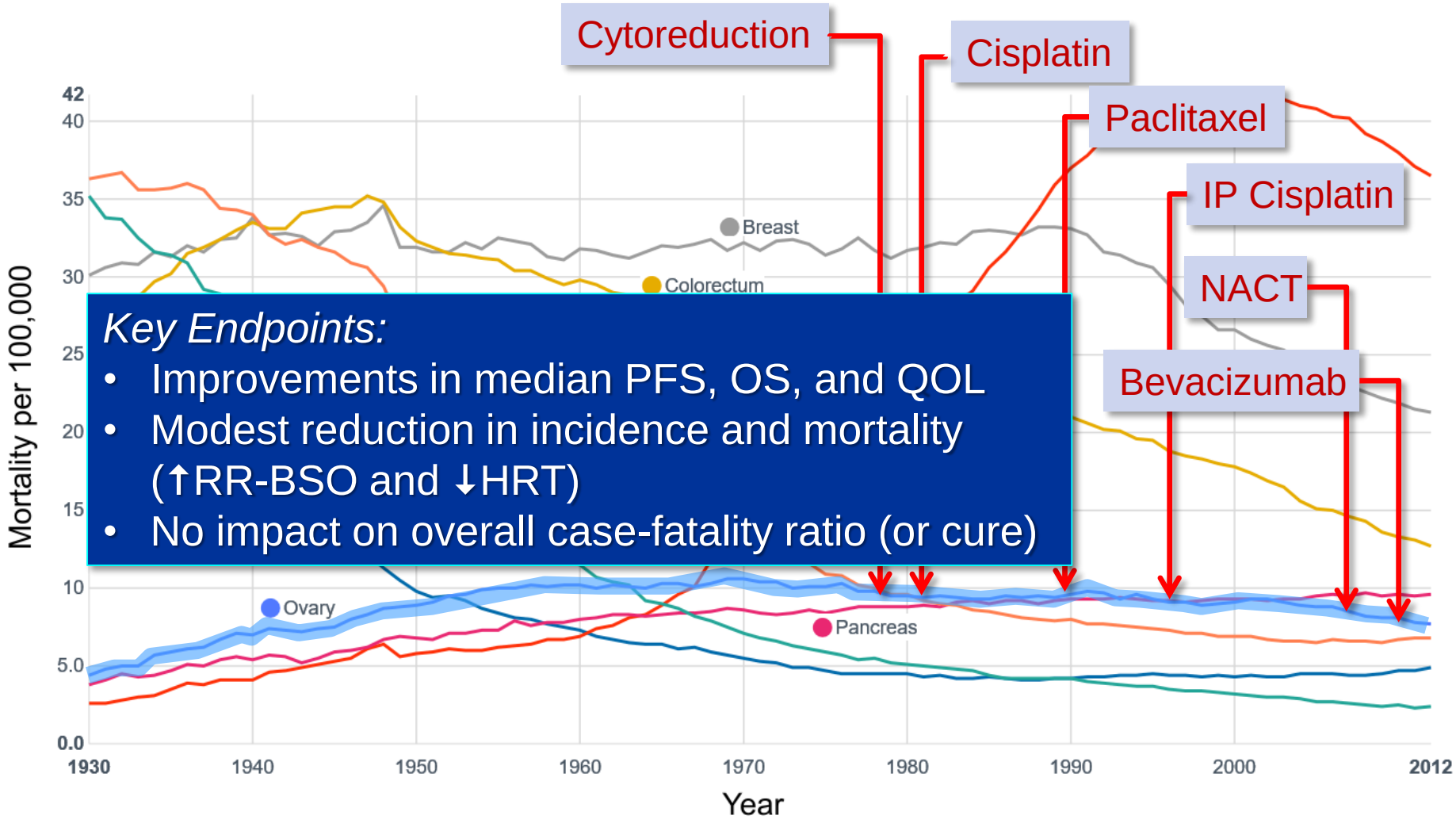
Cancer Death Rates (US 1930-2012)

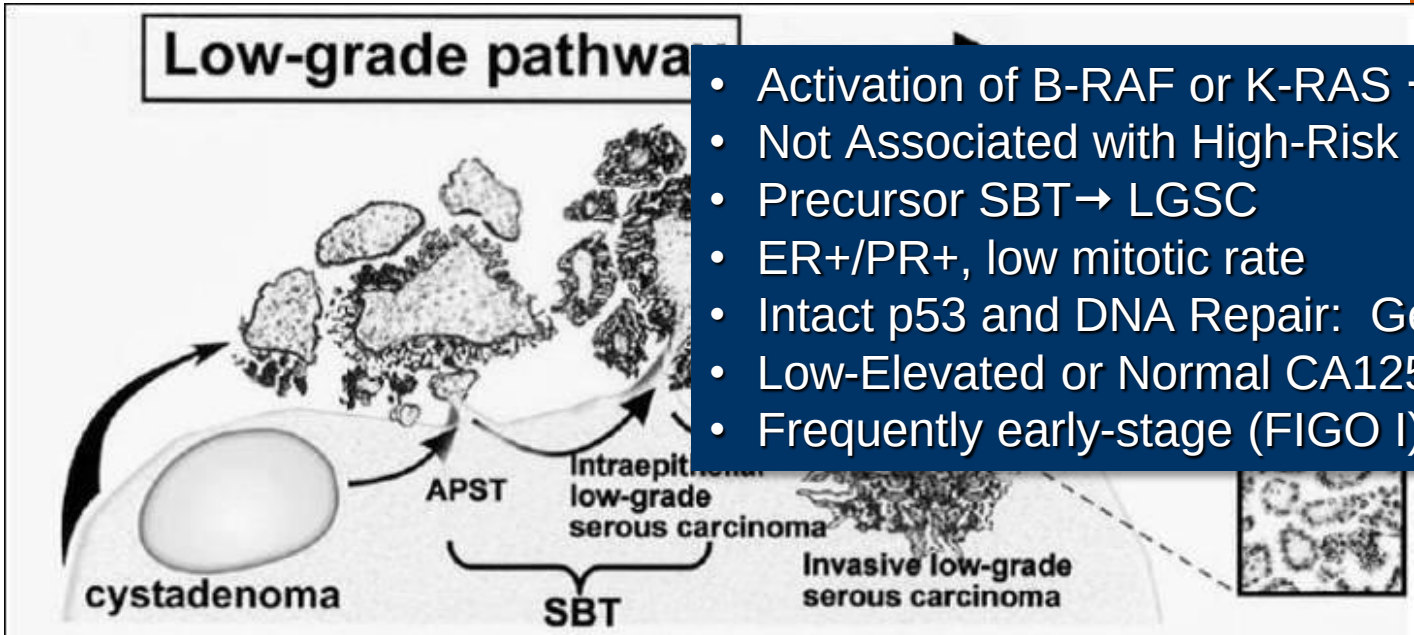


Key Endpoints:

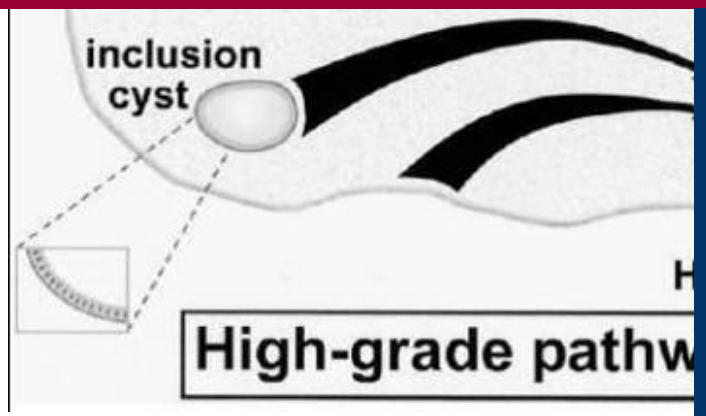
- Improvements in median PFS, OS, and QOL
- Modest reduction in incidence and mortality (↑RR-BSO and ↓HRT)
- No impact on overall case-fatality ratio (or cure)

