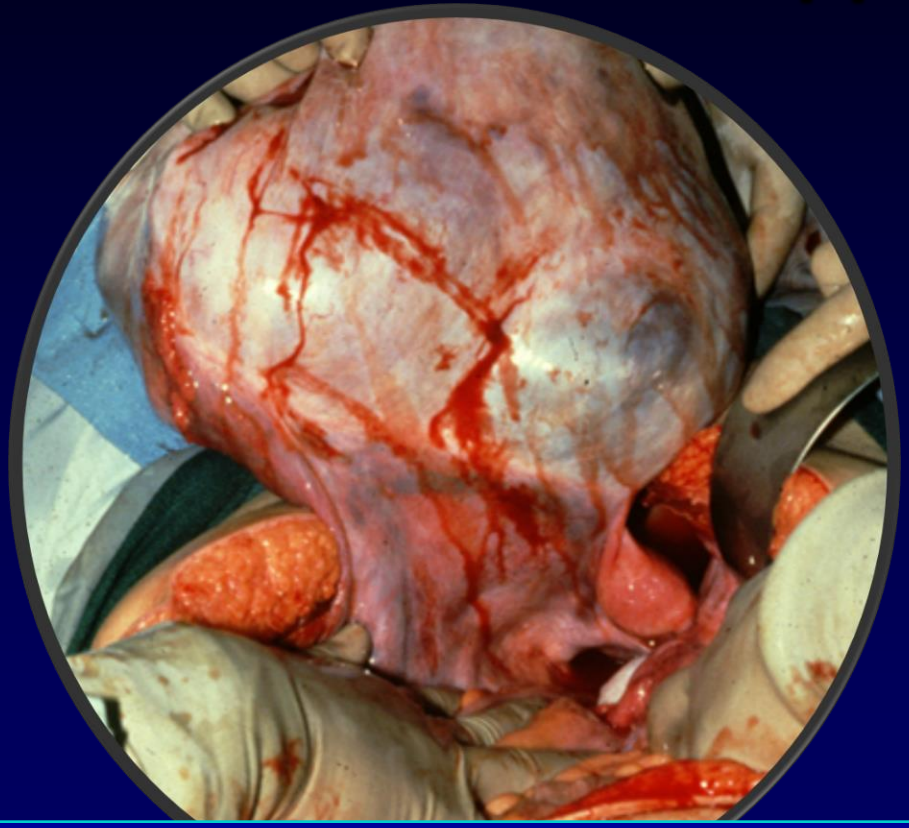
Ovarian Cancer:
Standards of Care and New Opportunities



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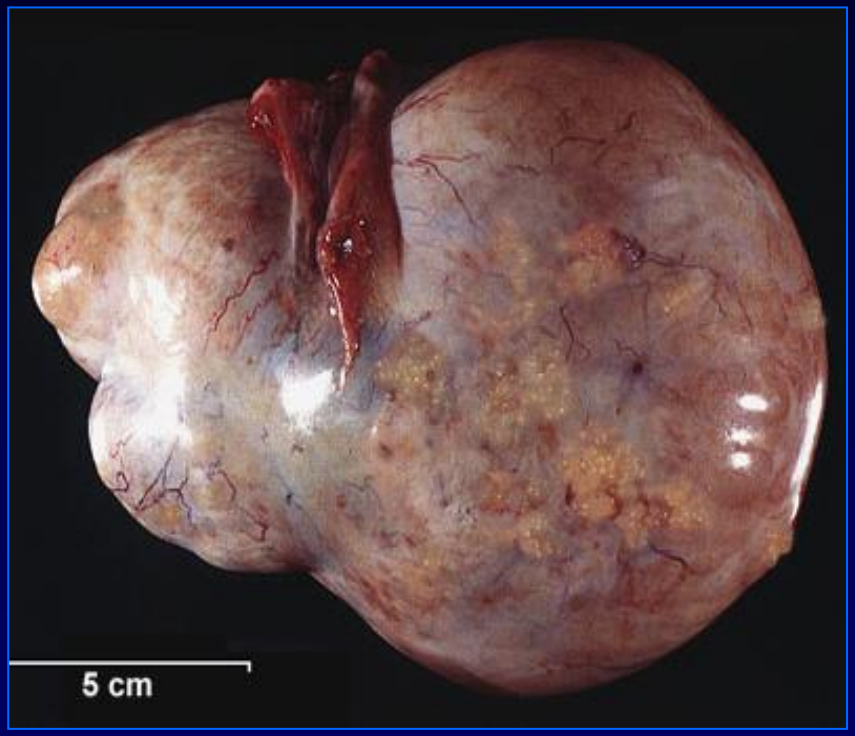
Disclosures Related to This Presentation

- Research Funding:
  - NCI-SPORE, AstraZeneca, Clovis, Roche/Genentech, V-Foundation, Novartis, Janssen, Array, Merck, Oncomed
- Scientific Steering Committee:
  - Abbvie, AstraZeneca, Biomarin, Clovis, Immunogen, NCCN, Pfizer,

Ovarian Cancer: Liner Notes

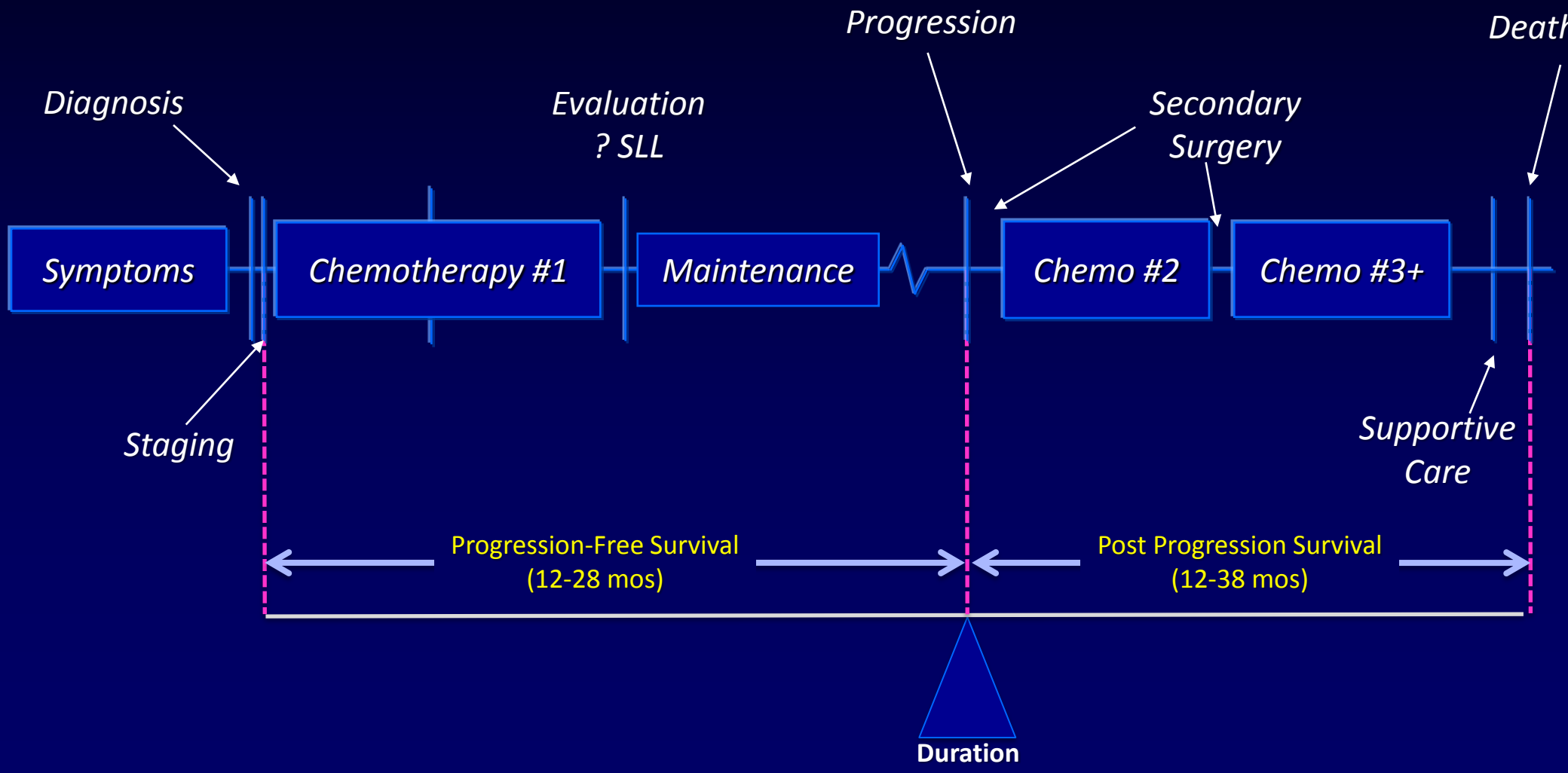
- Globally 7th most incident and lethal cancer
  - New cases: 225,000 annually
  - Deaths: 140,000 annually
- Burden of disease is greater in developed countries
- The incidence increases with age
- Almost 75% of cases present with advanced stage III / IV disease



- Risk of relapse of advanced stage disease is as high as 70%

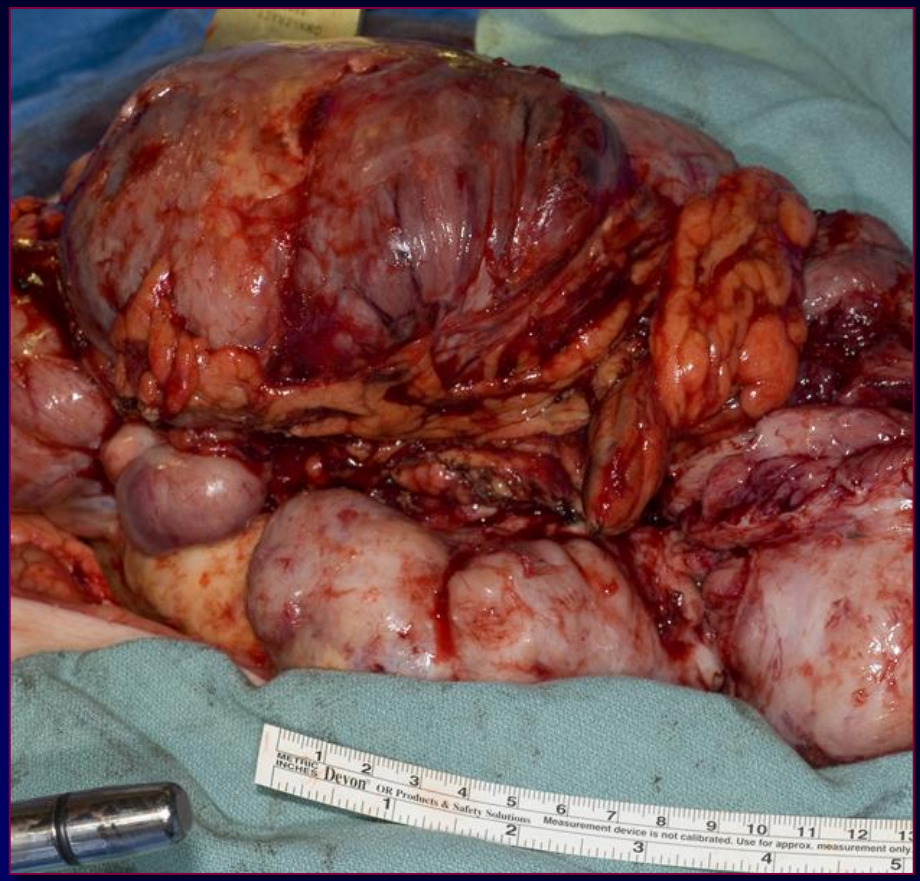
CA Cancer, 2014

Ovarian Cancer: Natural History

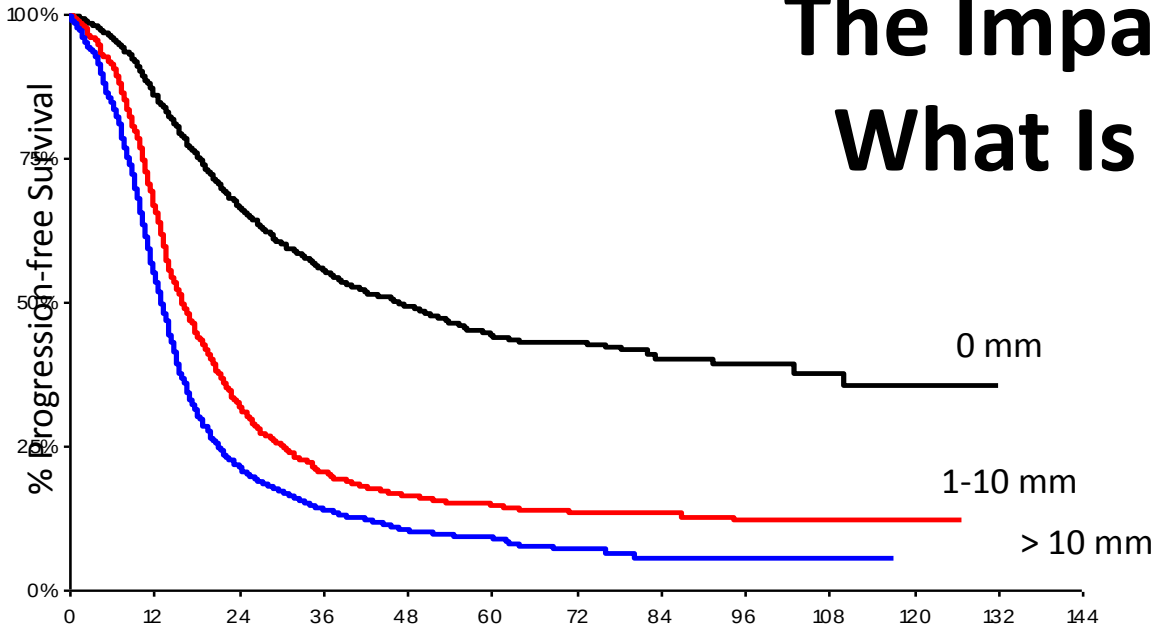


Surgical Management of Primary Ovarian Cancer

- Theoretical:
  - Reduced the volume of hypoxic, poorly perfused cells
  - Host immunocompetence is improved with lower tumor burden
  - Recruitment of residual cells into G1 potentiating the effects of cytotoxic therapy
  - Removal of chemoresistant clones
- Practical:
  - Immediate relief of symptoms
  - Diagnosis

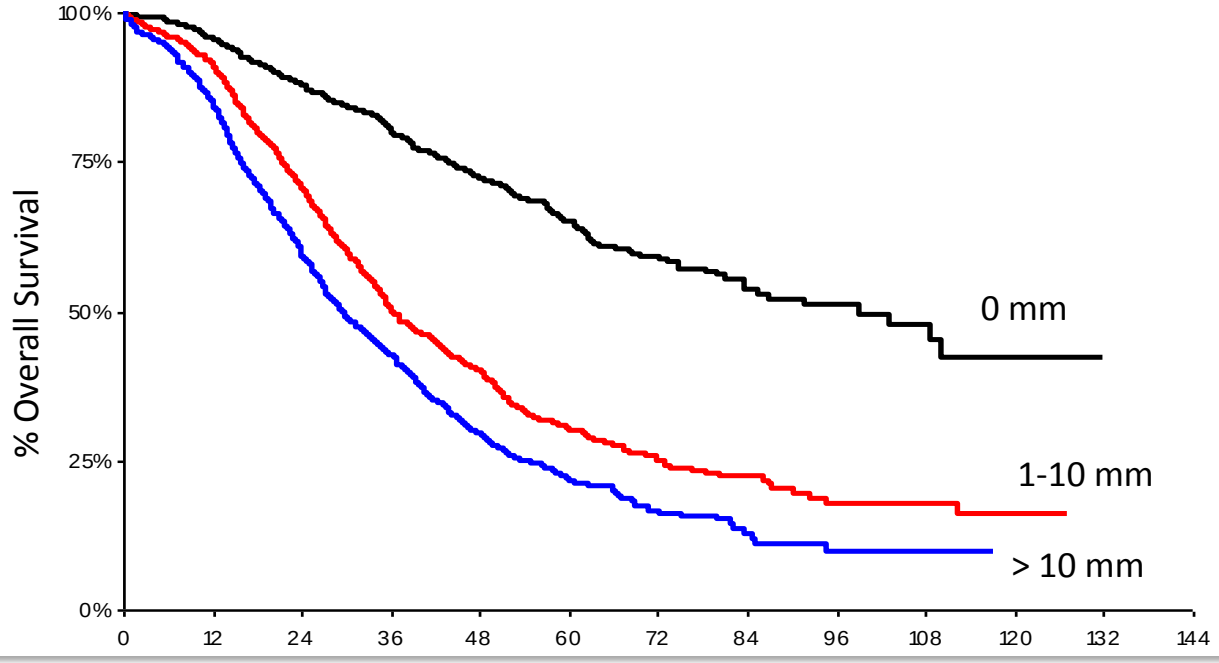


The Impact of Residual Tumor: What Is Optimal Debulking?



