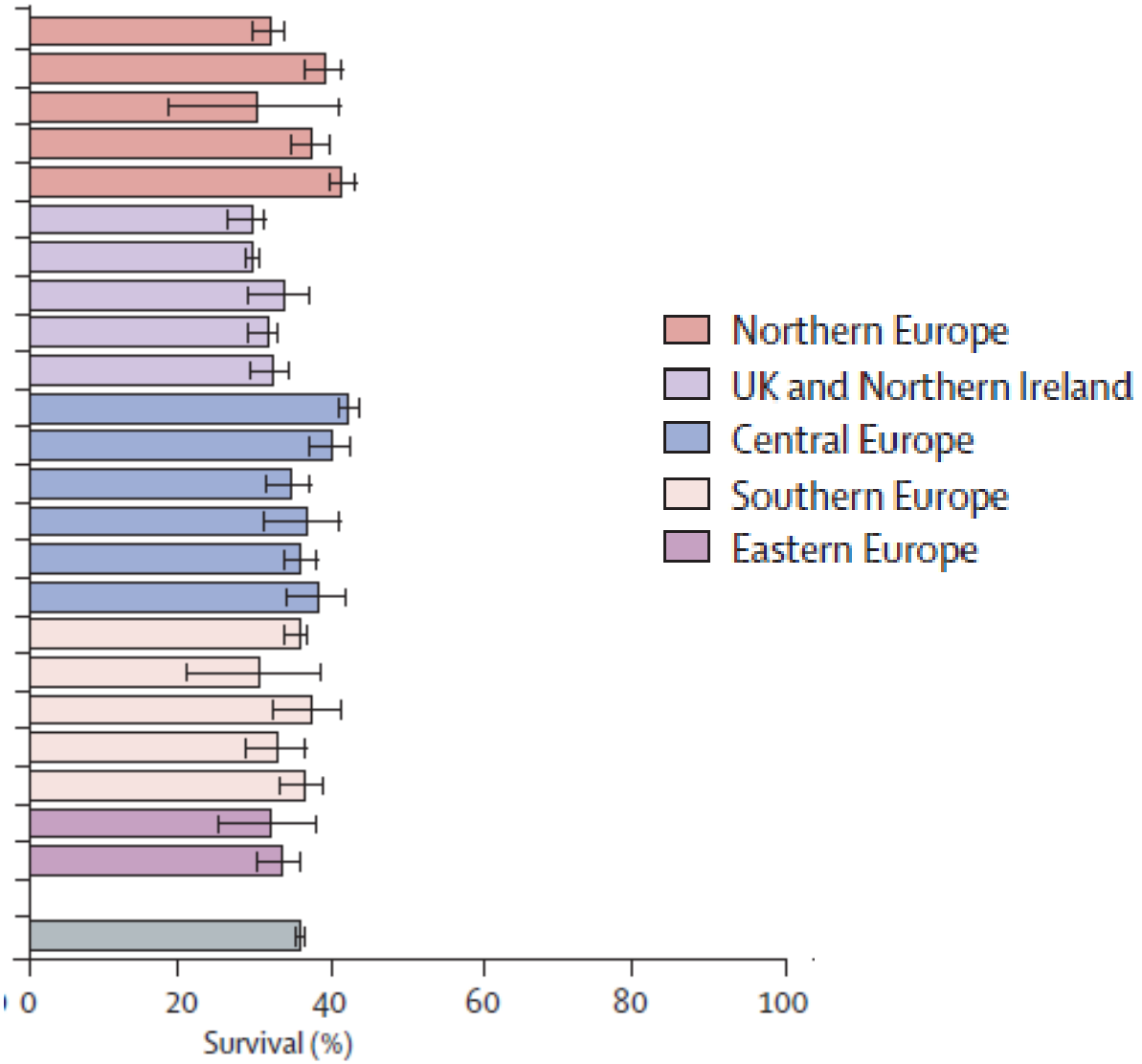
Optimal First-line Treatment for Ovarian Cancer