National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2015

Molecular and Clinical Pathobiology

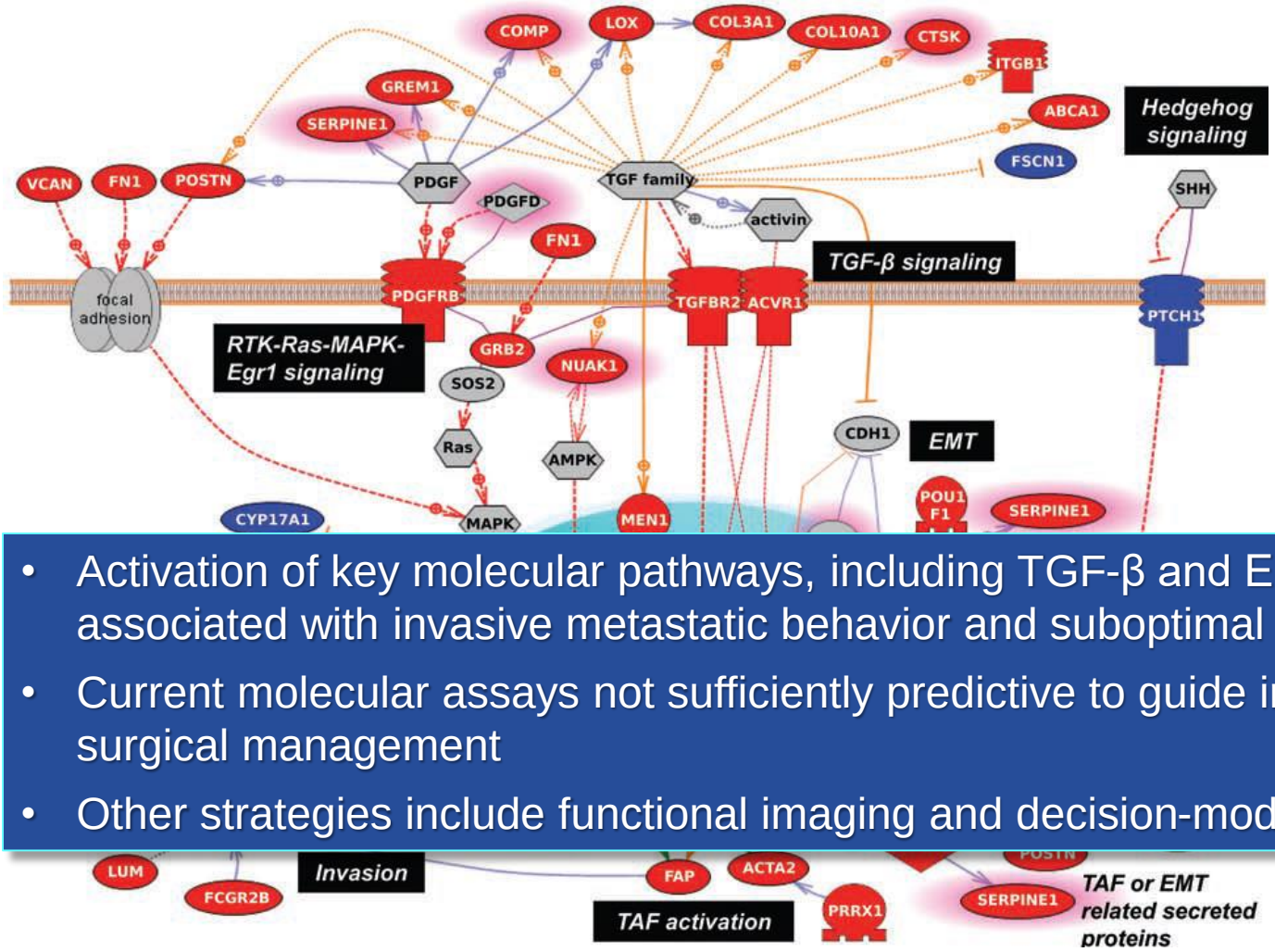


- Activation of B-RAF or K-RAS → MEK
- Not Associated with High-Risk Families
- Precursor SBT→ LGSC
- ER+/PR+, low mitotic rate
- Intact p53 and DNA Repair: Genomic Stability
- Low-Elevated or Normal CA125
- Frequently early-stage (FIGO I)



- Uniform loss of p53
- Frequent loss 17q21 (BRCA1), 13q12 (BRCA2), 13q14 (RB1)
- Associated with High-Risk Families
- DNA Repair Defect (HRD): Genomic Instability
- ↑CA125
- Advanced-stage (FIGO III-IV)

Predicting Suboptimal Cytoreduction



↑Expression:

ACVR1 Suboptimal

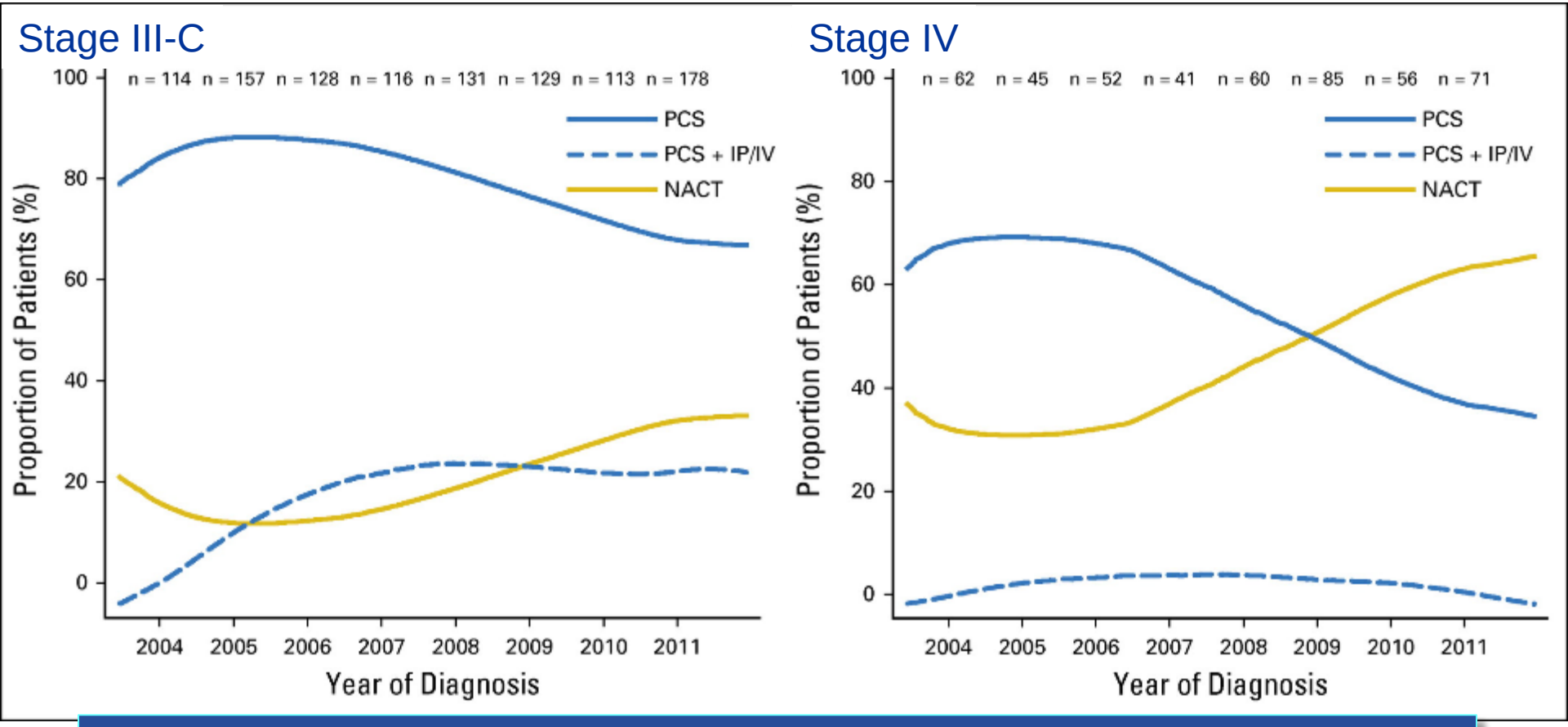
FSCN1 Optimal

CXCR14 ↓Prognosis

- Activation of key molecular pathways, including TGF-β and EMT, are associated with invasive metastatic behavior and suboptimal outcomes
- Current molecular assays not sufficiently predictive to guide individual surgical management
- Other strategies include functional imaging and decision-mode laparoscopy

Reister M, et al. *J Natl Cancer Inst* 2014;106 doi:10.1093/jnci/dju048

Adoption of NACT (US)