	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

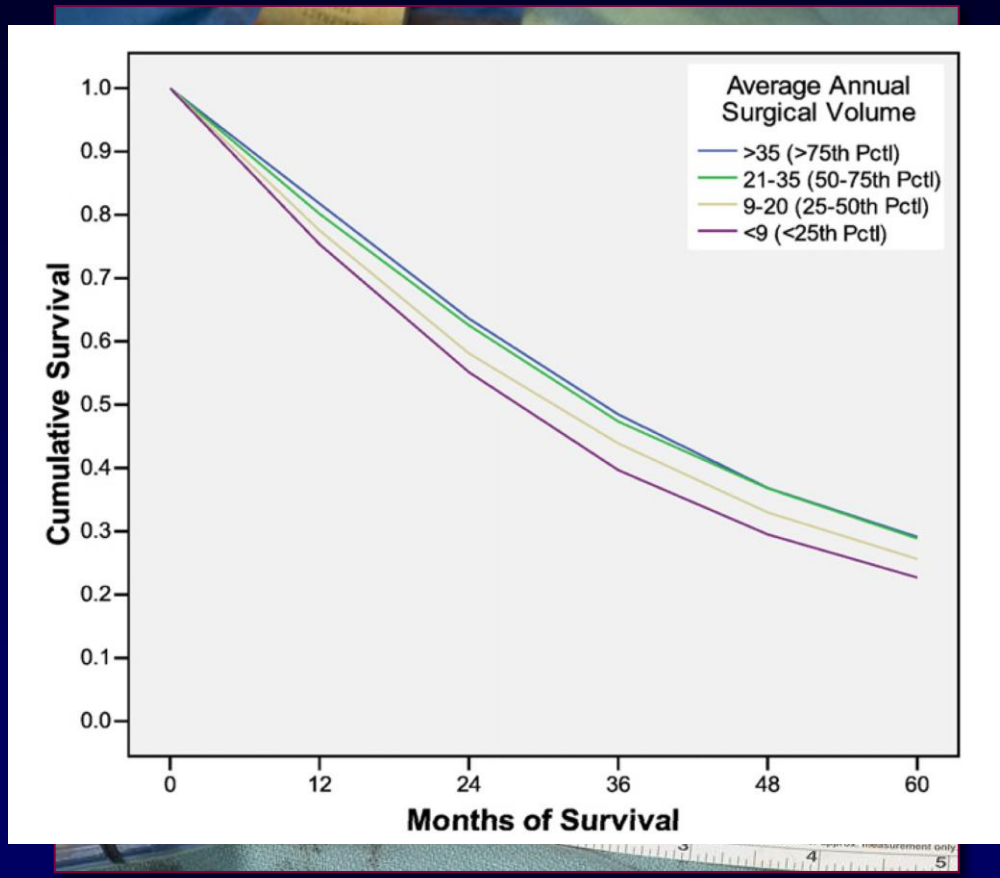
	HR	(95%CI)
1-10 mm vs. 0 mm:	2.70	(2.37; 3.07)
>10 mm vs. 1-10 mm:	1.34	(1.21; 1.49)

log-rank: $p < 0.0001$

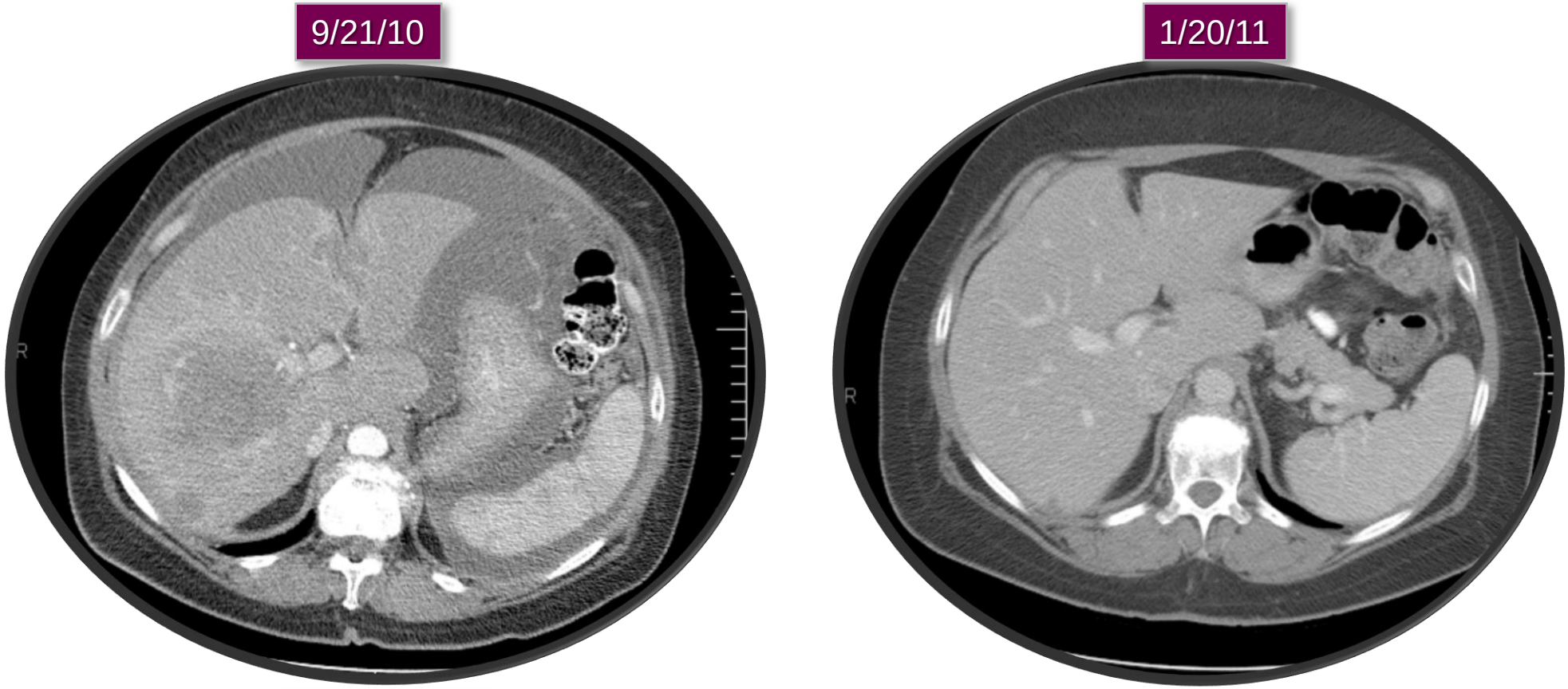
DuBois, Cancer (2009)115:1234

Surgical Management of Primary Ovarian Cancer

- "Biology" vs "Brawn"
  - Does innate biology drive surgical resectability?
  - Can surgical effort overcome or supersede biological determinism?
- Short answer:
  - Yes/Yes
  - Biology > Surgical effort
    - » Horowitz, JCO 2015
  - Surgeon/Hospital/NCI-CCC dependent
    - » Bristow JNCI 2015, J Am Coll Surg 2015



Neoadjuvant Chemotherapy in Ovarian Cancer



Primary Approach: What's Best?

The NEW ENGLAND JOURNAL of MEDICINE

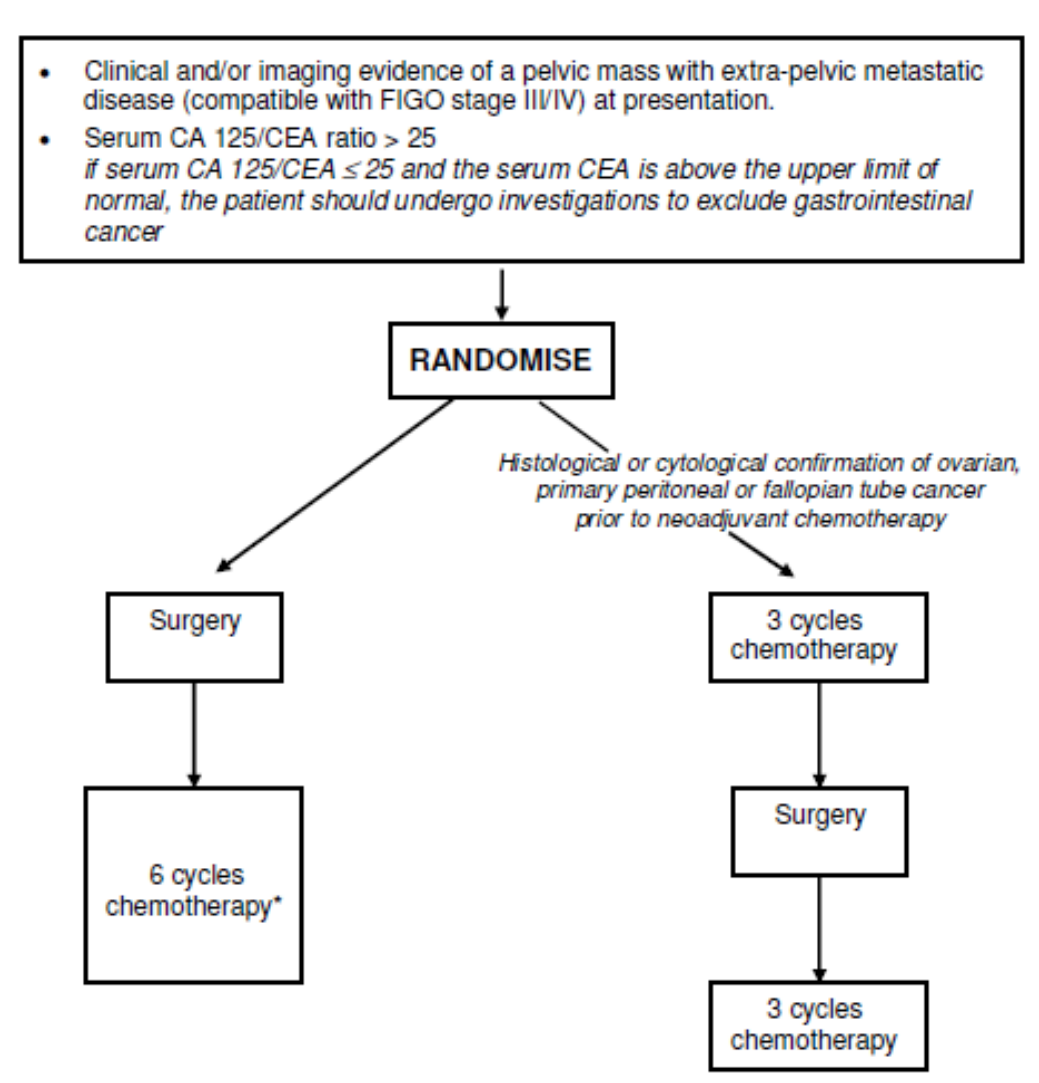
ORIGINAL ARTICLE

Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D., Frédéric Amant, M.D., Ph.D., Gunnar B. Kristensen, M.D., Ph.D., Tom Ehlen, M.D., Nick Johnson, M.D., René H.M. Verheijen, M.D., Ph.D., Maria E.L. van der Burg, M.D., Ph.D., Angel J. Lacave, M.D., Pierluigi Benedetti Panici, M.D., Ph.D., Gemma G. Kenter, M.D., Ph.D., Antonio Casado, M.D., Cesar Mendiola, M.D., Ph.D., Corneel Coens, M.Sc., Leen Verleye, M.D., Gavin C.E. Stuart, M.D., Sergio Pecorelli, M.D., Ph.D., and Nick S. Reed, M.D., for the European Organization for Research and Treatment of Cancer–Gynaecological Cancer Group and the NCIC Clinical Trials Group* — a Gynecologic Cancer Intergroup Collaboration

N Engl J Med (2010) 363:943

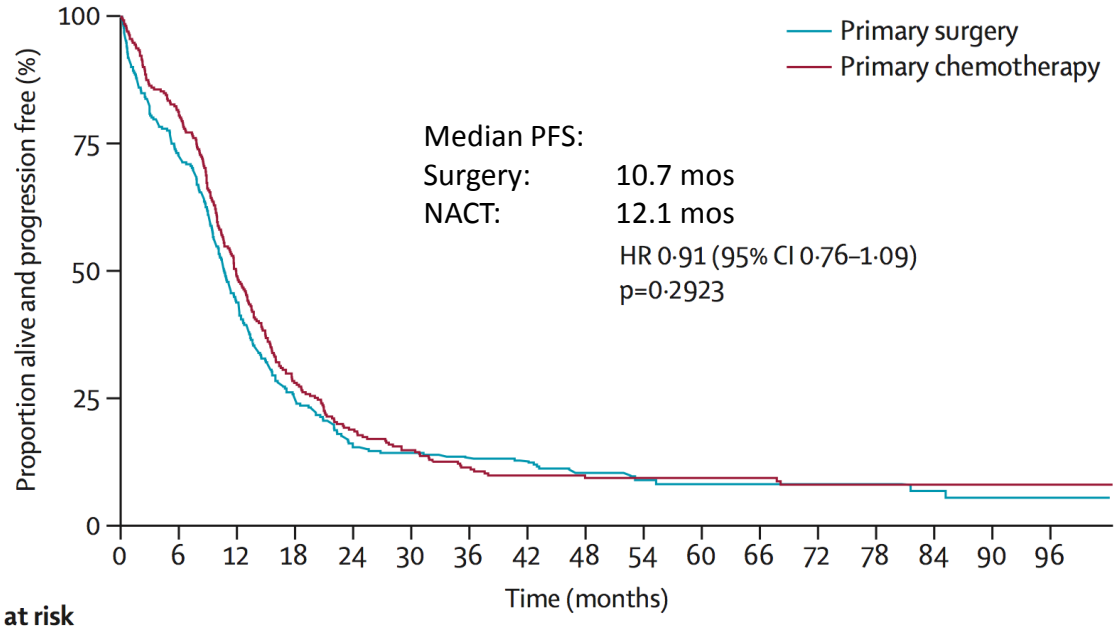
CHORUS: Chemo or Upfront Surgery



	Primary surgery (n=276)	Primary chemotherapy (n=274)	Total (n=550)
Median age (years)	66 (26–87, 57–72)	65 (34–88, 59–71)	65 (26–88, 58–72)
Median tumour size (cm)	8 (0·7–30, 5–12)	8 (0·9–28, 5–12)	8 (0·7–30, 5–12)
≤2 cm	13 (5%)	13 (5%)	26 (5%)
≤5 cm	59 (21%)	60 (22%)	119 (22%)
≤10 cm	111 (40%)	110 (40%)	221 (40%)
≤20 cm	79 (29%)	79 (29%)	158 (29%)
>20 cm	7 (3%)	7 (3%)	14 (3%)
Unmeasurable disease	7 (3%)	5 (2%)	12 (2%)
Clinical FIGO stage			
III	206 (75%)	206 (75%)	412 (75%)
IV	70 (25%)	68 (25%)	138 (25%)
CA125/CEA ratio			
>25	272 (99%)	268 (98%)	540 (98%)
≤25	4 (1%)	6 (2%)	10 (2%)
WHO performance status			
0	83 (30%)	88 (32%)	171 (31%)
1	138 (50%)	133 (49%)	271 (49%)
2	53 (19%)	49 (18%)	102 (19%)
3	1 (<1%)	4 (1%)	5 (1%)
Missing data	1	0	1
Prespecified chemotherapy regimen			
Single agent carboplatin	66 (24%)	63 (23%)	129 (23%)
Carboplatin plus paclitaxel	207 (75%)	210 (77%)	417 (76%)
Carboplatin plus other chemotherapy agent	3 (1%)	1 (<1%)	4 (1%)

Data are median (range, IQR) or n (%; percentages calculated for patients with non-missing data). FIGO=International Federation of Gynaecology and Obstetrics. CA125=cancer antigen 125. CEA=carcinoembryonic antigen.