Jonathan A Ledermann
UCL Cancer Institute
University College London, UK

ESMO, Vienna Sept 2012

Ovarian cancer: survival rates

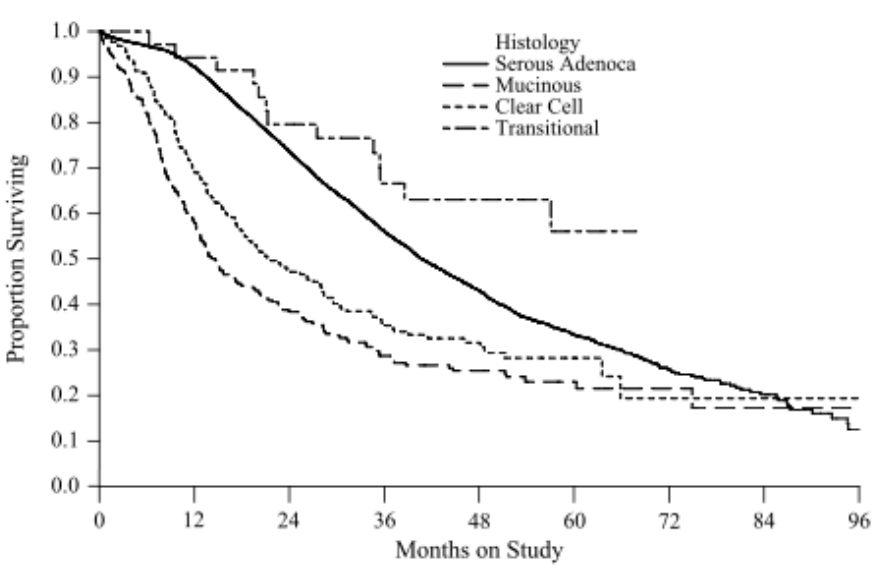


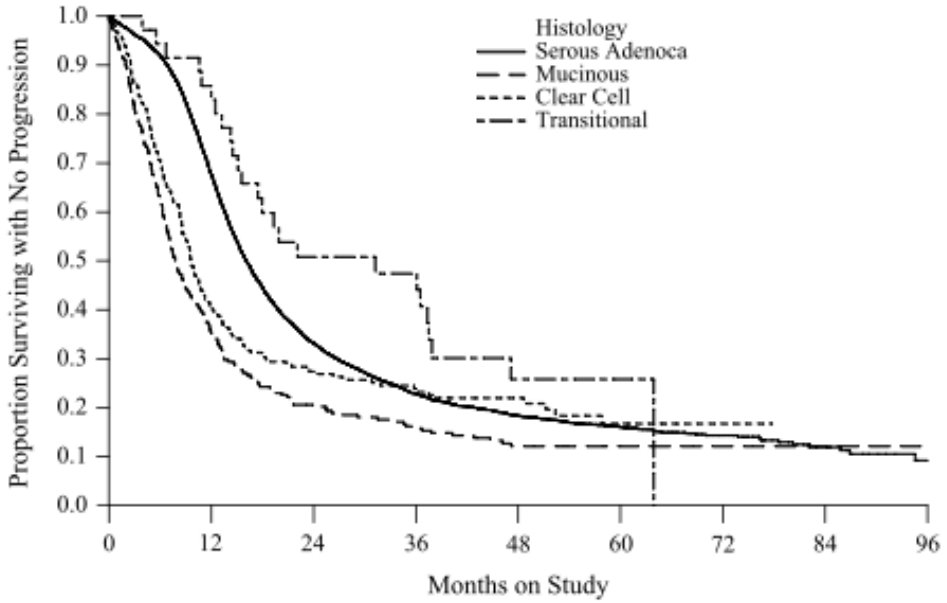
Bars indicate 95% CI

Berrino R, *et al. Lancet Oncol* 2007;8:773–783

Ovarian Cancer not one disease

8704 patients from 7 Randomised trials





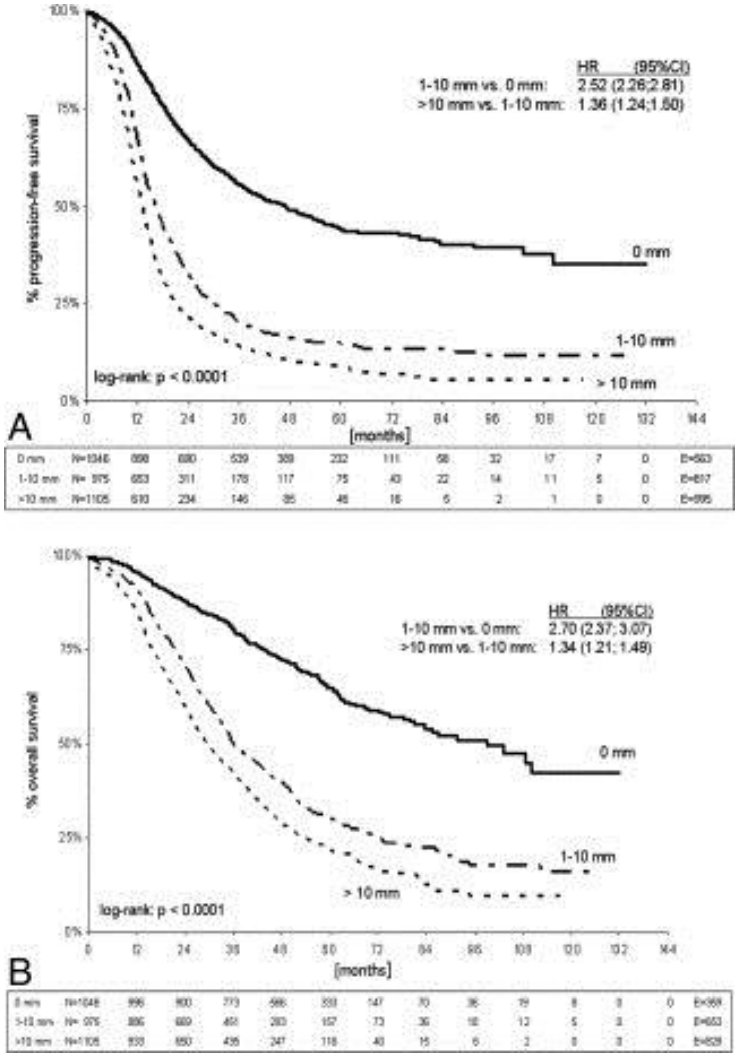
Mackay et al Int J Gyn Cancer 2010

Surgery

- How important is complete surgical debulking?
- What is the importance of specialised care and centralisation?