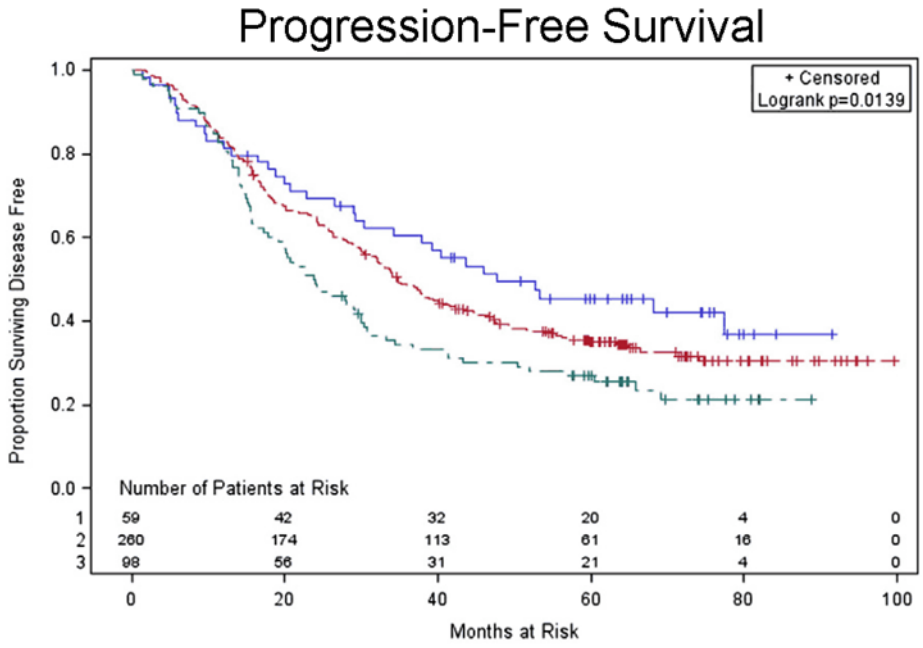


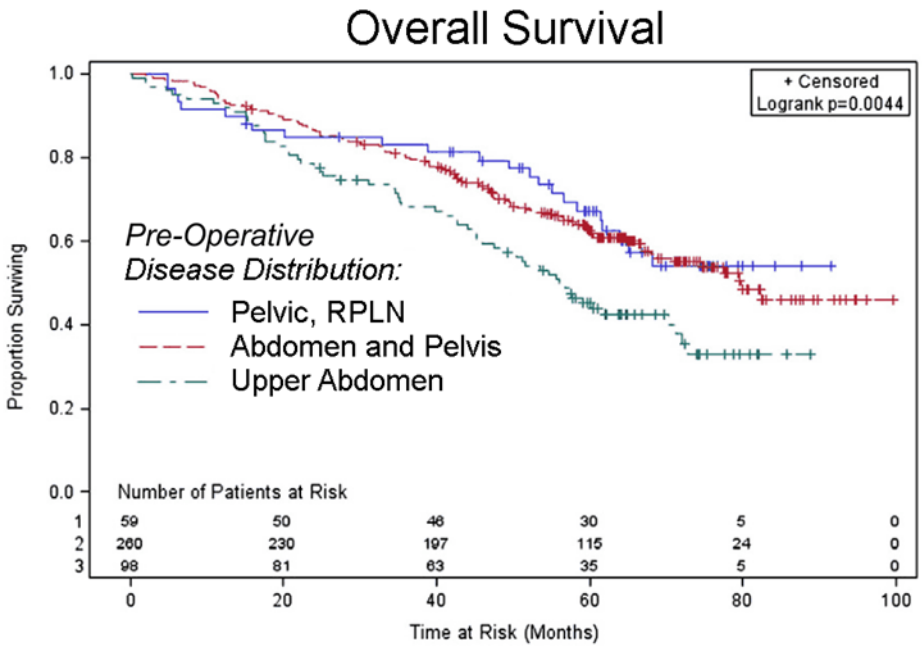
Within NCCN, NACT use increased from 16% to 34% in stage IIIC (P trend < .001), and from 41% to 62% in stage IV (P trend < .001)

Meyer L, et al. *J Clin Oncol* 34:3854-3863, 2016

Impact of Initial Disease Distribution

- All patients achieved optimal (R0 microscopic) Cytoreduction
- Combined analysis GOG 114, 158, 172 intravenous chemo (n = 417)



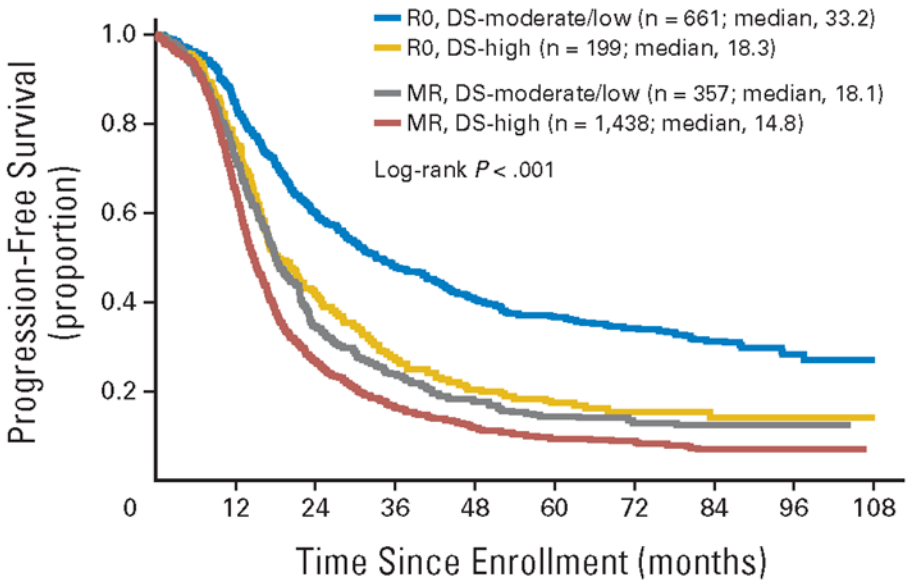


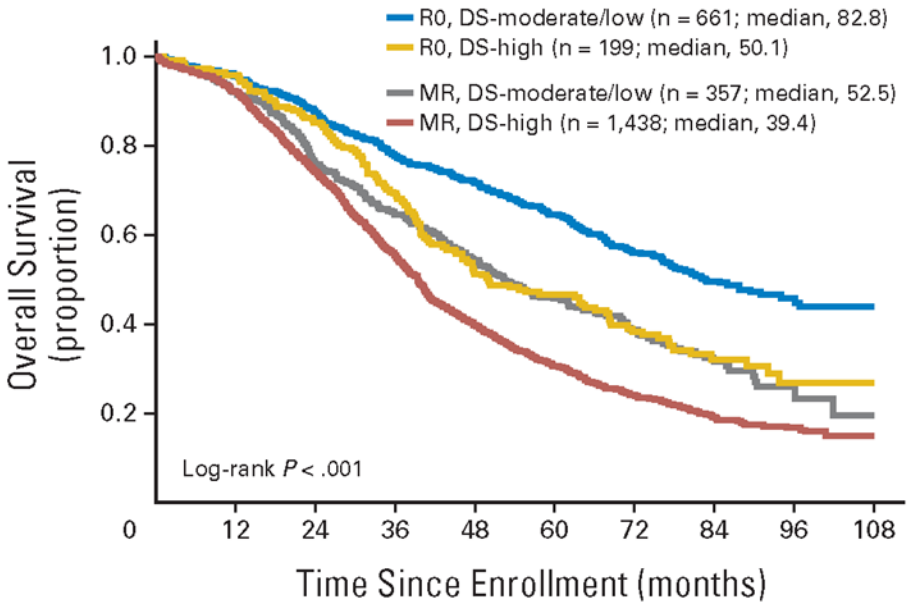
Upper abdominal tumor burden correlated with inferior long-term clinical outcomes, even though all patients achieved R0 status

Hamilton CA, et al. *Gynecol Oncol* 122:521-6, 2011

Impact of Disease Scoring

Data from GOG0182 FIGO Stage III-IV (n = 2,655)
Analyzed according to R0 (microscopic) or MR (macroscopic) residual, and pre-operative DS (disease score)



