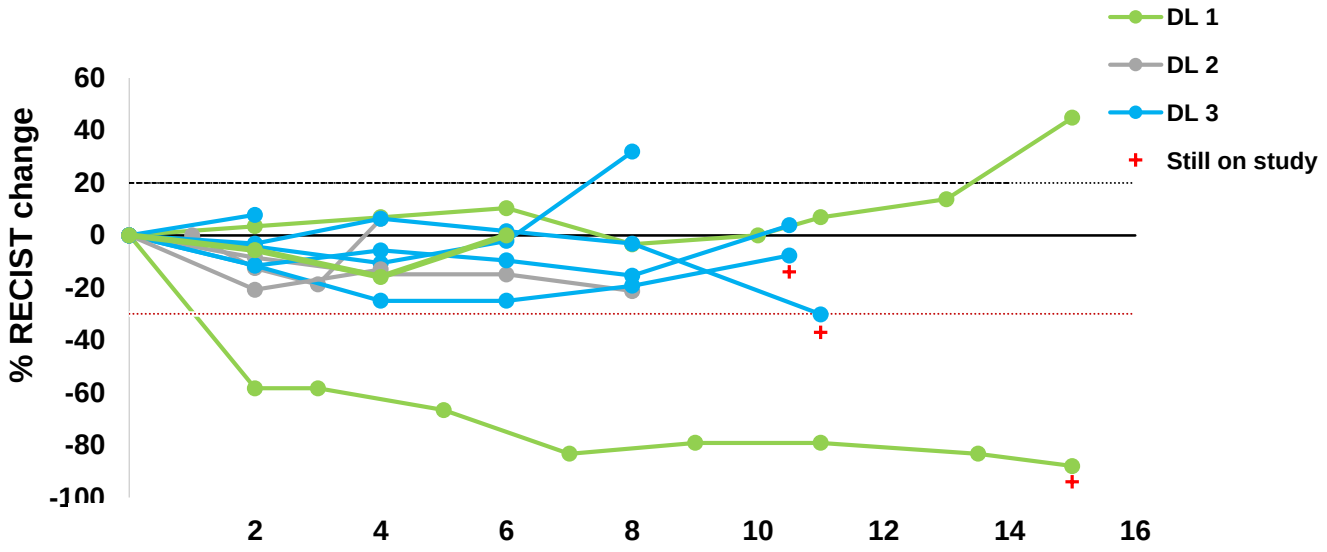
Anticipated completion of accrual: Sep 2020

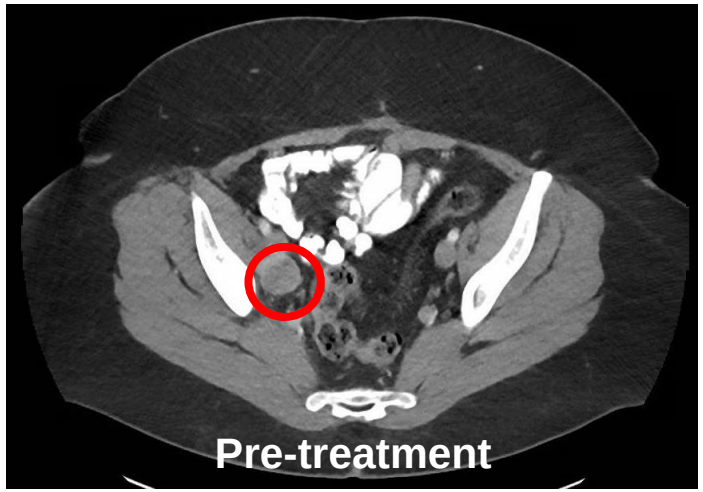


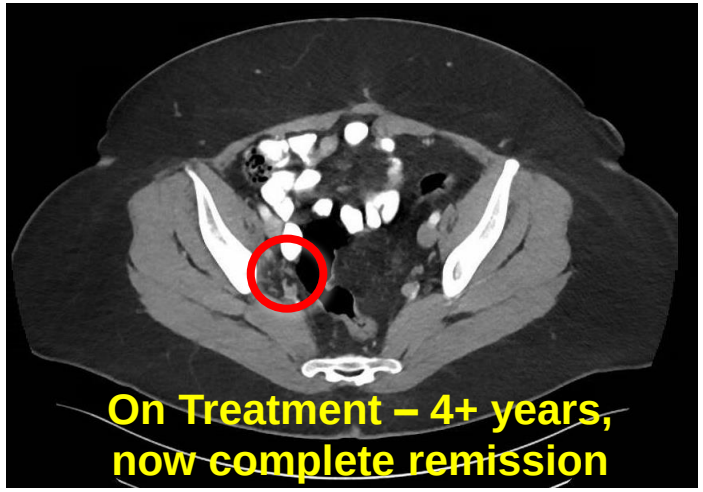
* **Weekly Taxol,** topotecan or PLD

First-in-human combination of PARP inhibition + anti-PD-L1

Phase I olaparib + durvalumab in recurrent ovarian cancer







Ongoing phase I/II trial at NCI Clinical Center (NCT02484404)

Lee *et al*, *J Clin Oncol* 2017

Conclusions

- Ovarian cancer is one of the leading cause of death in the industrialized countries

- The standard of care includes surgical resection and paclitaxel-platinum based chemotherapy

- IP chemotherapy would benefit the selected population

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- Ovarian cancer is one of the leading cause of death in the industrialized countries

- The standard of care includes surgical resection and paclitaxel-platinum based chemotherapy

- IP chemotherapy would benefit the selected population

- Ovarian cancer recurrence is common

- Paclitaxel is active either in combination with bevacizumab or as monotherapy in recurrent setting

- There are still unmet needs for highly effective less toxic therapies

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