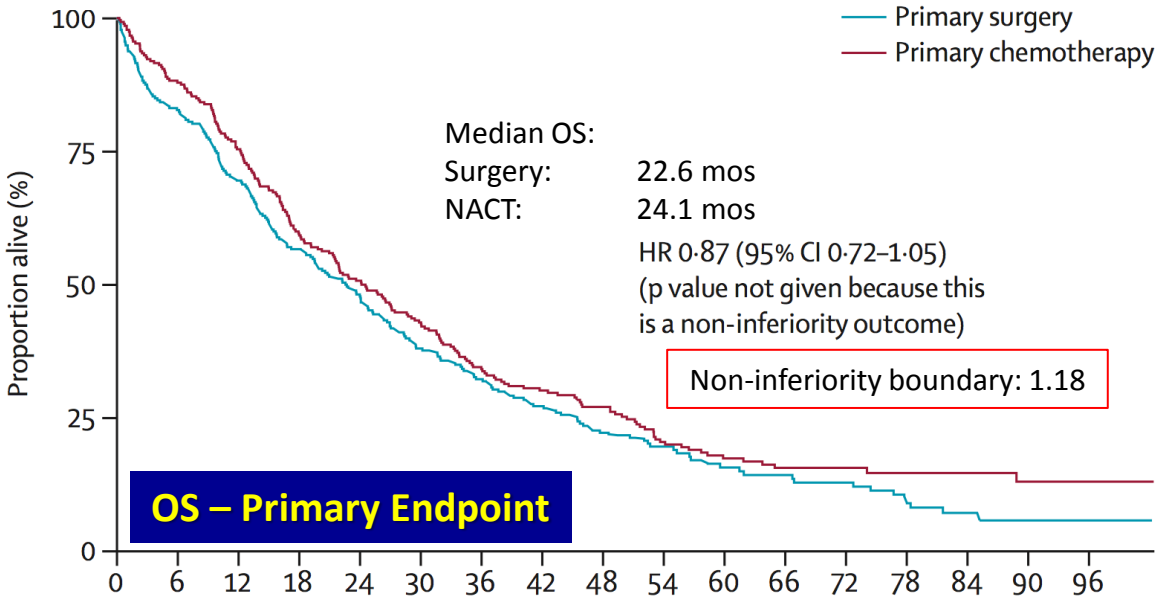
PFS



Median PFS:
Surgery: 10.7 mos
NACT: 12.1 mos
HR 0·91 (95% CI 0·76–1·09)
p=0·2923

Number at risk

Primary surgery	276	198	119	68	41	35	23	10	9	5	3
Primary chemotherapy	274	221	133	76	51	30	19	17	11	7	2



Median OS:
Surgery: 22.6 mos
NACT: 24.1 mos
HR 0·87 (95% CI 0·72–1·05)
(p value not given because this is a non-inferiority outcome)

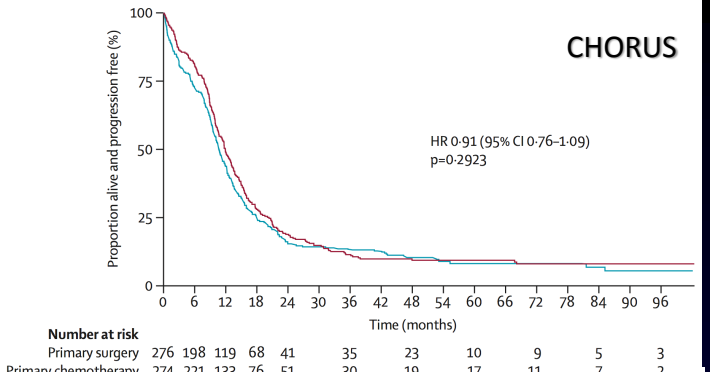
Non-inferiority boundary: 1.18

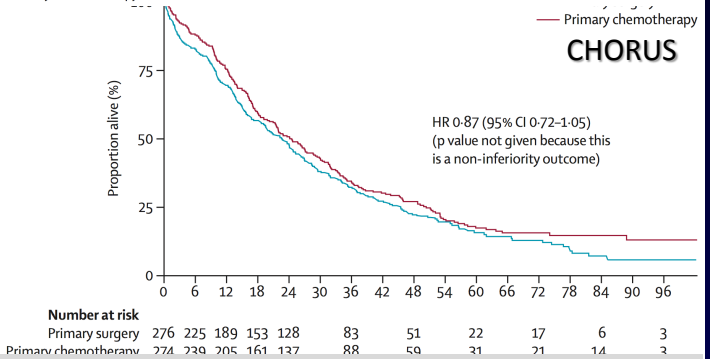
OS – Primary Endpoint

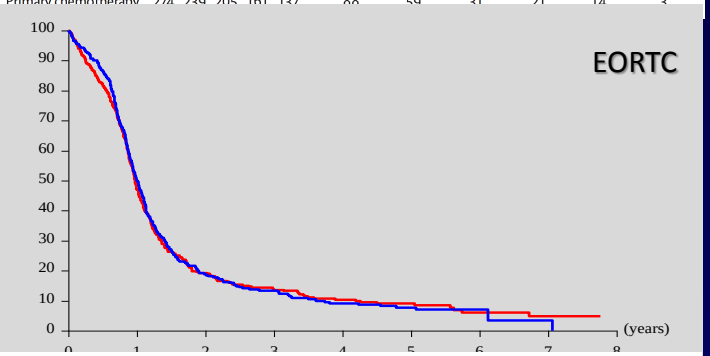
Number at risk

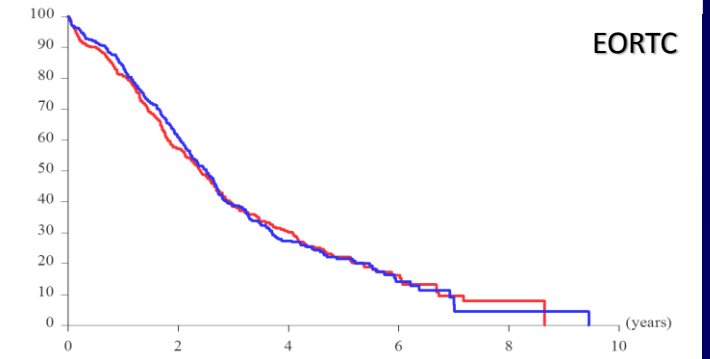
Primary surgery	276	225	189	153	128	83	51	22	17	6	3
Primary chemotherapy	274	239	205	161	137	88	59	31	21	14	3

Kehoe Lancet Oncol 2015









EORTC & CHORUS Criticisms:

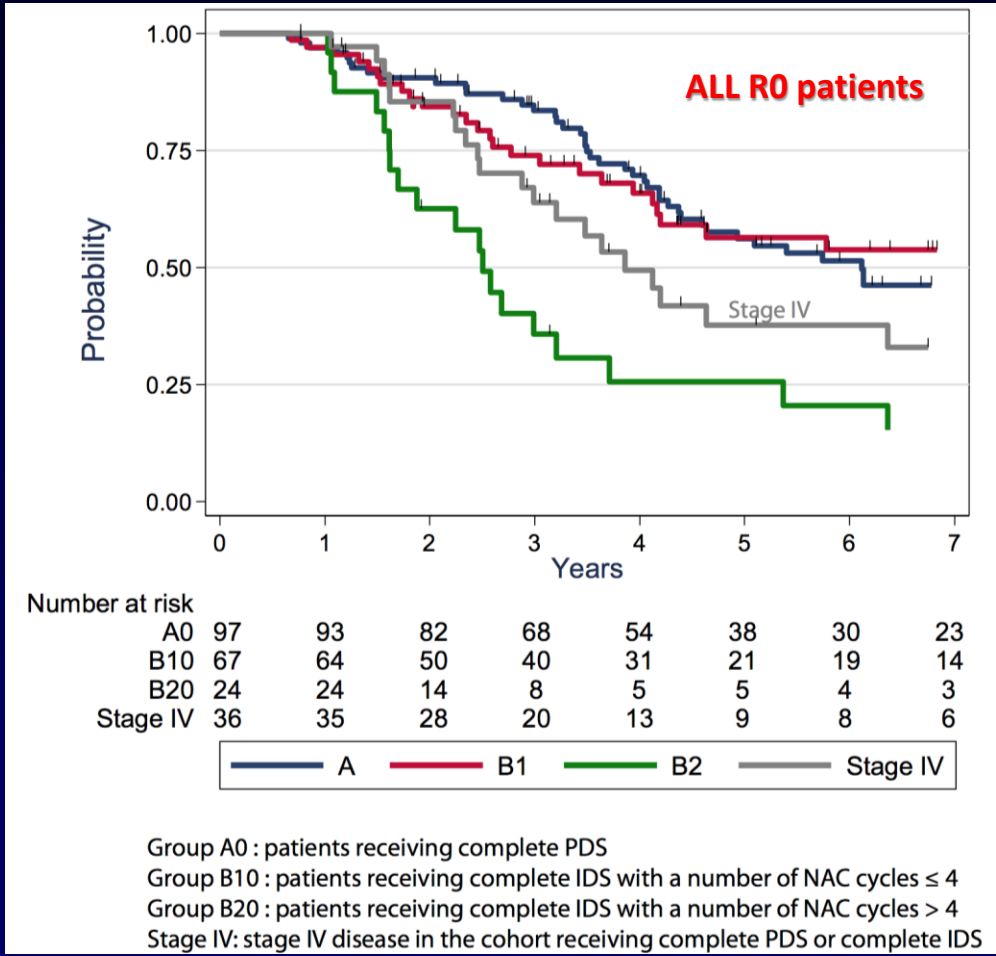
- Although randomized trials represent high-risk population
- Lack of surgical effort or standardization
- Low rates of R0
- Lower than expected survival statistics (PFS and OS)

Selection of Surgical Candidates

- Easy to assess:
  - Medically unfit/unstable
    - » High intraoperative surgical risk (cardiovascular, pulmonary, etc)
    - » High postoperative healing risk (uncontrolled DM, steroid dependency, etc)
- Harder to assess:
  - Heavy disease burden not amenable to resection
    - » Hepatic, portal, extra-abdominal disease
  - Heavy disease burden not amenable to optimal resection
    - » Upper abdomen, diaphragm, pleural
- Few validated tools to help (serum biomarker, genomics, imaging, nomograms, laparoscopy)

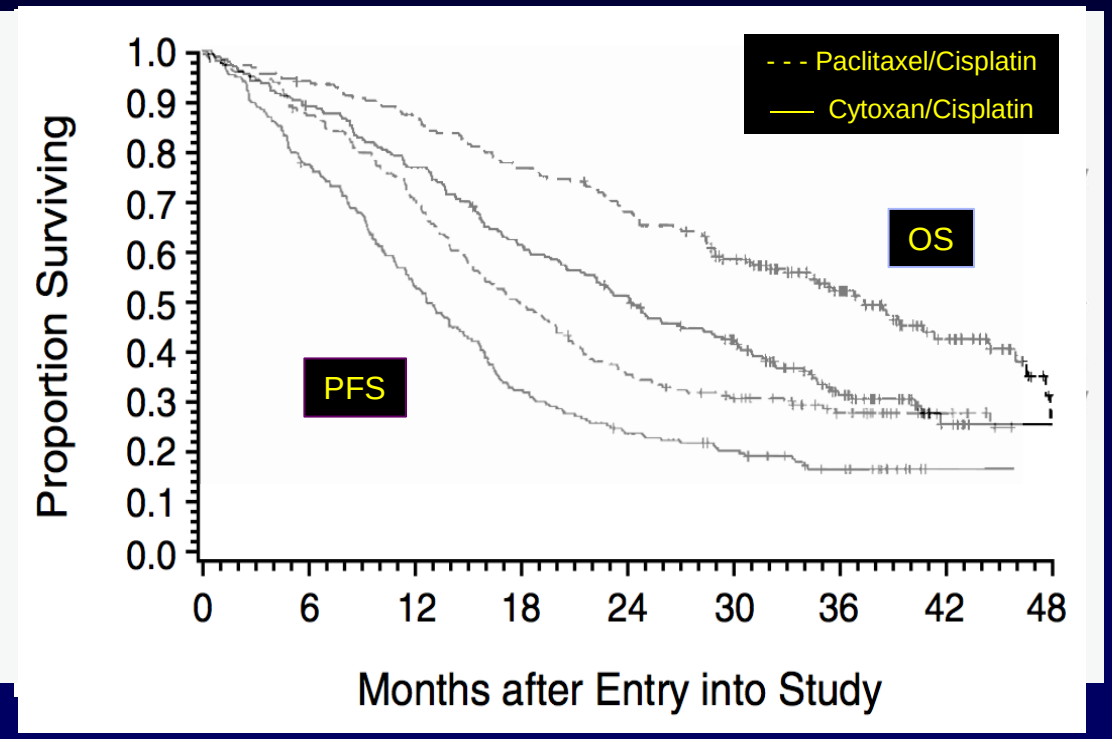
Is There a "Sweet Spot" for NACT Induction

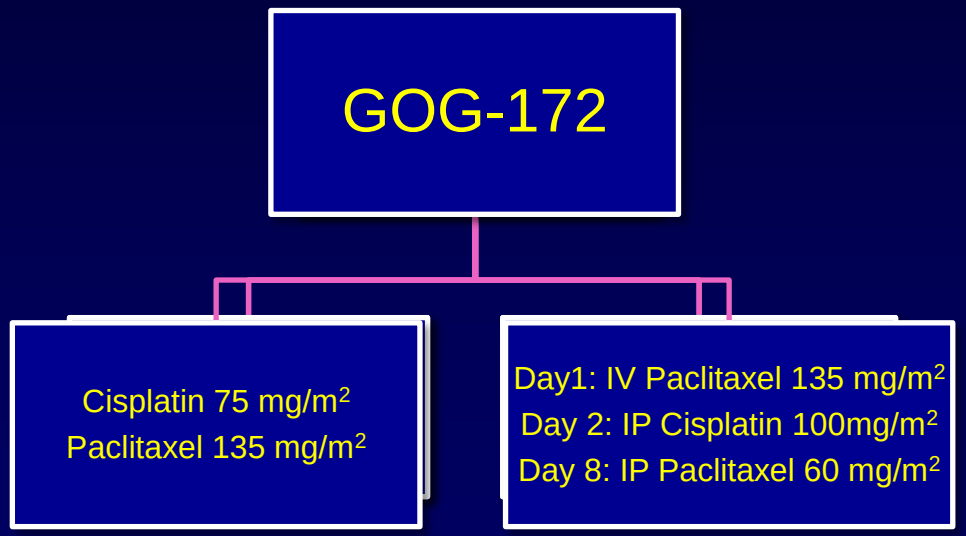
- N = 367
- PDS: 220 (44% R0)
- NACT/IDS: 147 (62% R0)
  - 110 <4 NACT cycles (62% R0)
  - 37 ≥ 4 NACT cycles (65% R0)



Principle Approach: I^{o} Therapy

Chemotherapy





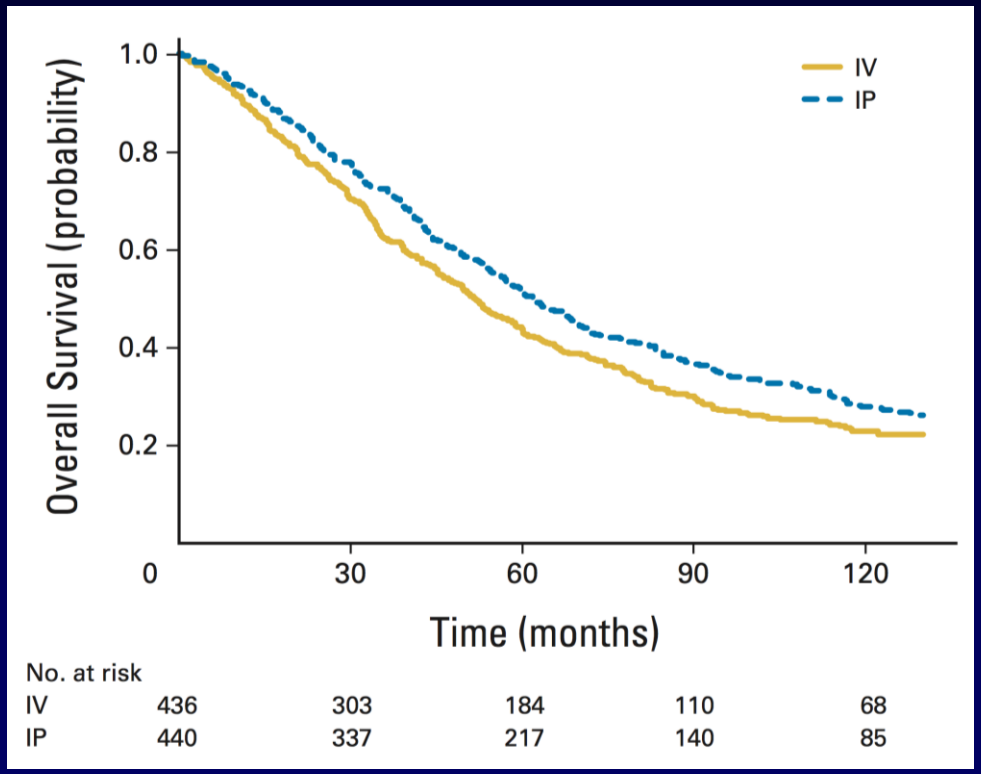
McGuire New Engl J Med (1996) 334:1
Ozols, J Clin Oncol (2003) 21:3194
Armstrong New Engl J Med (2006) 354:34