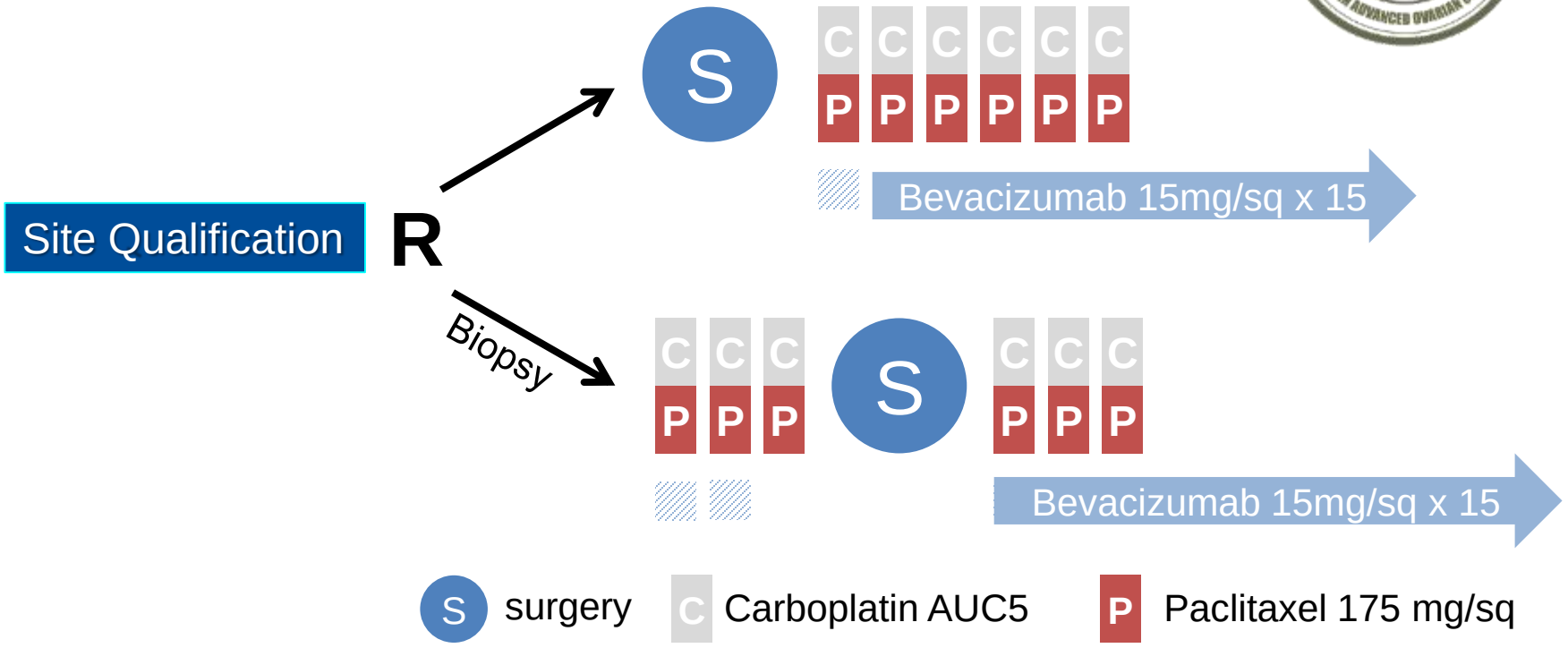


- Achieving R0 generally associated with better outcomes
- Outcomes with R0 not improved with high PRE-operative DS
- Value of aggressive cytoreduction not resolved in extensive disease

Horowitz NS, et al. *J Clin Oncol* 10.1200/JCO.2014.56.3106

Trial on Radical Upfront Surgical Therapy

- Primary Endpoint: OS ITT population
- Secondary Endpoints PFS, resection rates, QOL, Fragility Index
- Strata: FIGO stage, Region, ECOG PS
- Site qualification process to ensure surgical quality

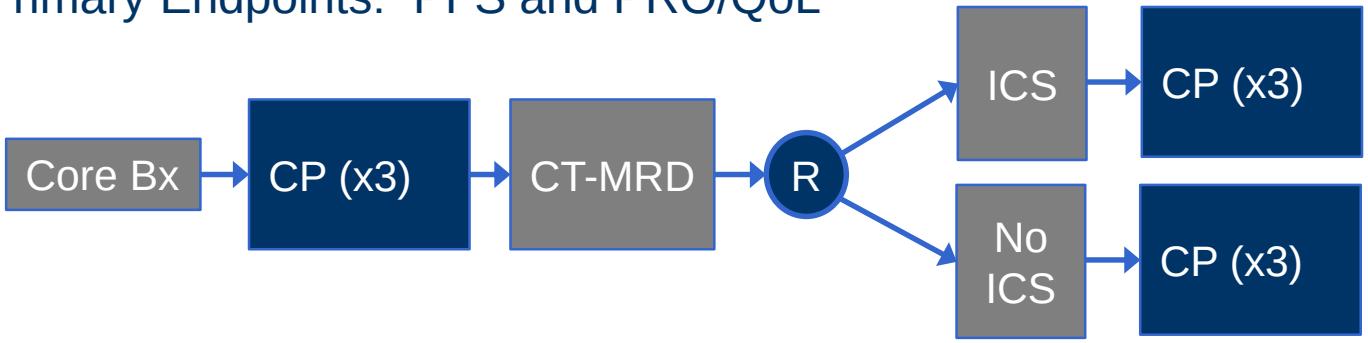


Accrual Status: 362/686 (April 2018)

Mahner S, Elser G, Fotopoulou C, et al. for TRUST

OV1741 (concept): NACT +/- ICS

- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with ICS
- Registered after CT with MRD, prior to planned ICS
- Permits minimally-invasive ICS
- Primary Endpoints: PFS and PRO/QoL



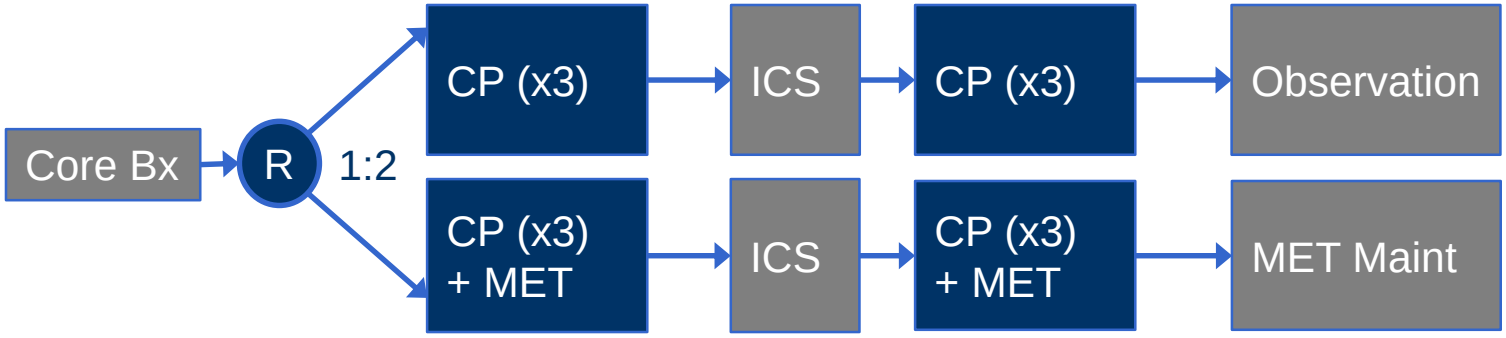
CP = Carboplatin AUC 6 (D1), Paclitaxel 80 mg/m2 (D1,8,15)
CT-MRD = CT post-chemotherapy with minimal residual disease
ICS = Interval Cytoreductive Surgery (minimally invasive allowed)

Status: Concept in planning
Target: Approximately 150 pts
Notes: Evaluating options for NCI support (DCP or CTEP)

Bregar A and Fleming G for NRG Oncology

NRG GY015: NACT +/- Metformin

- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with ICS
- No known diabetes or use of metformin
- Primary Endpoints: PFS and molecular/metabolic targeting