- Are patients disadvantaged by delaying primary surgery- ‘neoadjuvant chemotherapy’?

Role of surgical outcome as prognostic factor

A combined exploratory analysis of 3 prospectively randomized phase 3 multicentre trials



Complete removal of visible tumour carries prognostic importance

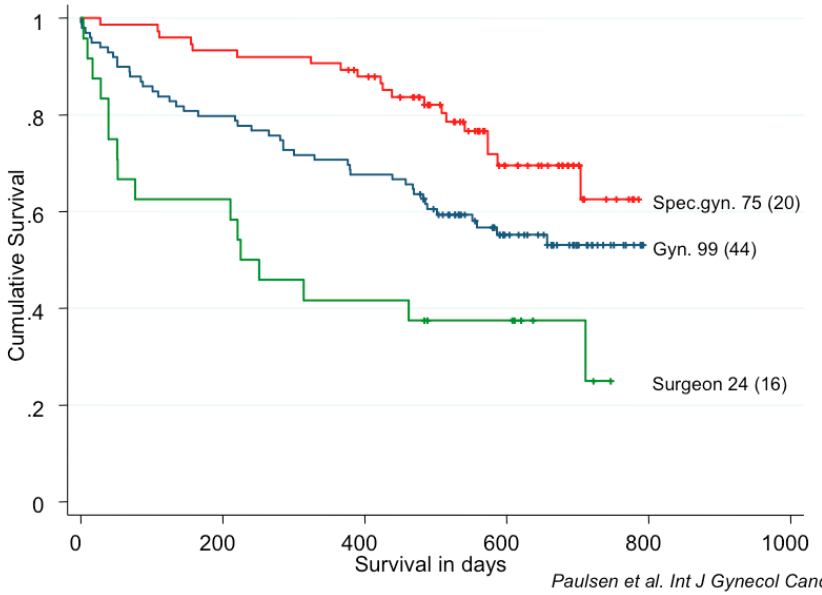
"optimal debulking ≠ < 1 cm disease"

No residual disease v < 1 cm HR 2.20 (95% CI 1.90-2.54)

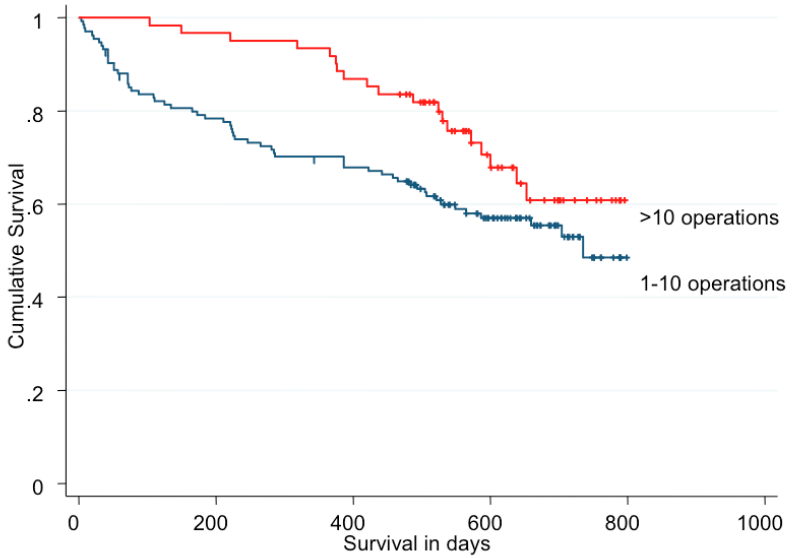
Cochrane meta-analysis. Elattar et al 2011