Intraperitoneal Chemotherapy: Summary

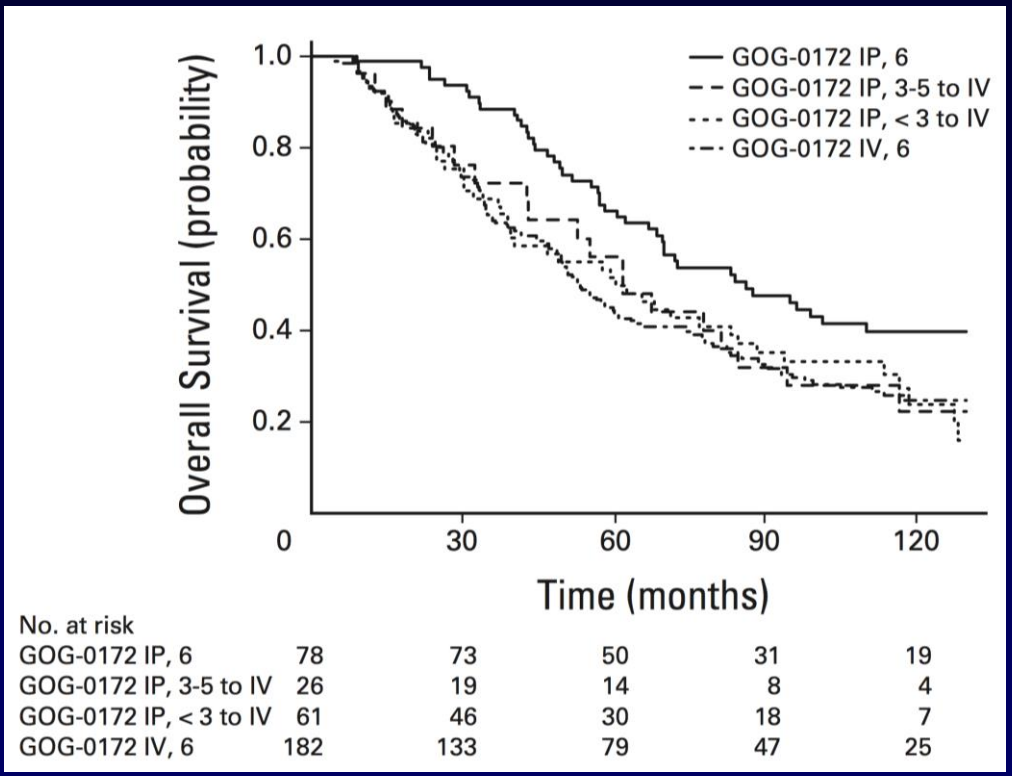
	Median PFS (mo)		HR	Median OS (mo)		HR
	IV	IP		IV	IP	
GOG 104 Alberts	--	--	--	41	49	0.76 (*P* = 0.02)
GOG 114 Markman	22	28	0.78 (*P* = 0.01)	52	63	0.81 (*P* = 0.05)
GOG 172 Armstrong	18.3	23.8	0.80 (*P* = 0.05)	50	66	0.75 (*P* = 0.03)

Long Term Results from IP

Combined GOG114/172 data 10 year Survival



GOG172 survival by #cycles



Tewari, D J Clin Oncol 2015

JOURNAL OF CLINICAL ONCOLOGY

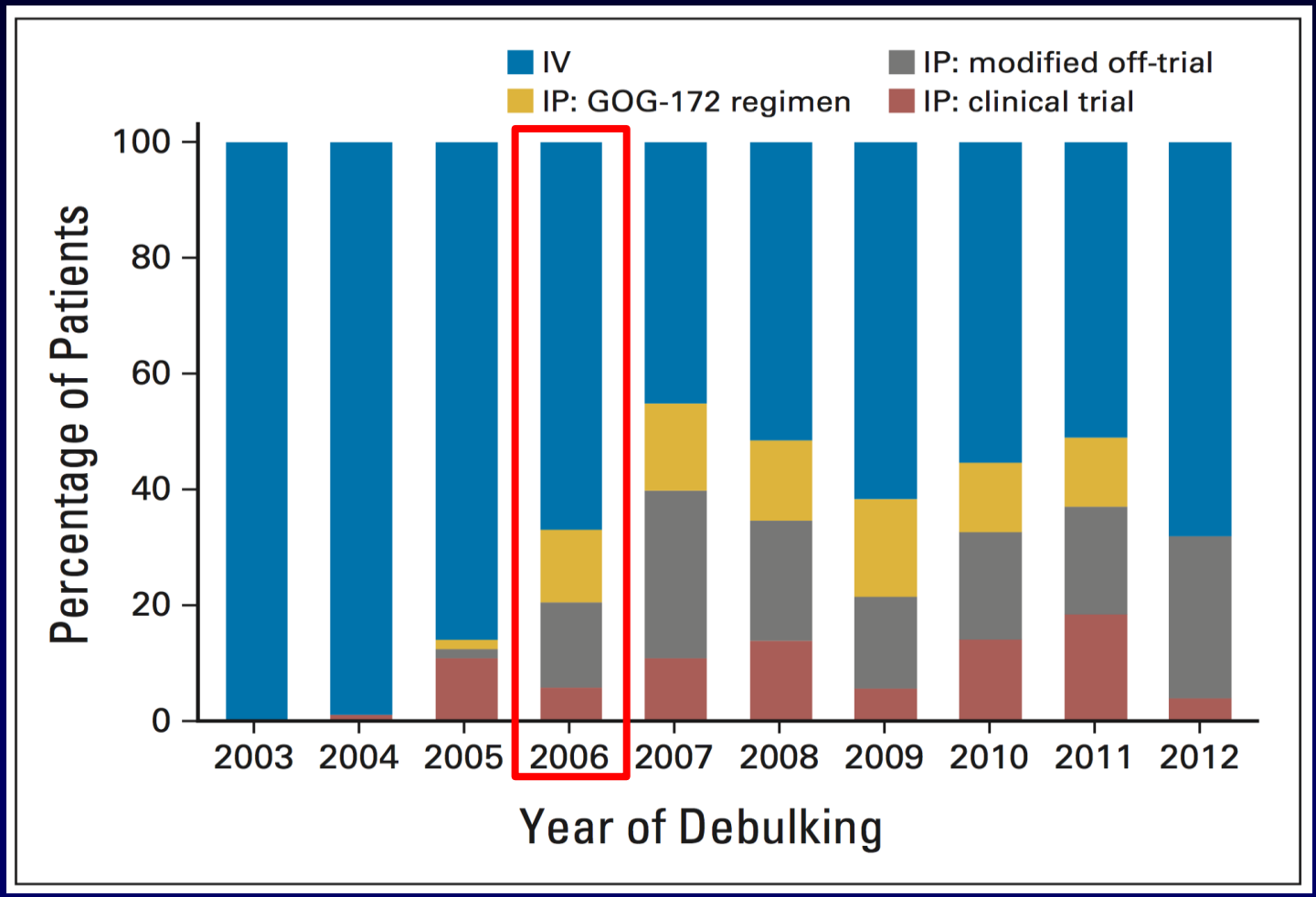
ORIGINAL REPORT

Use and Effectiveness of Intraperitoneal Chemotherapy for Treatment of Ovarian Cancer

Alexi A. Wright, Angel Cronin, Dana E. Milne, Michael A. Bookman, Robert A. Burger, David E. Cohn, Mihaela C. Cristea, Jennifer J. Griggs, Nancy L. Keating, Charles F. Levenback, Gina Mantia-Smaldone, Ursula A. Matulonis, Larissa A. Meyer, Joyce C. Niland, Jane C. Weeks, and David M. O'Malley

Aug, 2015

- N=832
- 6 NCCN sites
- Stage III, ≤1cm
- Usual practice



Moving The Bar: Primary Therapy

- Triplets
- Dose-dense therapy
- IP Chemotherapy modifications
- Biological targets: angiogenesis, PARP, angiopoietin, immune checkpoint, Wee-1, etc

International Phase III Experience

	CP	CPG	CP±PLD	CT→CP	CG→CP	PLD-C	CE	Total
GOG0182-ICON5	864	864	862	861	861			4312
SCOTROC						9		1077
AGO-GINECO							647	1282
NSGO-EORTC-NCIC-G							443	887
MITO								326
AGO-GINECO-GERCO NSGO								1742
NCIC-EORTC-GEICO G								819
MITO-2	410		410					820
Regimen Total:	4762	1724	1272	1836	861	539	1090	**11265**

No Significant Effect

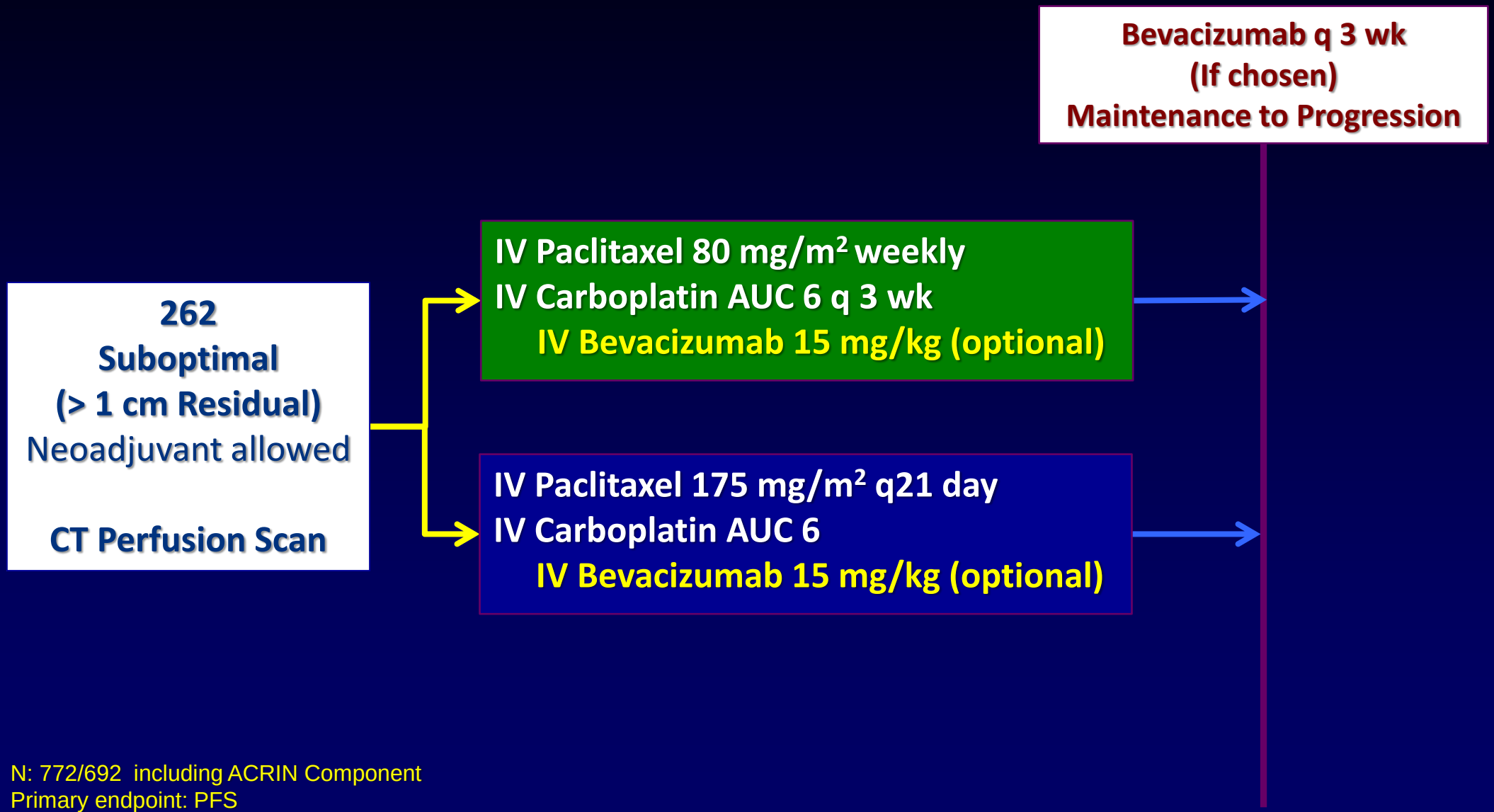
More ≠ Better

Different ≠ Better

Dose-Dense Chemotherapy: Summary

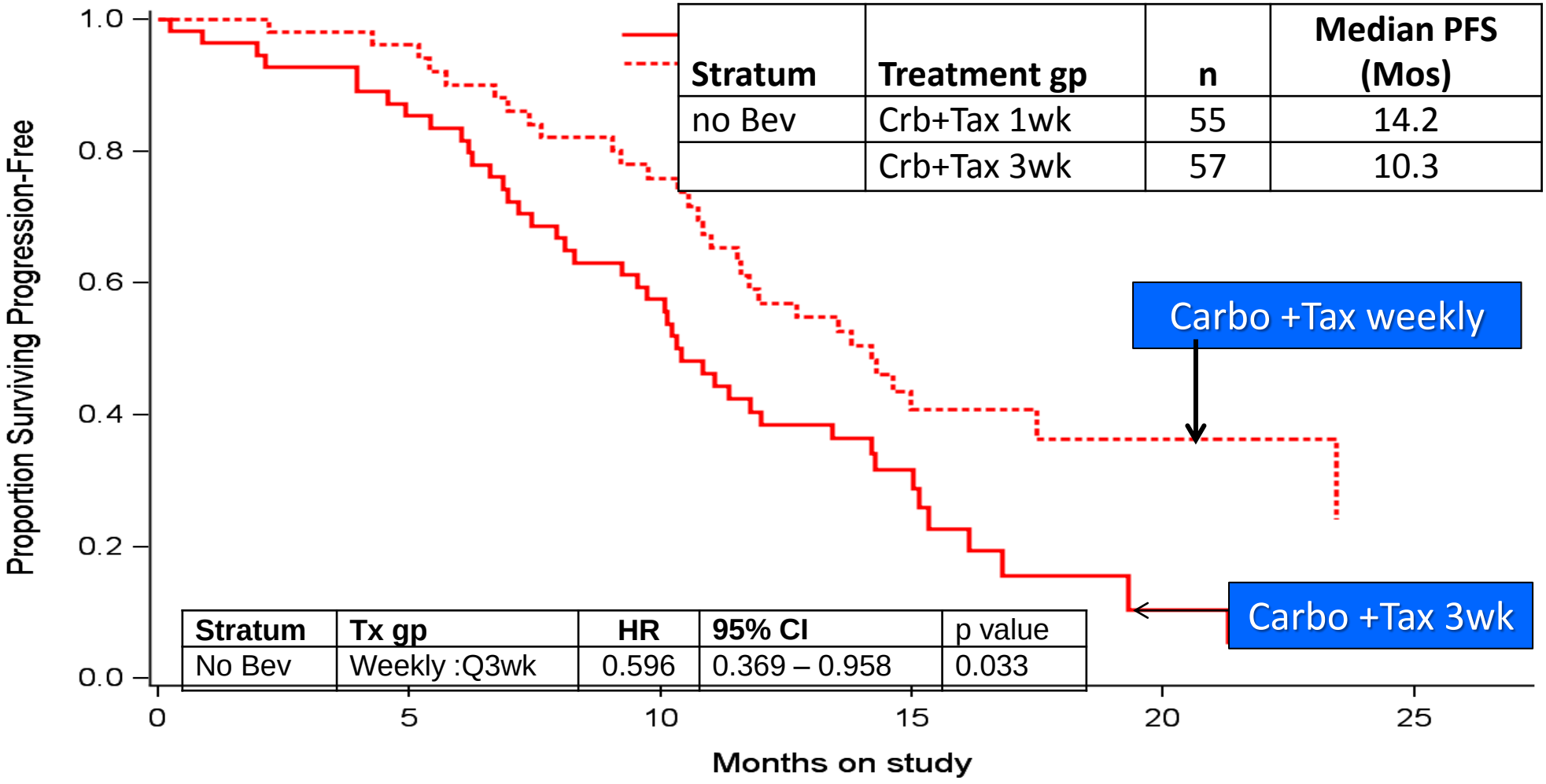
	Median PFS (mo)		HR	Median OS (mo)		HR	Comments
	q21	dd		q21	dd		
JGOG3016 N = 631	17.5	28.2	0.76 (*P* = 0.003)	62.2	NR	0.79 (*P* = 0.04)	Stage II-IV Allowed 6-9 cycles No benefit in rare subtypes
MITO-7 N = 810	17.3	18.3	0.96 (*P* = NS)	2yr: 79%	2yr: 77%	1.20 (*P* = NS)	Carboplatin also give dd (AUC2)
GOG 262 N = 692	14.3	14.8	0.97 (*P* = NS)	28.0	NR	NS (immature)	Bevacizumab was optional (chosen 84%) If chosen, given to progression