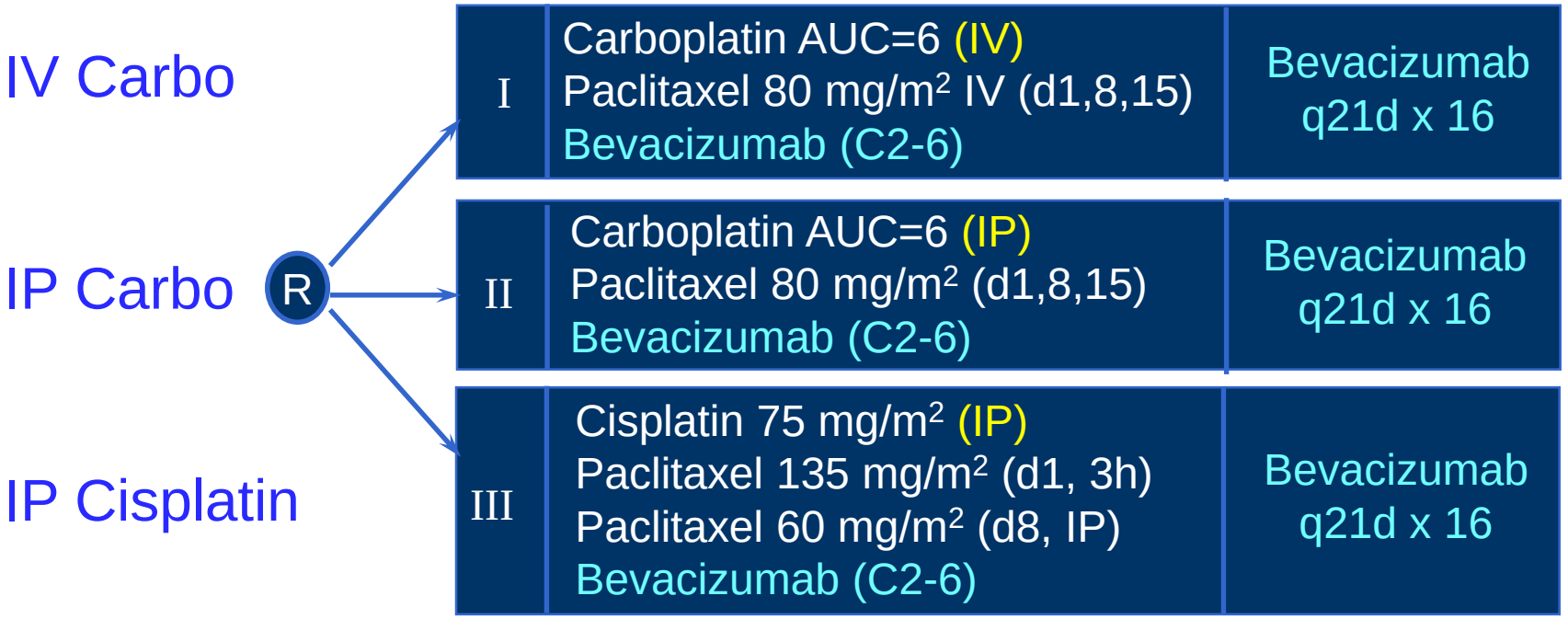
CP = Carboplatin AUC 6 (D1), Paclitaxel 80 mg/m2 (D1,8,15)
MET = Metformin 850 mg PO BID
ICS = Interval Cytoreductive Surgery

Open: JUN 2014
Status: Ongoing Accrual (U Chicago SPORE)
Target: 76 pts

Yamada D, for NRG Oncology and U Chicago SPORE

GOG0252: IP Therapy

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Optimal and Suboptimal Disease (through April 2011)
- Primary Endpoint: PFS (Analysis JAN 2016)

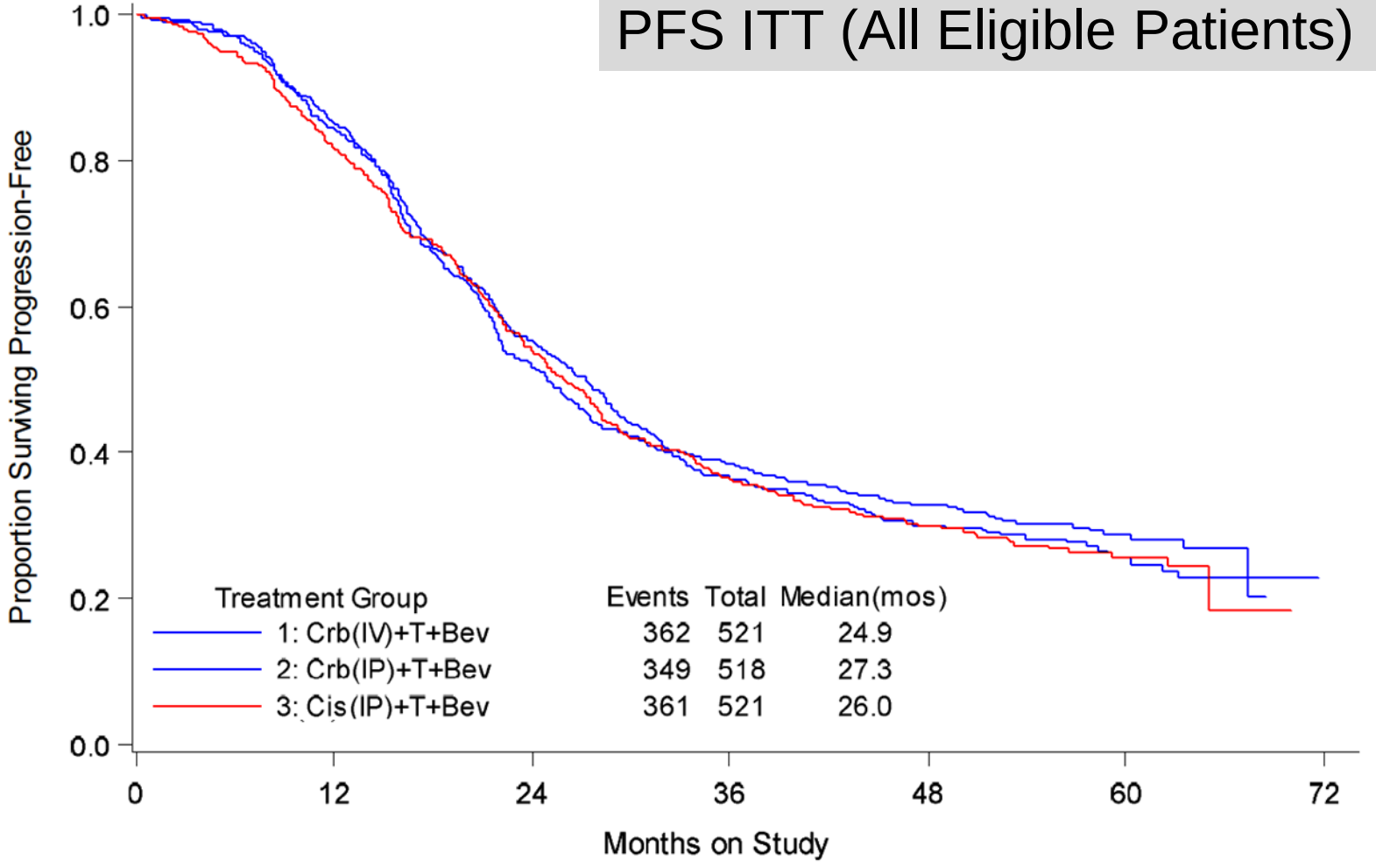


Open: 27-Jun-2009
Closed: 29-Oct-2011
Accrual: 1560 pts (max 250 suboptimal)

Walker J. for GOG, SGO 2016

GOG0252: IP Therapy (PFS)

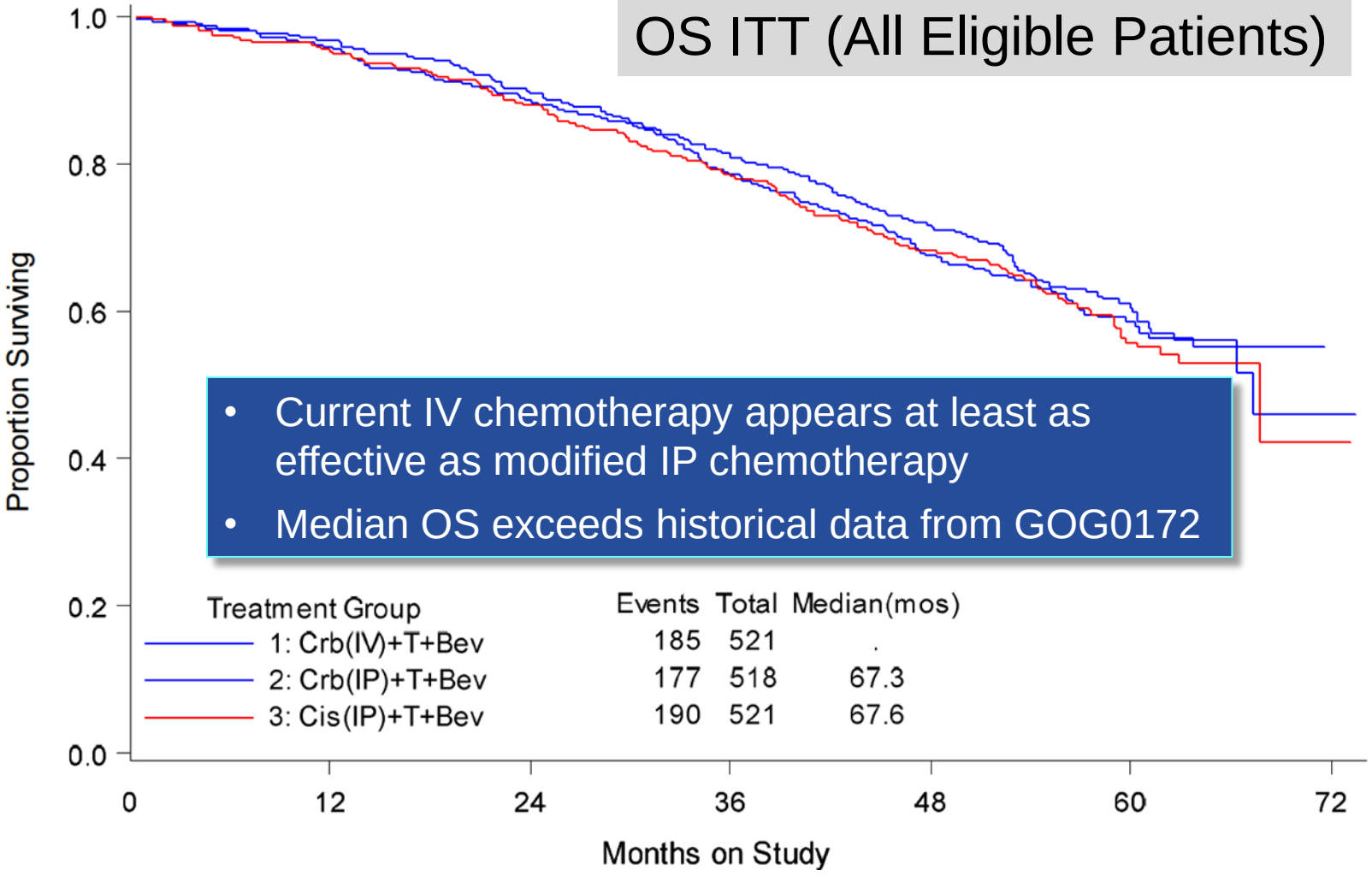
PFS ITT (All Eligible Patients)