GOG Ovarian Strategy: 262



N: 772/692 including ACRIN Component
Primary endpoint: PFS

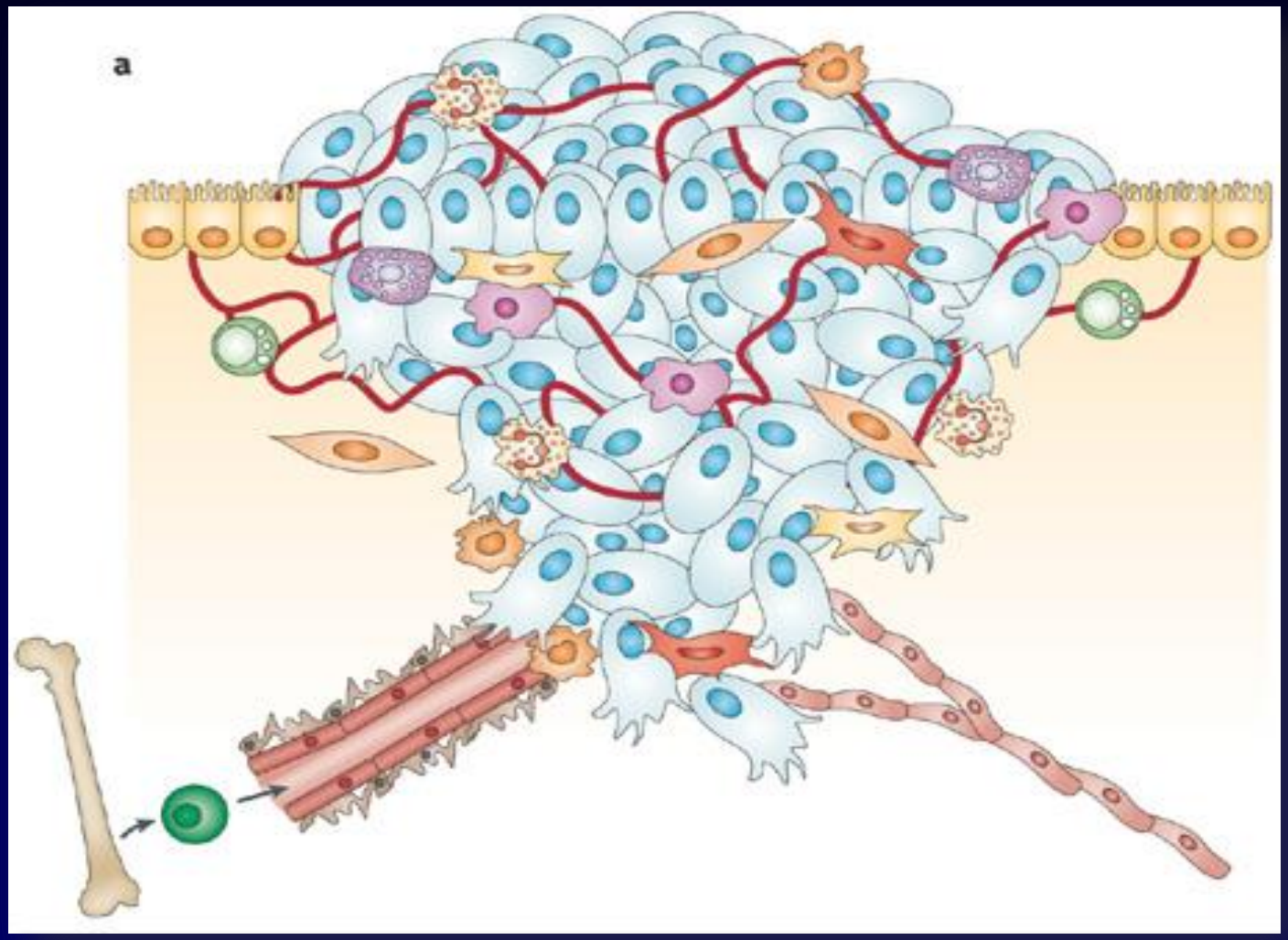
GOG 262: PFS by Randomized Treatment ddT vs. q3wkT stratified by those not choosing Bevacizumab (n=112, 16%)

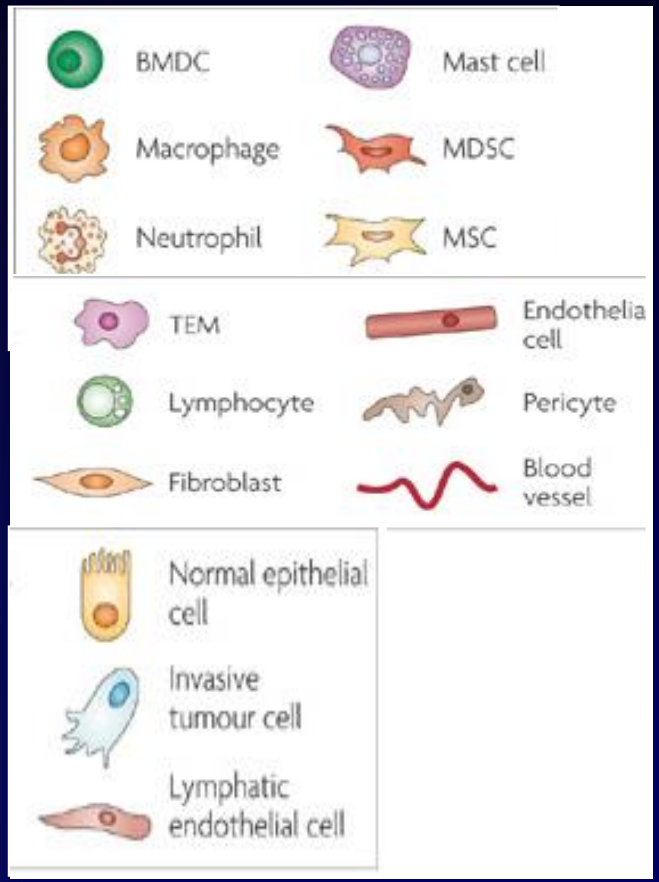


Stratum	Treatment gp	n	Median PFS (Mos)
no Bev	Crb+Tax 1wk	55	14.2
	Crb+Tax 3wk	57	10.3

Stratum	Tx gp	HR	95% CI	p value
No Bev	Weekly :Q3wk	0.596	0.369 – 0.958	0.033

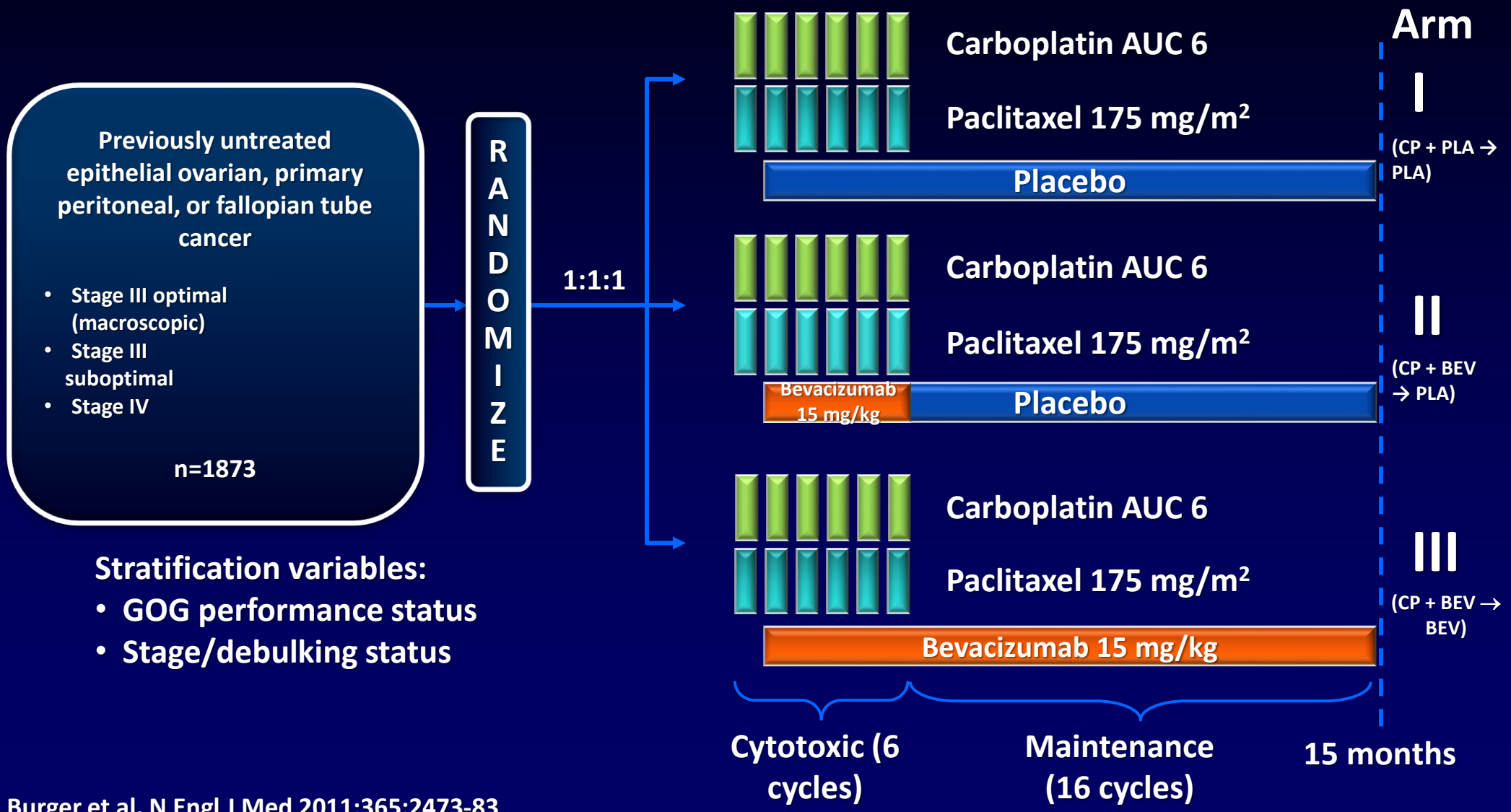
Angiogenesis: The Microenvironment





Joyce JA, et al. *Nat Rev Cancer.* 2009;9(4): -252.

GOG-0218 study schema



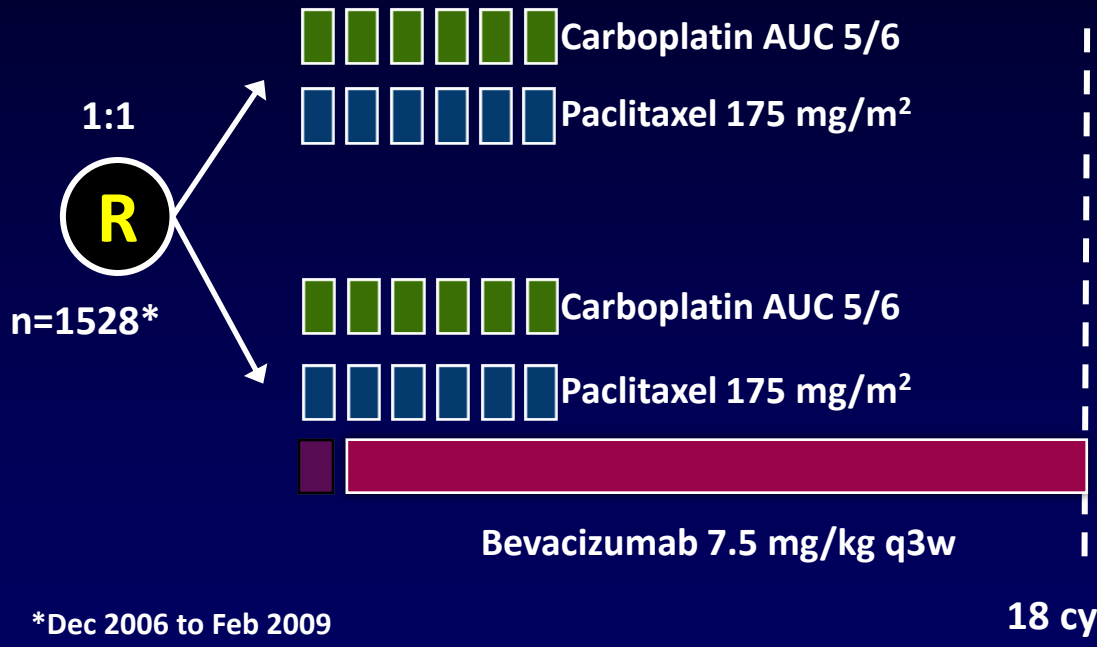
Stratification variables:

- **GOG performance status**
- **Stage/debulking status**

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

Schema

ICON7
Bevacizumab in Ovarian Cancer



*Dec 2006 to Feb 2009

Stratification variables:

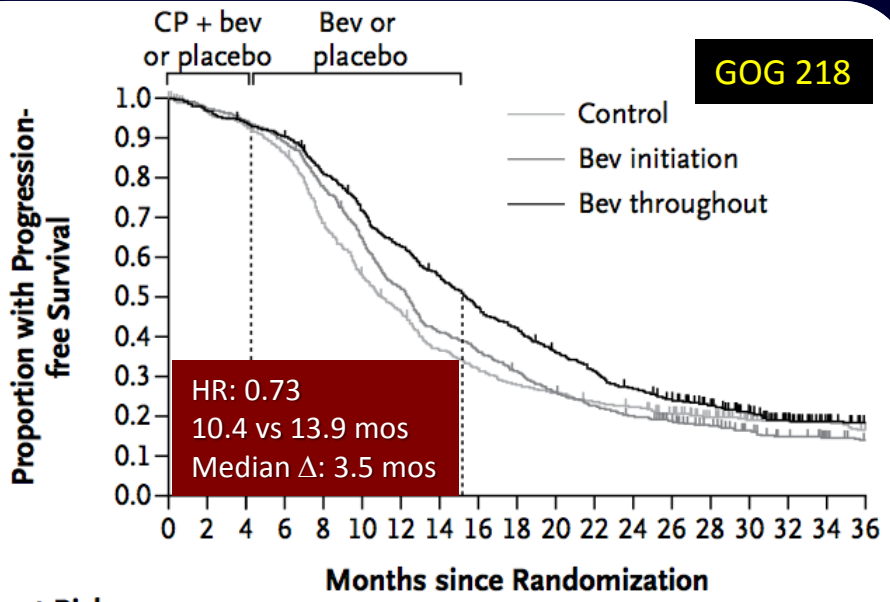
- **Stage & extent of debulking: I–III debulked ≤1cm vs stage I–III debulked >1 cm vs stage IV and inoperable stage III**
- **Timing of intended treatment start ≤4 vs >4 weeks after surgery**
- **GCIG group**

Academic-led, industry-supported trial to investigate use of bevacizumab and to support licensing

Perrin, N Engl J Med 2011;365:2484-96

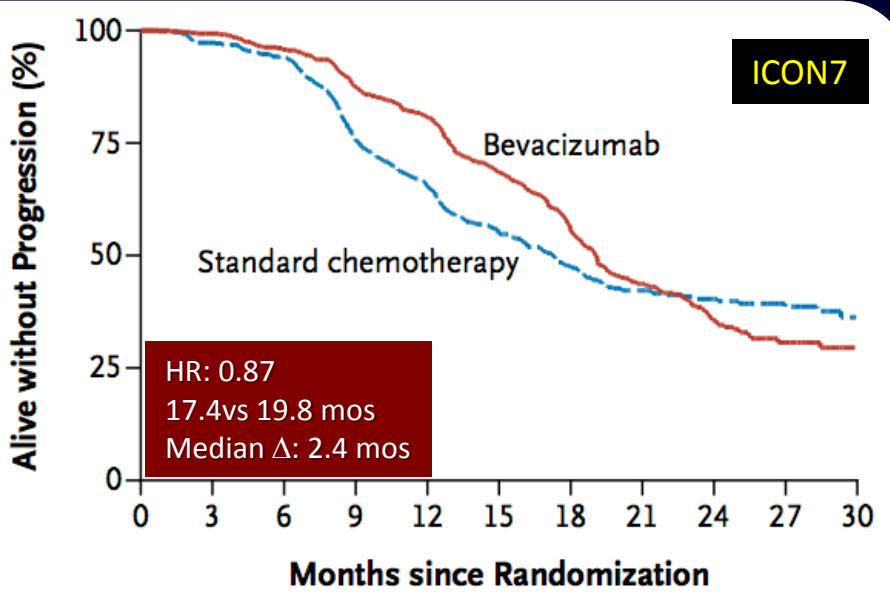
Anti-VEGF Targeting: Frontline

PFS



No. at Risk							
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

Burger, NEJM (2011) 365:2473



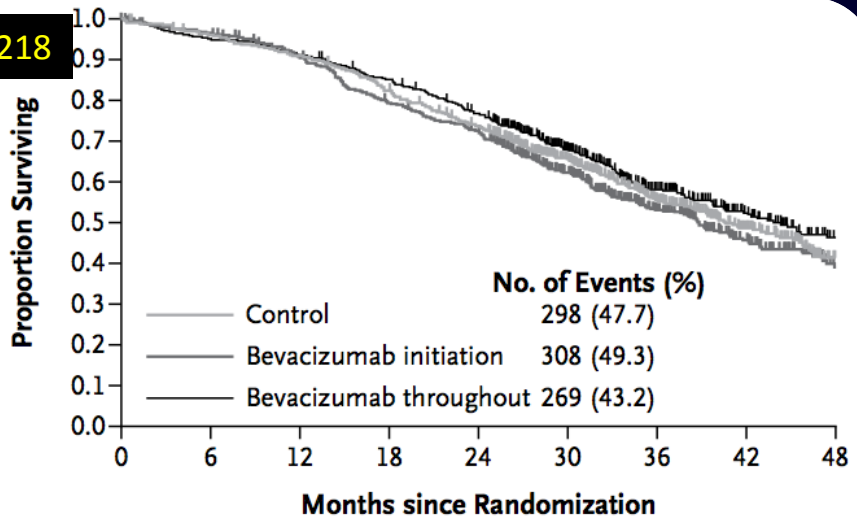
No. at Risk						
Standard chemo-therapy	764	693	464	216	91	25
Bevacizumab	764	715	585	263	73	19

Perren, NEJM (2011) 365:2484

Anti-VEGF Targeting: Frontline

Overall Survival

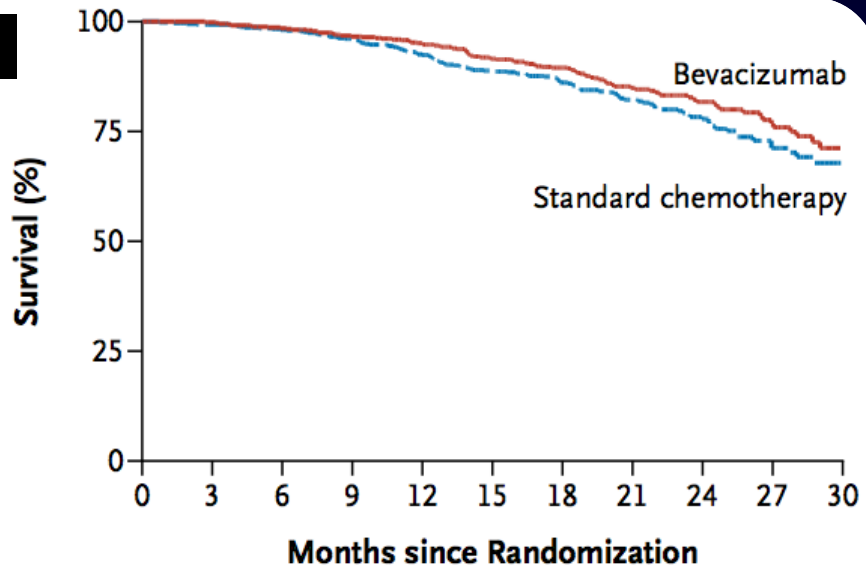
GOG 218



No. at Risk									
Control	625	595	558	506	446	322	200	116	56
Bevacizumab initiation	625	598	557	486	440	304	191	108	54
Bevacizumab throughout	623	587	561	519	463	321	201	114	62

Burger, NEJM (2011) 365:2473

ICON7



No. at Risk						
Standard chemo-therapy	764	724	652	368	159	33
Bevacizumab	764	737	678	404	162	40

Perren, NEJM (2011) 365:2484

Angiogenesis as a Target: Ovarian

Study	Agent	Setting	HR-PFS (95% CI)	HR-OS (95% CI)
GOG 218[1]	Bevacizumab	Front-line/Maintenance	0.72 (0.63-0.82)	0.89 (0.75-1.04)
ICON7[2]	Bevacizumab	Front-line/Maintenance	0.81 (0.70-0.94)	0.99 (0.85-1.14)
AGO-OVAR12[3]	Nintedanib	Front-line/Maintenance	0.84 (0.72-0.98)	Neg
AGO-OVAR16[4]	Pazopanib	Primary Maintenance	0.77 (0.64-0.91)	0.99 (0.75-1.32)
AURELIA[5]	Bevacizumab	Recurrence, Platinum-resistant, 1-2 priors	0.48 (0.38-0.60)	0.85 (0.66-1.08)
TRINOVA-1[6]	Trebananib	Recurrence, Platinum-resistant/sensitive, 1-3 priors	0.66 (0.57-0.77)	0.86 (0.69-1.08)
OCEANS[7]	Bevacizumab	Recurrent, Platinum-sensitive, 1 prior	0.53 (0.41-0.70)	0.96 (0.76-1.21)
ICON6[8]	Cediranib	Recurrent, Platinum-sensitive, 1 prior	0.57 (0.44-0.74)	**0.70 (0.51-0.99)**
GOG-213	Bevacizumab	Recurrent, Platinum-sensitive, 1 prior	0.61 (0.52-0.72)	0.83 (0.68-1.005)*

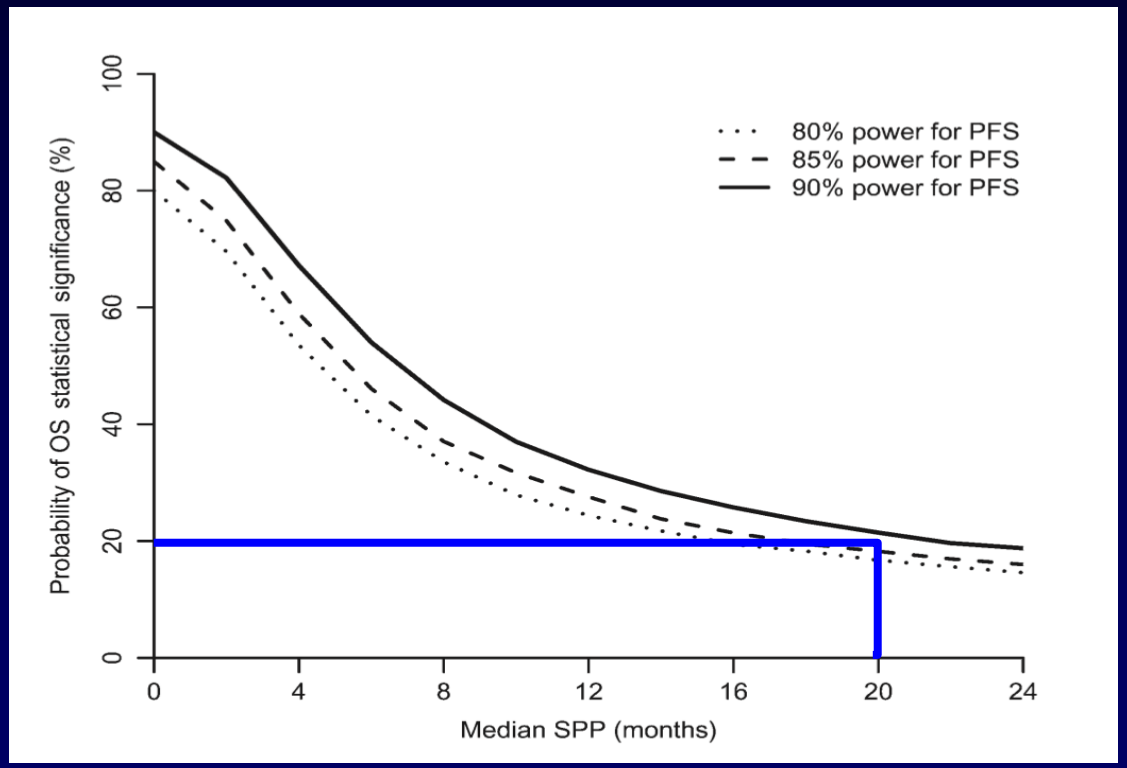
1. Burger RA et al. *N Engl J Med*. 2011;365:2473–2483.
2. Perren TJ et al . *N Engl J Med*. 2011;365:2484–2496.
3. du Bois A et al. *J Clin Oncol*. 2013;31(18suppl):LBA5503.
4. du Bois A et al. LBA ESGO 2013 Liverpool, UK
5. Pujade-Lauraine E et al. *J Clin Oncol*. 2012;30(18suppl):LBA5002.
6. Monk BJ, et all., LBA ESGO, Liverpool, UK
7. Aghajanian C et al. *J Clin Oncol*. 2012;30:2039–2045.
8. Ledermann JA et al . *Eur J Cancer*. 2013;*49*(suppl):LBA

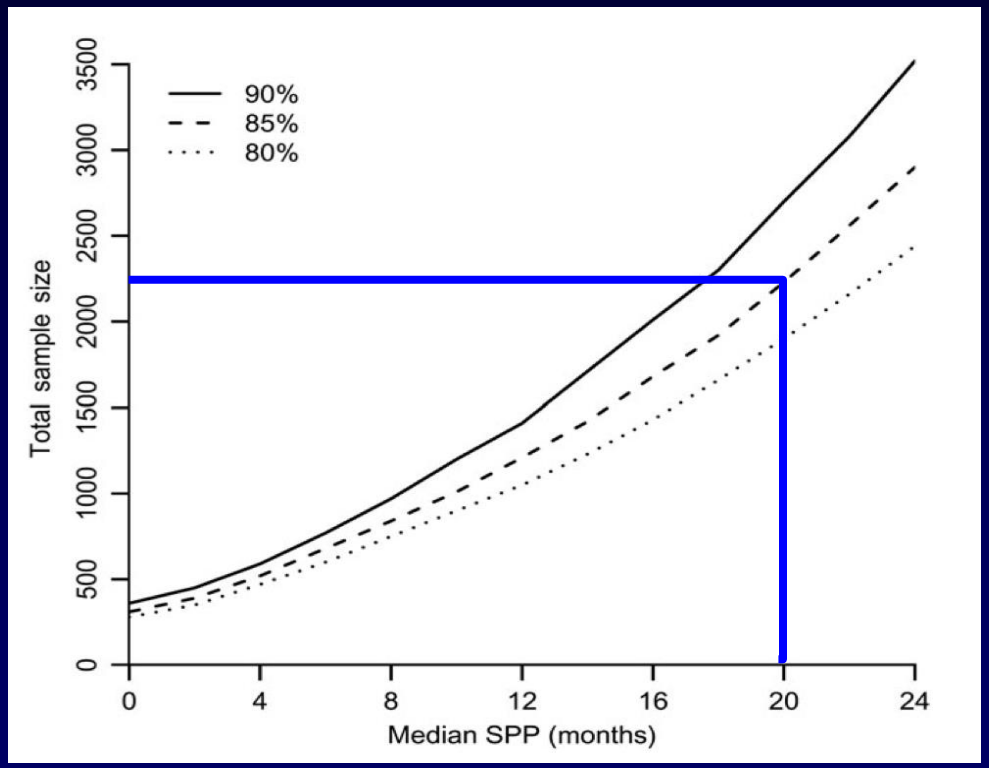
Challenges to Defining a New Standard Frontline Strategy

- PFS ≠ OS
- Trials treating “all comers”, i.e. no selection
- Exposure of maintenance therapy not long enough
- Individual drug to tumor interaction
- Lack of dynamic monitoring

Power to Preserve a PFS Effect

Assumption PFS gain 6 to 9 mos, HR: 0.66

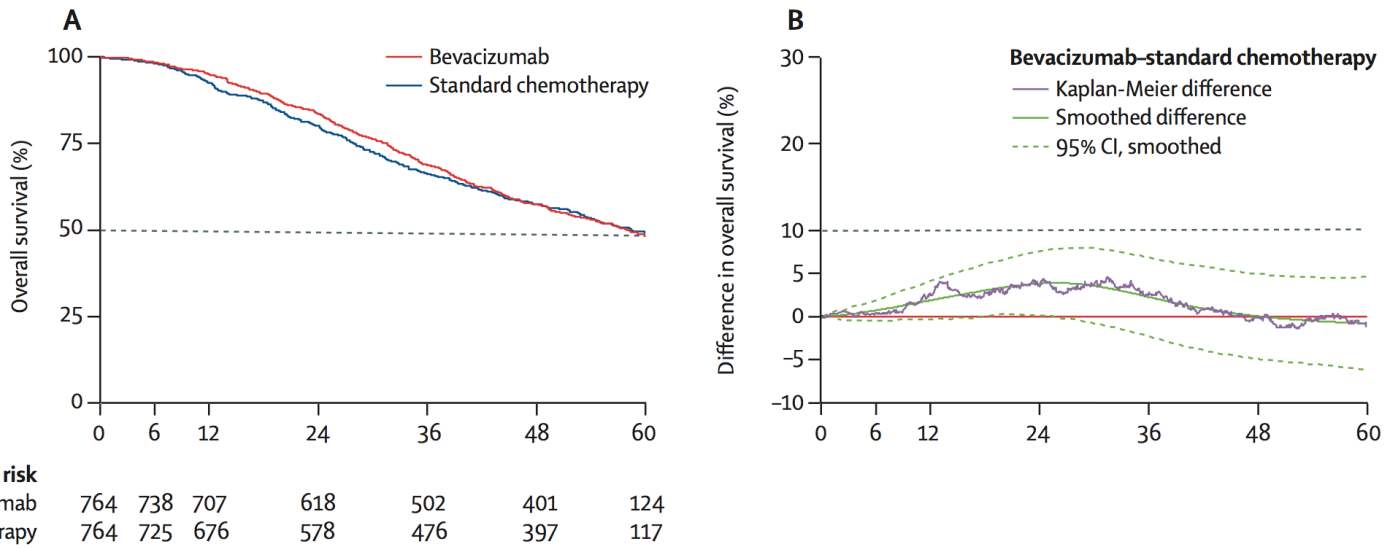




Broglio & Berry, J Natl Cancer Inst (2009) 101:1642-1649

Updated ICON7 OS

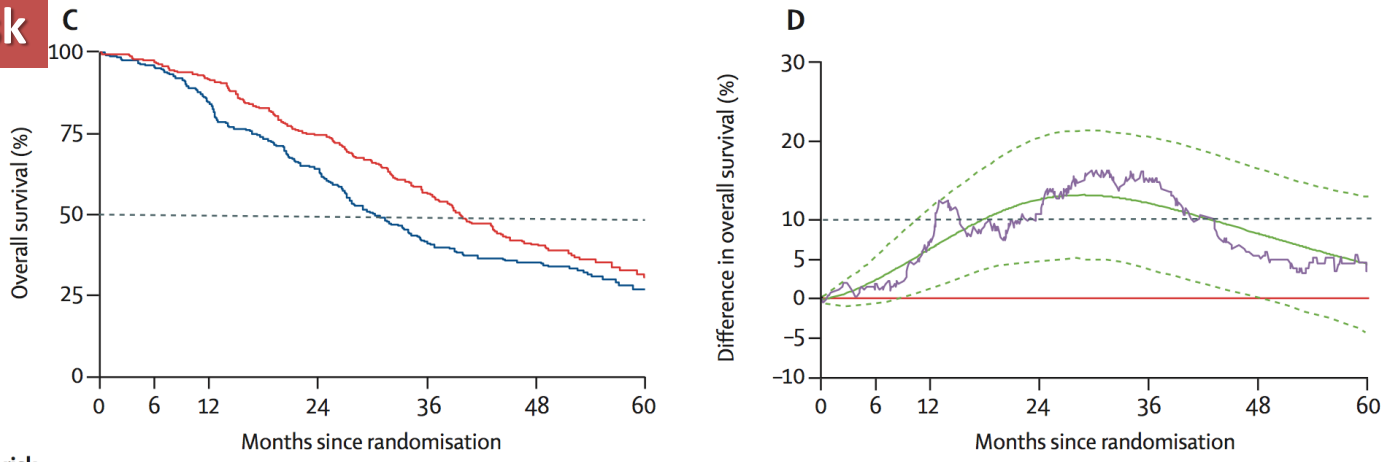
ITT



Number at risk

Bevacizumab	764	738	707	618	502	401	124
Standard chemotherapy	764	725	676	578	476	397	117