Walker J. for GOG, 2016

GOG0252: IP Therapy (OS-Prelim)

OS ITT (All Eligible Patients)

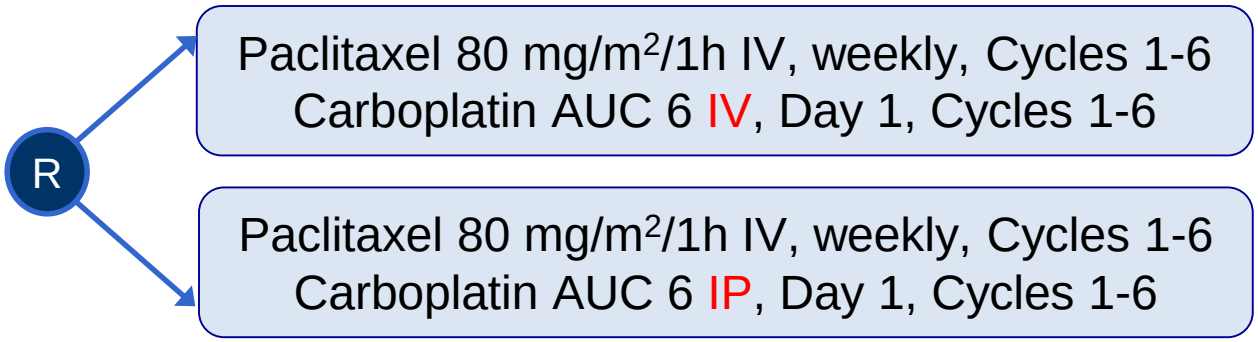


- Current IV chemotherapy appears at least as effective as modified IP chemotherapy
- Median OS exceeds historical data from GOG0172

Walker J. for GOG, 2016

iPocc: IP Carboplatin

- Stage II to IV ovarian, primary peritoneal, or fallopian tube cancer (including suboptimal cytoreduction)
- Primary Endpoint: PFS
- Secondary Endpoints: OS, Toxicty, QoL, Cost/Benefit

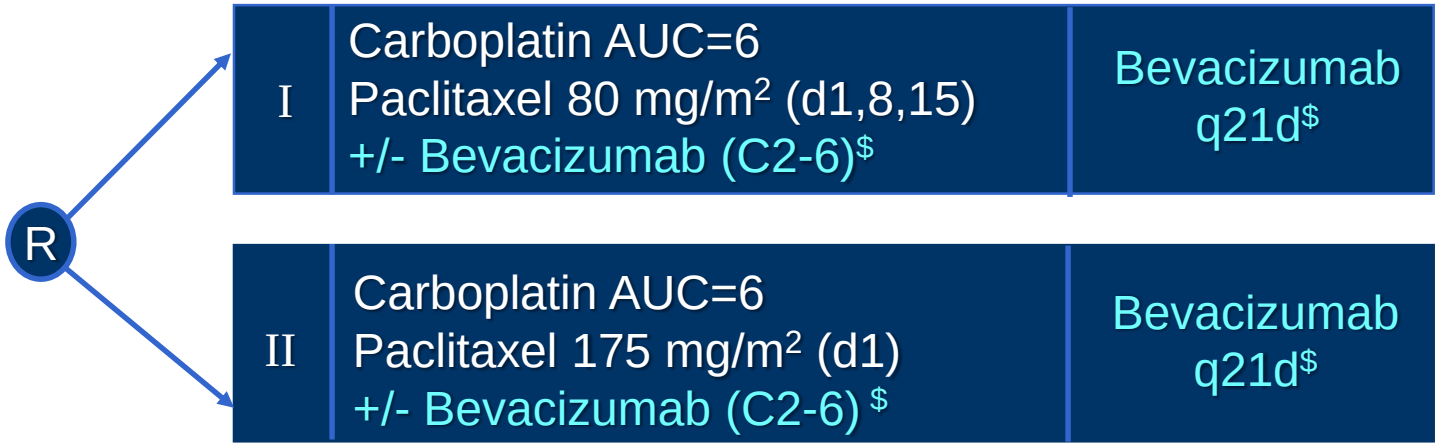


Target: 655 pts (closed OCT2016)

Fujiwara K, for GOTIC and JGOG

GOG262 ACRIN6695: Dose-Dense

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Suboptimal residual disease (optional NACT-ICS)
- Primary Endpoint: PFS
- Early perfusion-based CT imaging (ACRIN 6695)

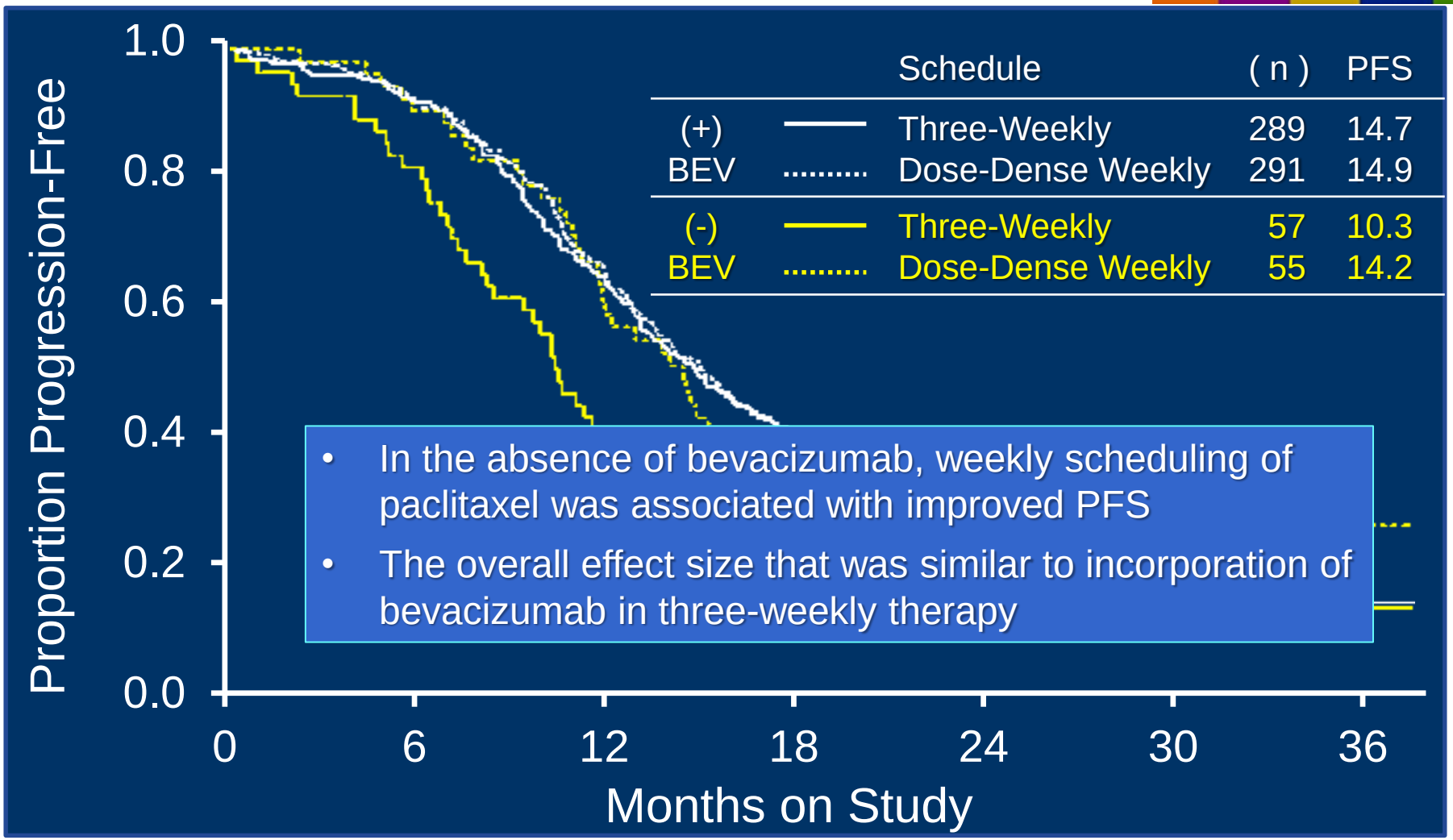


$ Use of Bevacizumab elected prior to randomization

Open: 27-SEP-2010
Closed: 08-FEB-2012 (ACRIN JUN-2013)
Target: 692 pts (randomized)

Chan JK, et al. *NEJM*, 2016

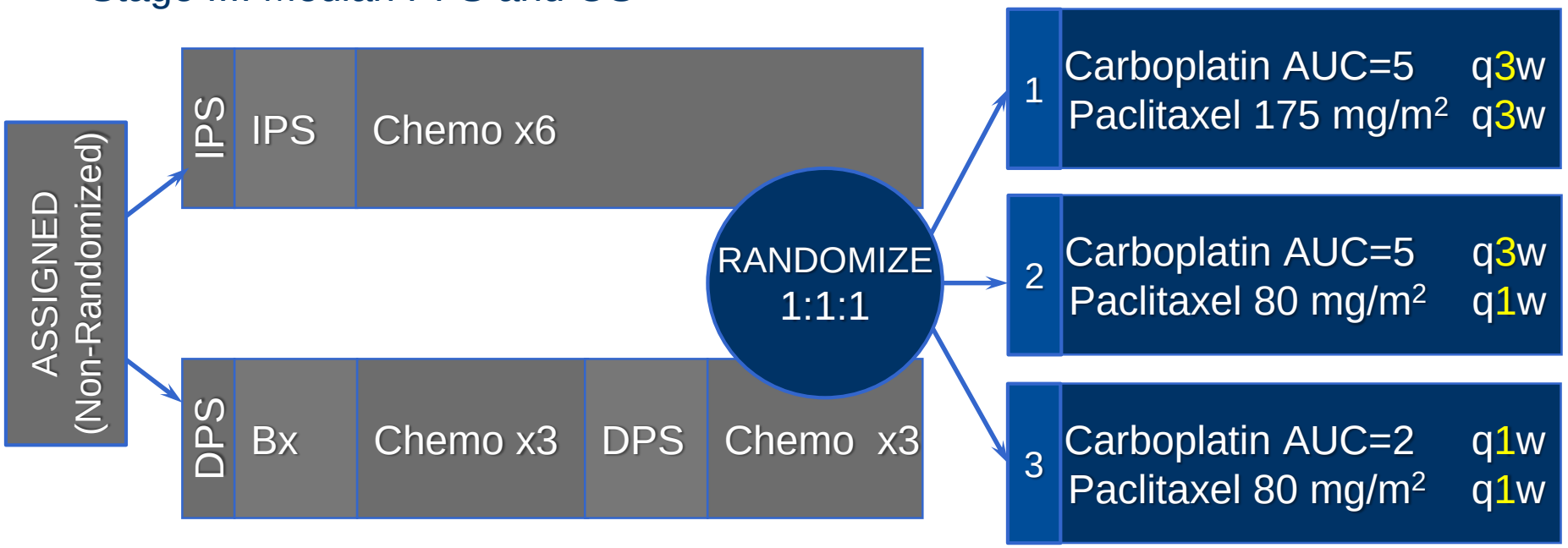
GOG262 ACRIN6695: Dose-Dense



Chan JK, et al. *NEJM*, 2016

MRC-UK ICON8: Dose-Dense

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Presumptive Stage IC-IV
- Assigned to Immediate (IPS) or Delayed (DPS) Primary Surgery
- Stage III: Median PFS and OS



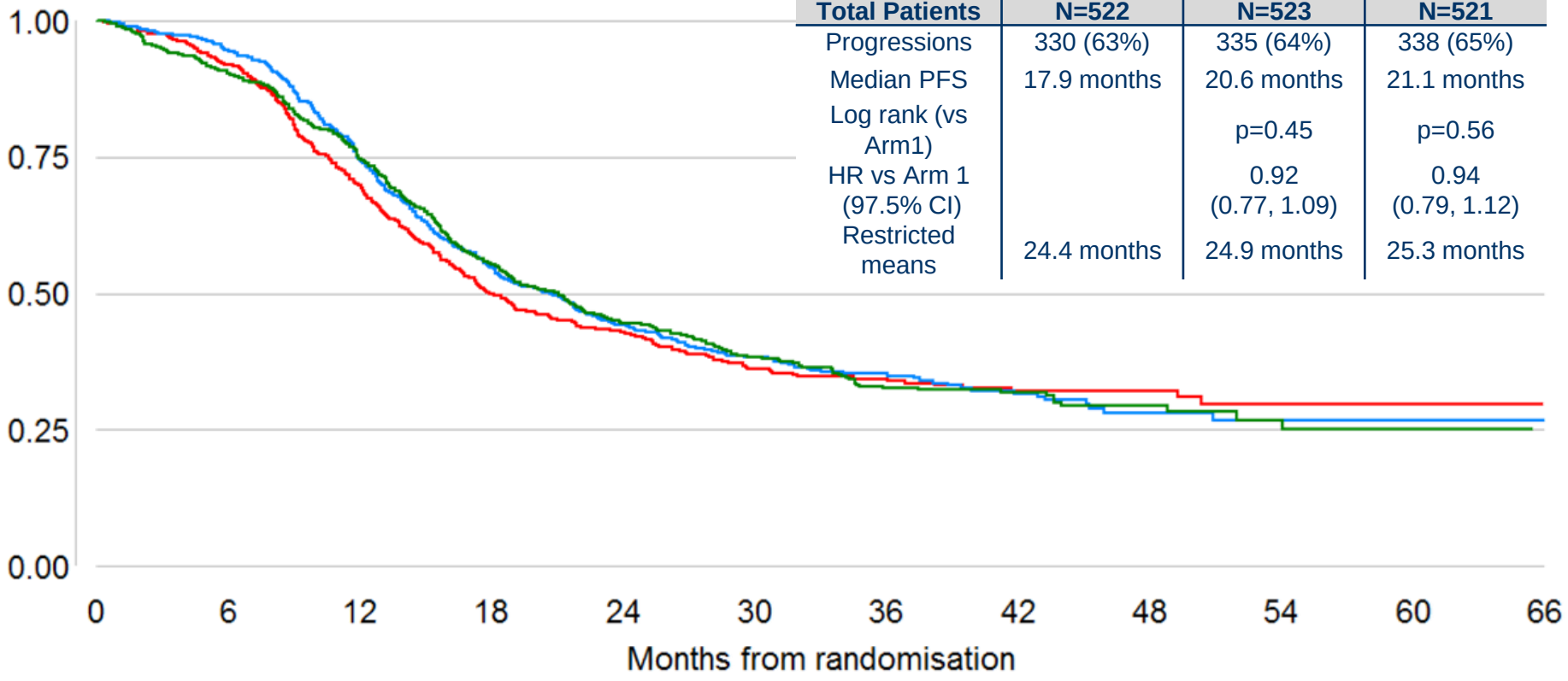
Open: JUN-2011
Closed: NOV-2014
Target: 1566 pts