High-Risk

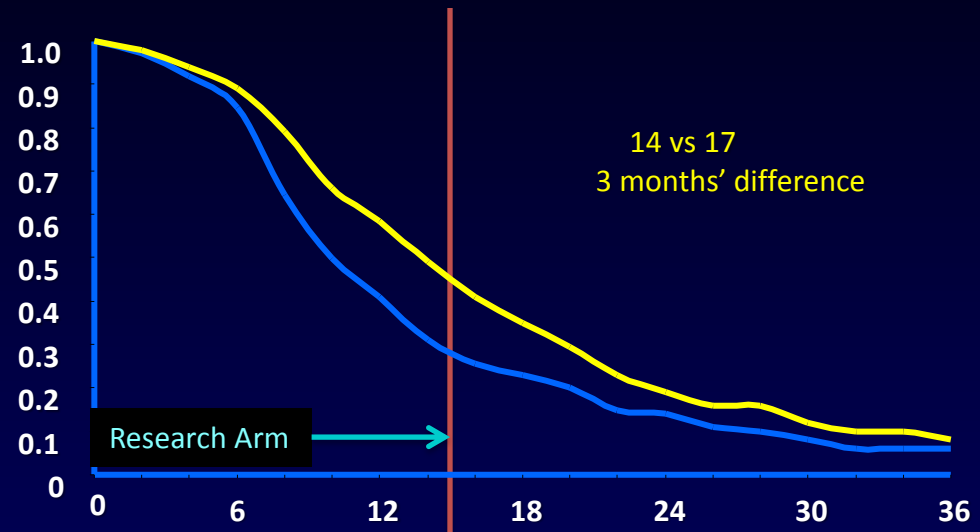


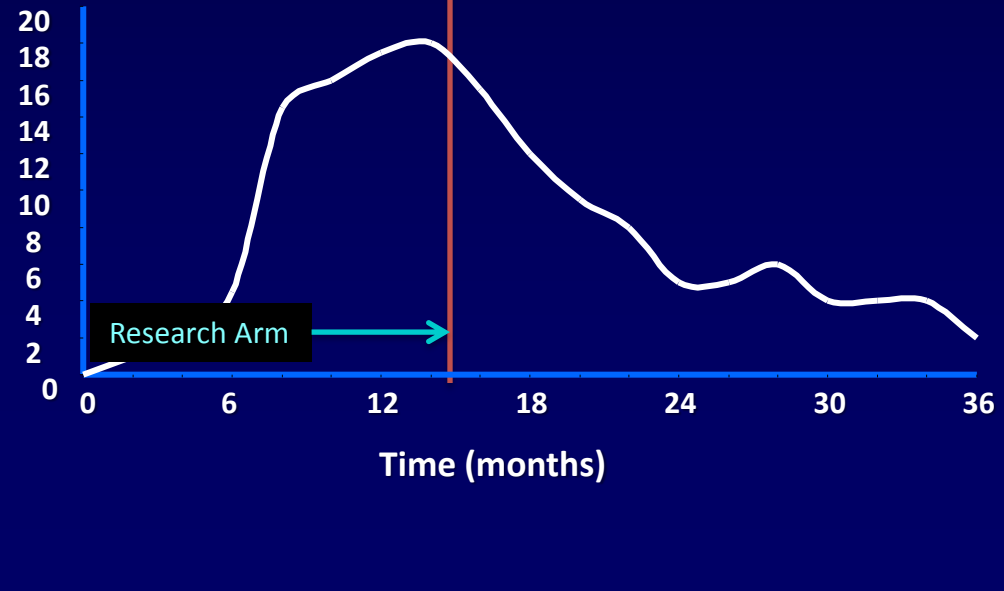
Number at risk

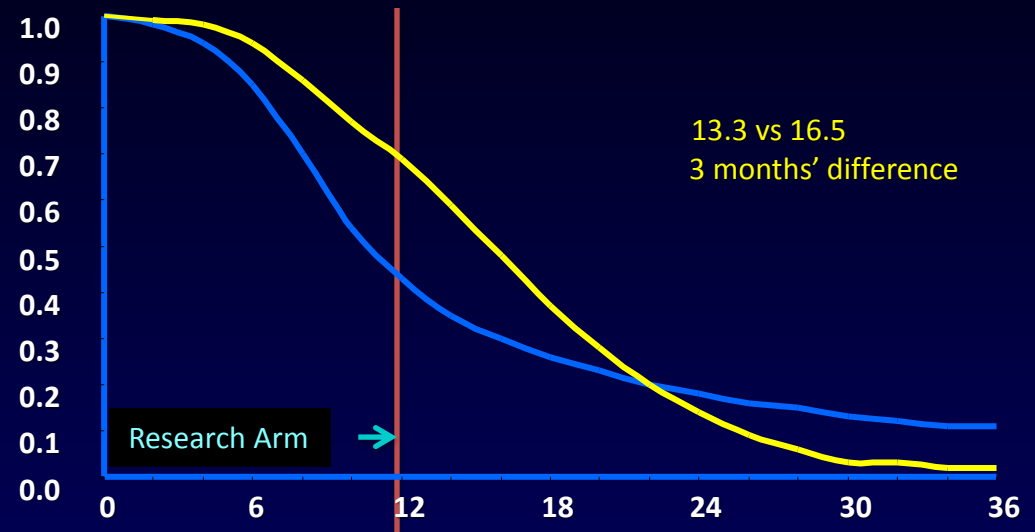
Bevacizumab	248	238	224	180	135	95	27
Standard chemotherapy	254	238	208	156	101	82	21

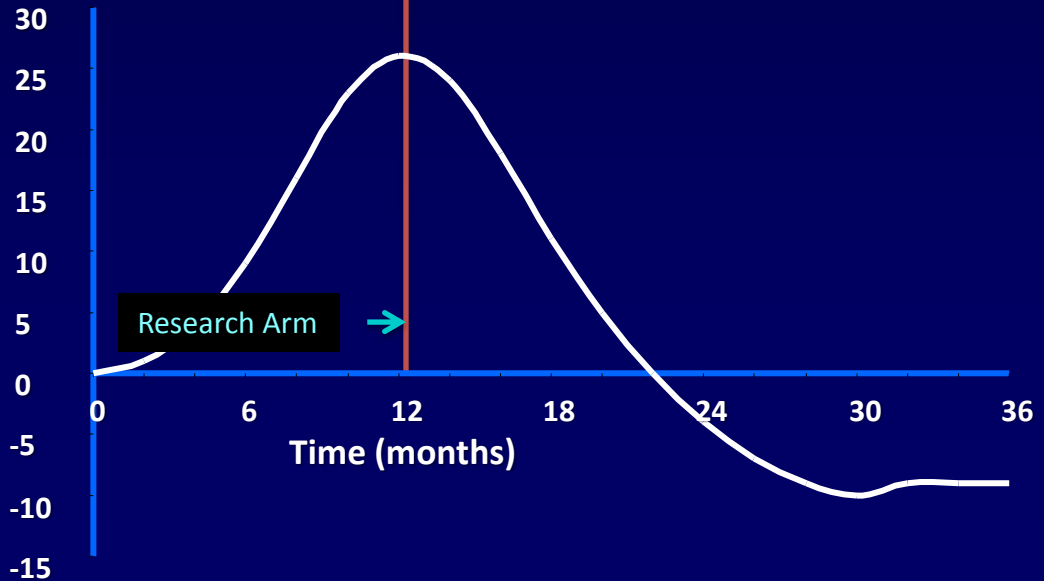
Oza Lancet Oncol 2015

GOG-0218 and ICON7:
Restricted Means Estimate – Benefit During Exposure Only?

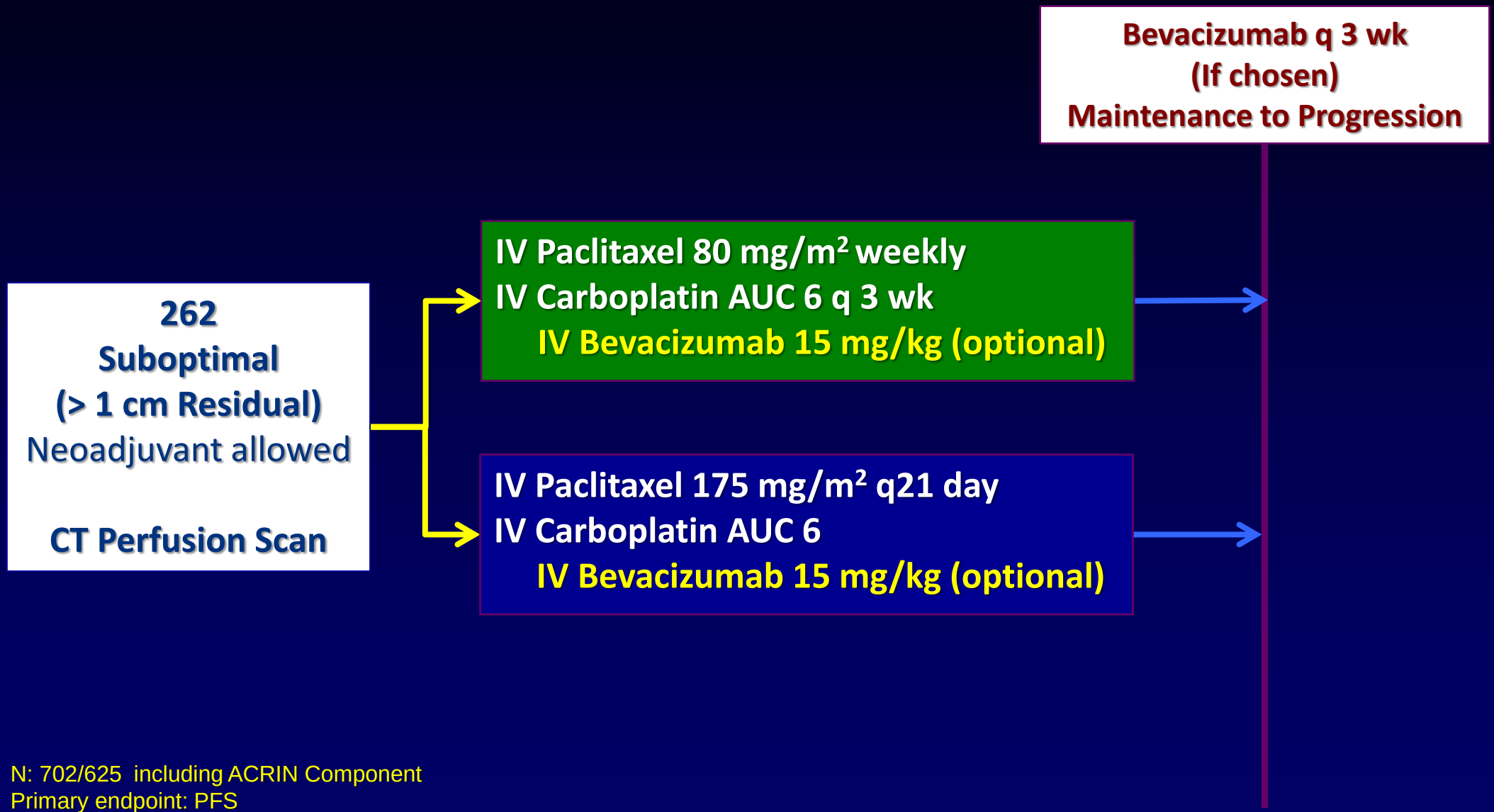






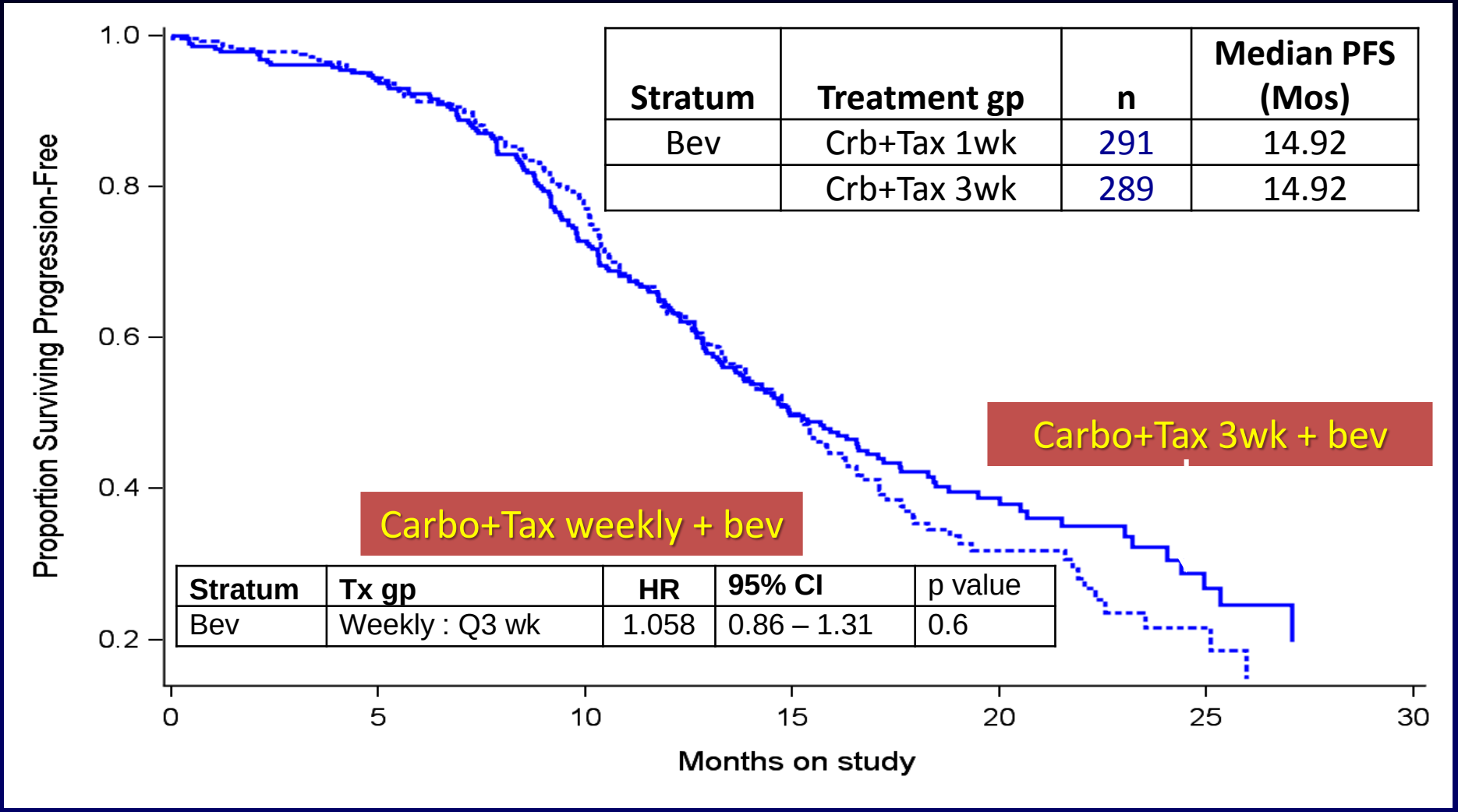


GOG Ovarian Strategy: 262



N: 702/625 including ACRIN Component
Primary endpoint: PFS

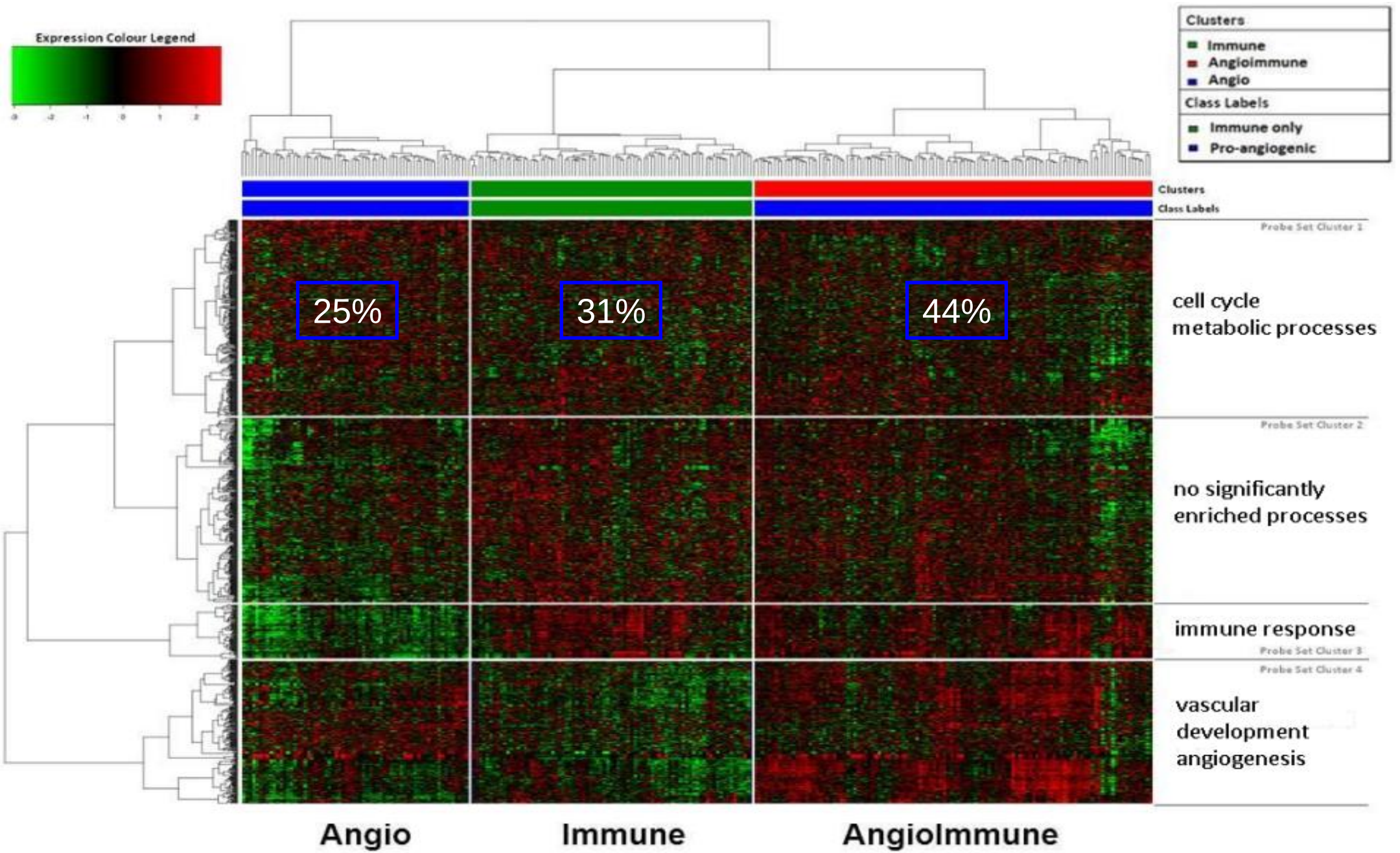
GOG 262: PFS by Randomized Treatment ddT vs. q3wk T stratified by those choosing Bevacizumab (n=580)