Clamp A, et al. ESMO 2017

MRC-UK ICON8: Dose-Dense

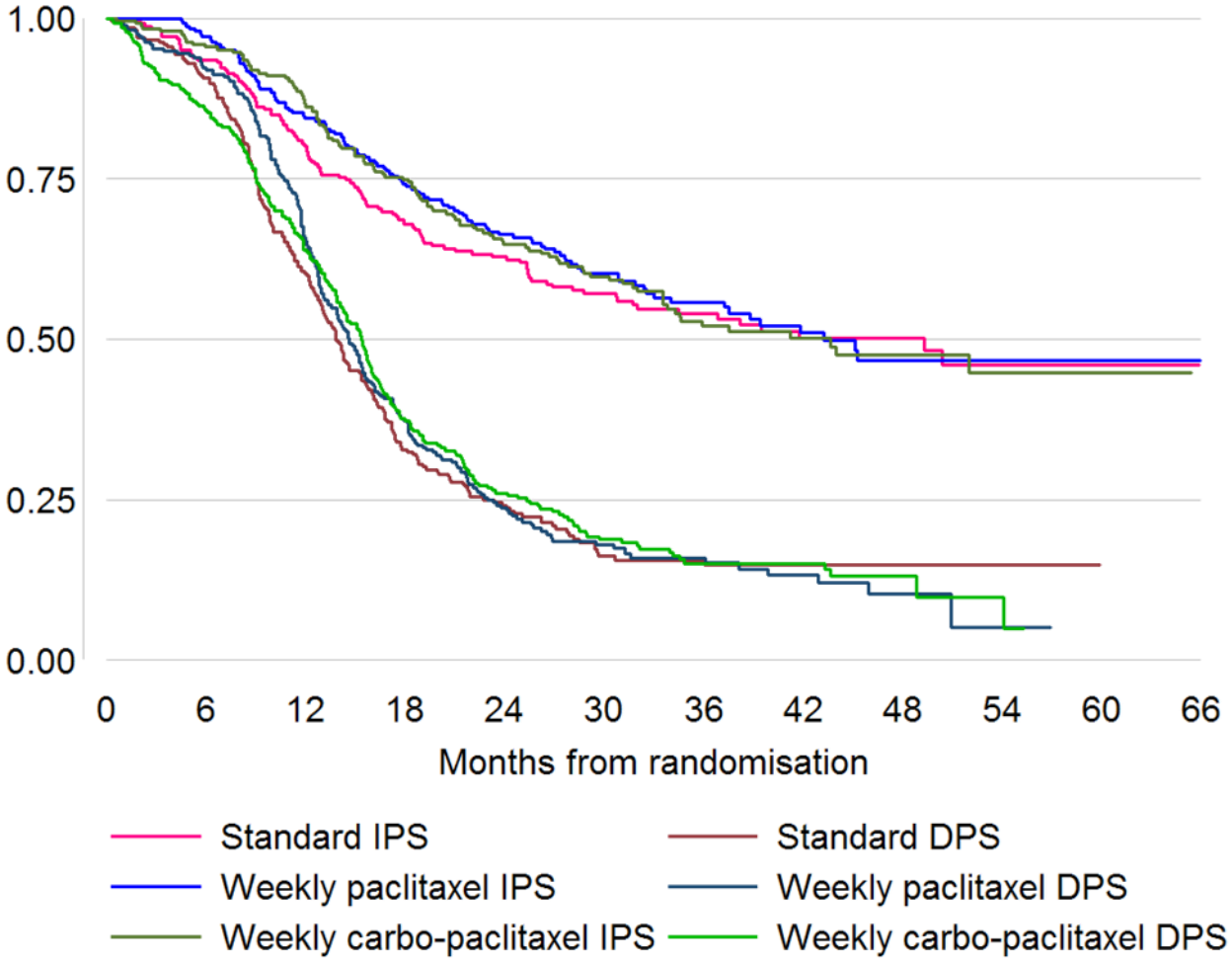
Primary Analysis PFS (ITT)

Total Patients	Arm 1 Standard N=522	Arm 2 Weekly paclitaxel N=523	Arm 3 Weekly carbo-paclitaxel N=521
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS	17.9 months	20.6 months	21.1 months
Log rank (vs Arm1)		p=0.45	p=0.56
HR vs Arm 1 (97.5% CI)		0.92 (0.77, 1.09)	0.94 (0.79, 1.12)
Restricted means	24.4 months	24.9 months	25.3 months



Clamp A, et al. ESMO 2017

MRC-UK ICON8: Dose-Dense



Clamp A, et al. ESMO 2017

Progression-free survival endpoint in the three phase trials of maintenance PARP inhibitors

Study	PARPi PFS (months)	Placebo PFS (months)	Hazard ratio
SOLO 2*	19.1	5.5	0.3
NOVA**			
gBRCA	21	5.5	0.27
Non-BRCA	9.3	3.9	0.45
Non-BRCA HRD+	12.9	3.8	0.38
ARIEL 3***			
gBRCA	16.6	5.4	0.23
HRD+ (+WT/gBRCA)	13.6	5.4	0.32

* Pujade-Lauraine et al Lancet Oncol 2017; 18:1274;
** Mirza et al NEJM 2016; 375:2154;
*** Coleman et al. Lancet 2017

PFS = progression-free survival

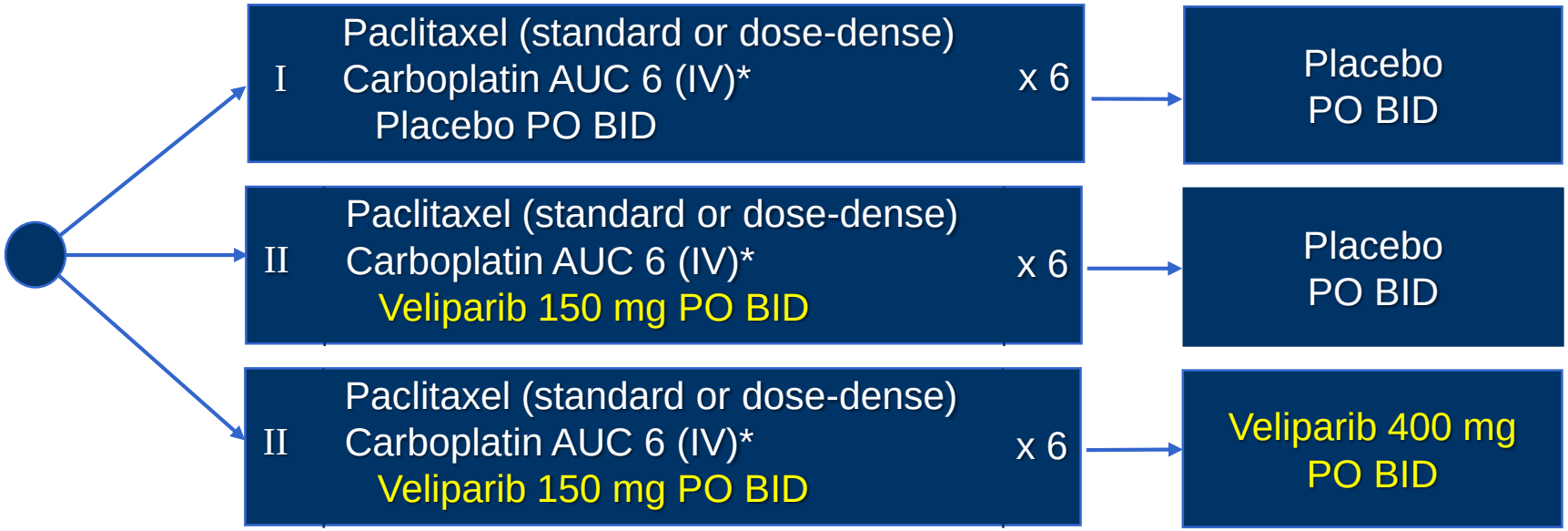
PARP Inhibitors

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Drug	Approval	Maintenance Rx	Recurrent
Olaparib	BRCA ±	yes	yes
Niraparib	BRCA ±	yes	yes
Rucaparib	BRCA +	yes	yes

GOG3005: PARPi Primary Therapy

- High-grade extrauterine serous tumors, Stage I-C, II, III, IV
- Election for NACT-ICS and scheduling of paclitaxel (no IP therapy)
- Primary endpoint PFS: (1) Entire Population, (2) BRCA1/2 Population
- Stratifications: Stage, Residual Disease, NACT-ICS, Region, gBRCA status



Collaborative development with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory approval

Open: JUL 2015
Closed: MAY 2017
Target: ~1100 pts (264 BRCA1/2 +)

Coleman R, for GOG Foundation

Ovarian Cancer

- The mortality of advanced-stage HGSC has not changed, in spite of recent advances in treatment and supportive care, with improved PFS-OS
- The role of primary aggressive cytoreductive surgery is being evaluated (TRUST), but may have limited impact in patients with high disease burden
- Contemporary IV chemotherapy appears equivalent to modified IP chemotherapy with either cisplatin or carboplatin
- Dose-dense weekly paclitaxel may have advantages in some populations, but data from randomized trials are conflicting
- NACT with ICS offers a valuable platform for clinical research
- PARP inhibition has become widely utilized (as therapy and maintenance) with questions about patient selection, timing, resistance, and combinations with other agents, including immunotherapy and antiangiogenics
- The role of immune checkpoint inhibition in HGSC is unknown, but likely to be complicated by multiple pathways of immunosuppression
- Novel approaches include antibody-drug-conjugates (ADC), vascular disruptive agents (VDA), and agents that target the DNA damage response