Stratum	Treatment gp	n	Median PFS (Mos)
Bev	Crb+Tax 1wk	291	14.92
	Crb+Tax 3wk	289	14.92

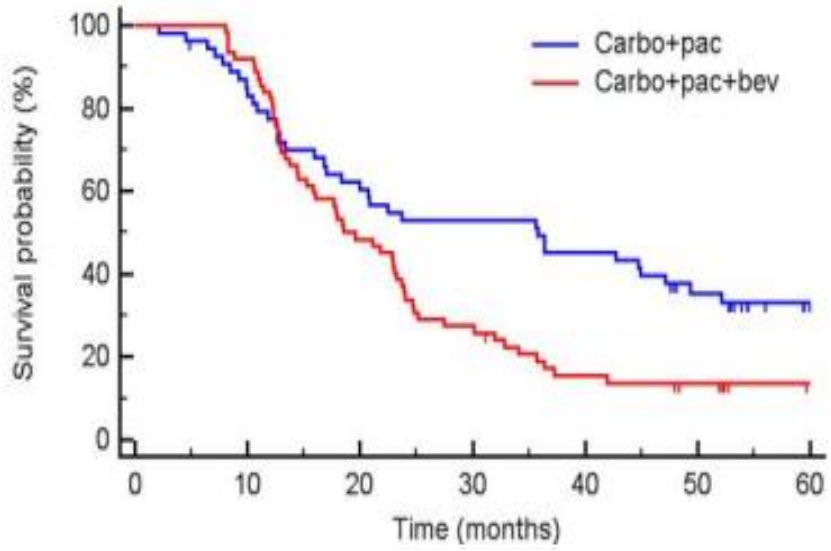
Stratum	Tx gp	HR	95% CI	p value
Bev	Weekly : Q3 wk	1.058	0.86 – 1.31	0.6

Predictive Models for Bevacizumab Effect

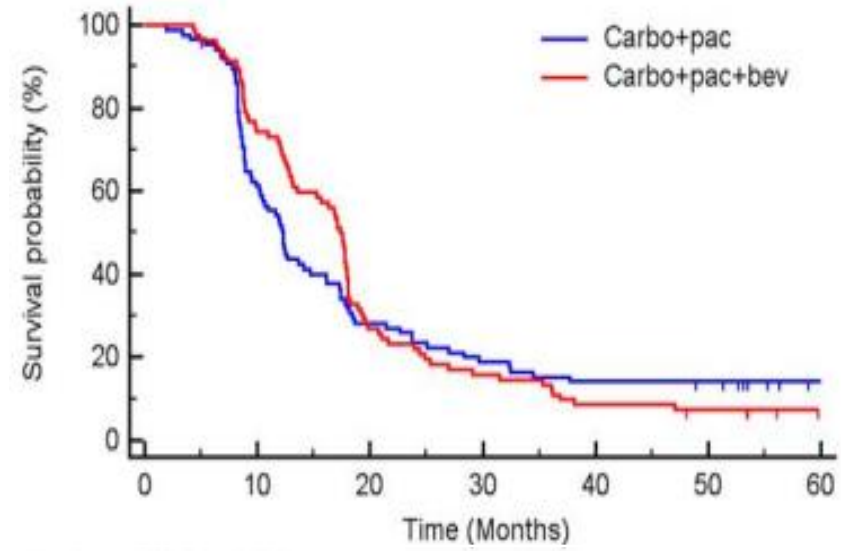


Predictive Models for Bevacizumab Effect

Immune subgroup;
41% of ICON7 TR patients



Pro-angiogenic subgroup;
59% of ICON7 TR patients

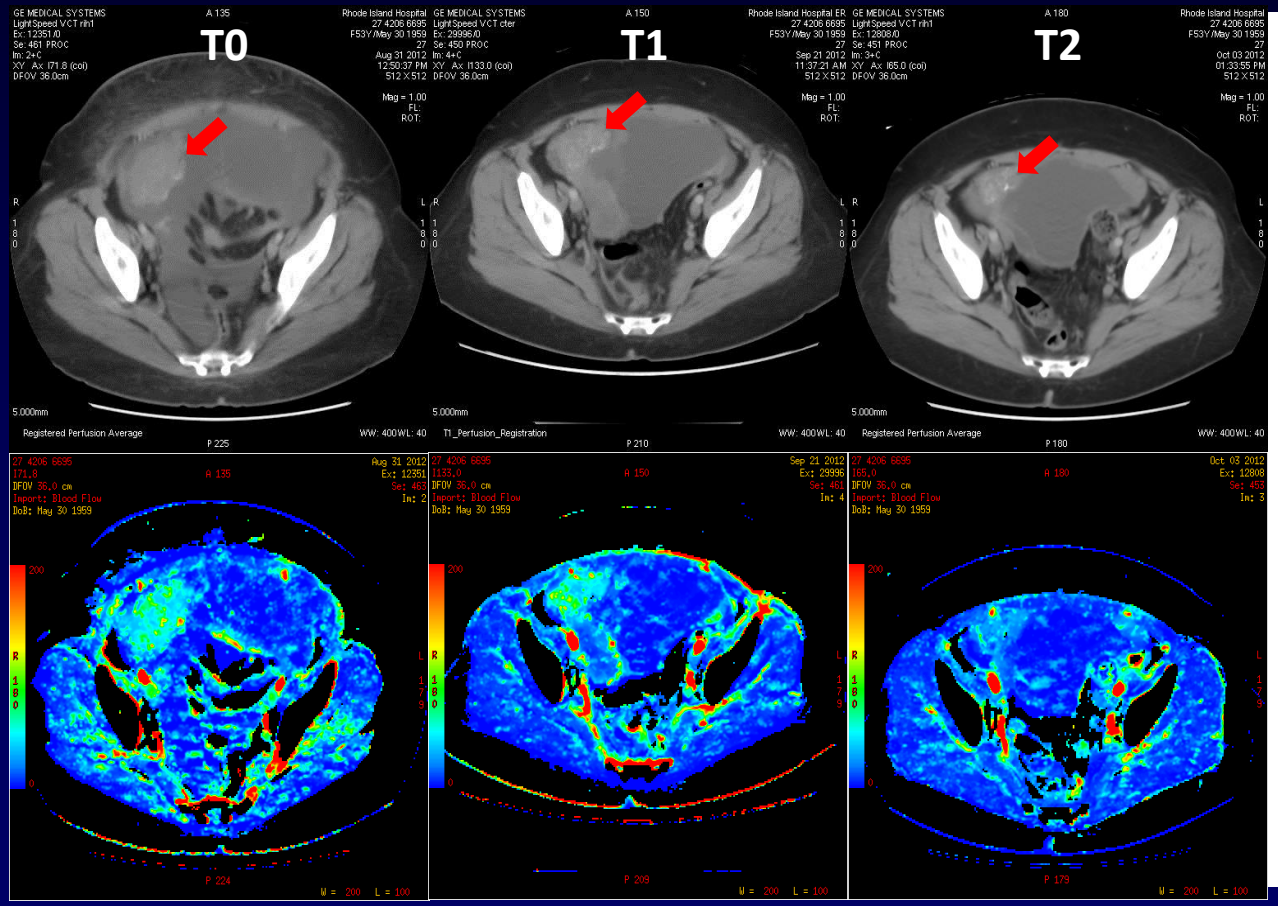


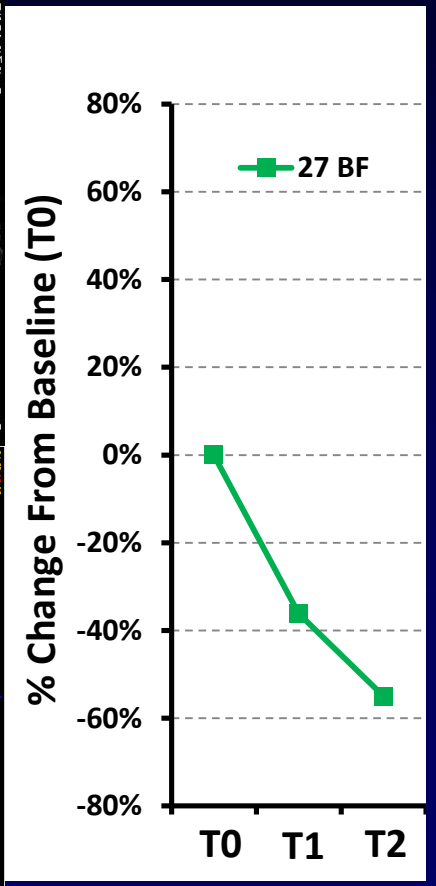
	Immune subgroup	Proangiogenic subgroup
Non-proportionality test	p=0.048	p=0.003
Restricted mean PFS in months (se)	C/P 29.7 (2.2) C/P/Bev 23.8 (1.8)	C/P 18.3 (1.5) C/P/Bev 19.3 (1.3)
Diff in restricted mean PFS (95% ci)	-5.9 (-11.5 to -0.3)	1.0 (-2.9 to 4.9)
	Test for interaction, p=0.015	
Median PFS in months	C/P 35.8 C/P/Bev 18.5	C/P 12.3 C/P/Bev 17.4

Gourley C et al J Clin Oncol 32:5s, 2014 (suppl; abstr 5502)

GOG-262: Imaging Biomarkers

Contrast CT Blood Flow



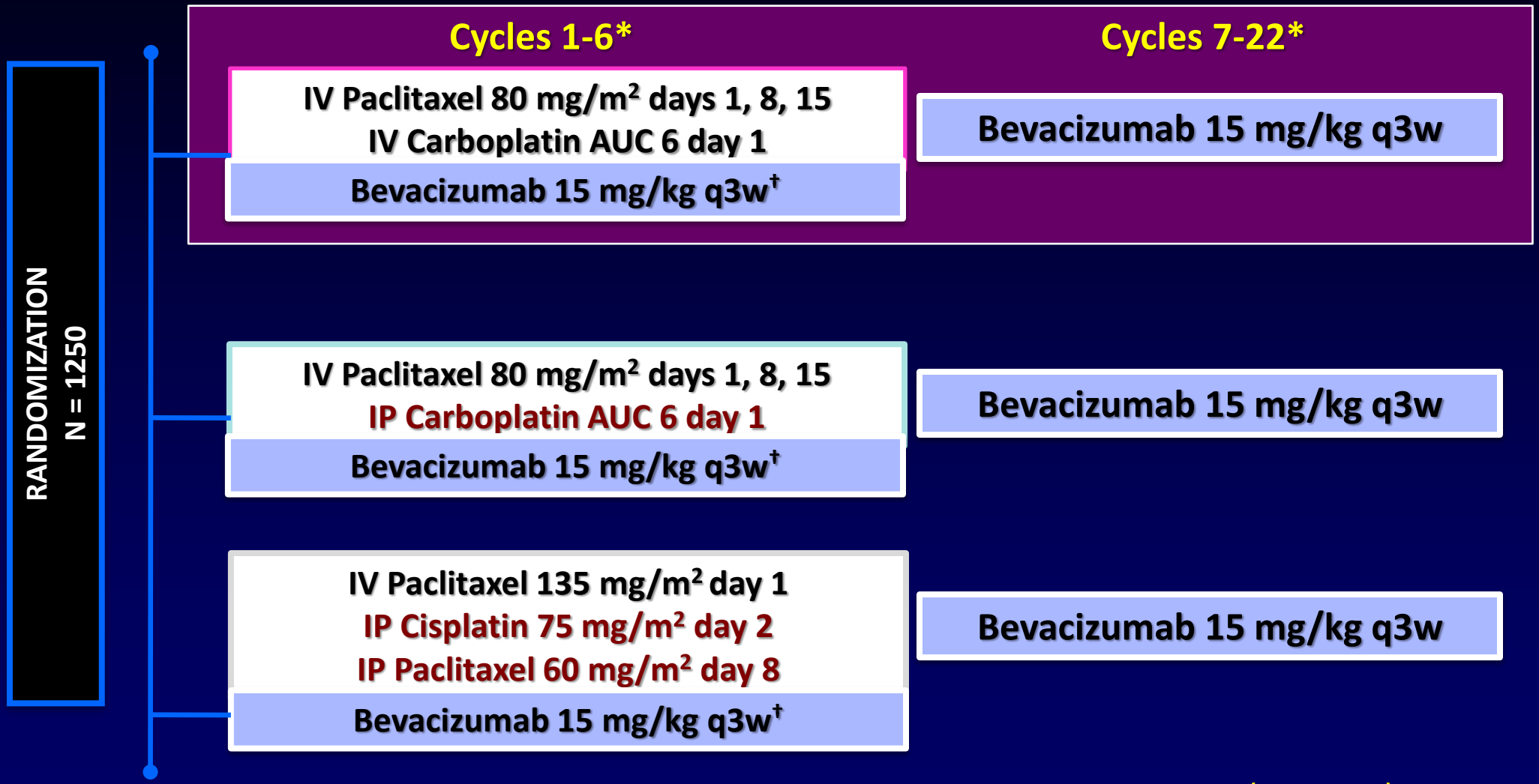


Lee, ACRIN 2015

Bottom Line…

- Determine good candidates for surgery
  - Potential for better selection tools, e.g. Laparoscopy
- Optimal radical resection
  - Goal: R0
- Adjuvant therapy
  - Want the best treatment option possible – several options without a clear signal give patient, treatment and tumor heterogeneity
  - OS only achieved with IP (US) and dose-dense (Asian population) but post-progression survivorship and drug exposure are vital to interpretation
  - Biomarkers for response/efficacy needed

Phase III GOG 252 Schema



N: 1554 (CLOSED)
Primary endpoint: PFS

*Each cycle is 3 weeks; †Begin cycle 2.

Walker JL. *Am Soc Clin Oncol Ed Book.* 2009:308-312.

ICON 8

MRC Clinical Trials Unit

Diagnosis of Stage IIIC-IV EOC/PPC/FTC

Immediate Primary Surgery (IPS) and residual >1cm

Randomise 1:1:1

Arm 1
6 cycles

Arm 2
6 cycles

Arm 3
6 cycles

Delayed Primary Surgery (planned)

Randomise 1:1:1

Arm 1 *
3 cycles

Arm 2
3 cycles

Arm 3*
3 cycles

Cycle 3d15 PTX omitted

Delayed Primary Surgery (DPS)

Arm 1*
3 cycles

Arm 2
3 cycles

Arm 3*
3 cycles

Arm 1	Carboplatin AUC 5	q3w
	Paclitaxel 175mg/m^2	q3w
	Bevacizumab 7.5mg/kg	q3w
Arm 2	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
Arm 3	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
	Bevacizumab 7.5mg/kg	q3w

*- Bevacizumab omitted from cycles 3 and 4

Bevacizumab maintenance to continue for maximum of 16 cycles in arms 1 and 3

Thank You!

The University of Texas
MD Anderson Cancer Center
R. Lee Clark Clinic
Margaret and Ben Love Clinic
Charles A. LeMaistre Clinic