Du Bois et al Cancer 2009

Surgical specialisation?



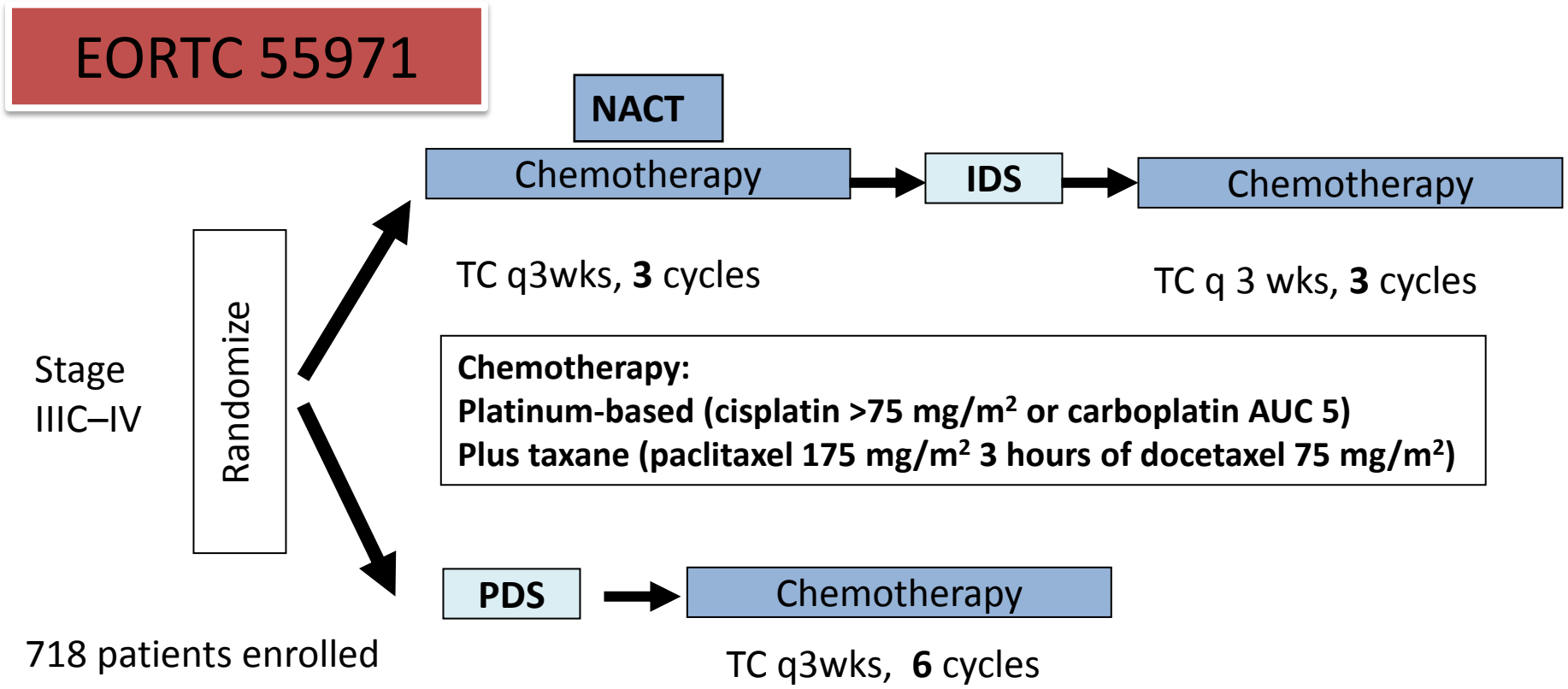
Paulsen et al. Int J Gynecol Cancer 2006



Paulsen et al. Int J Gynecol Cancer 2006

Primary (Neoadjuvant) Chemotherapy

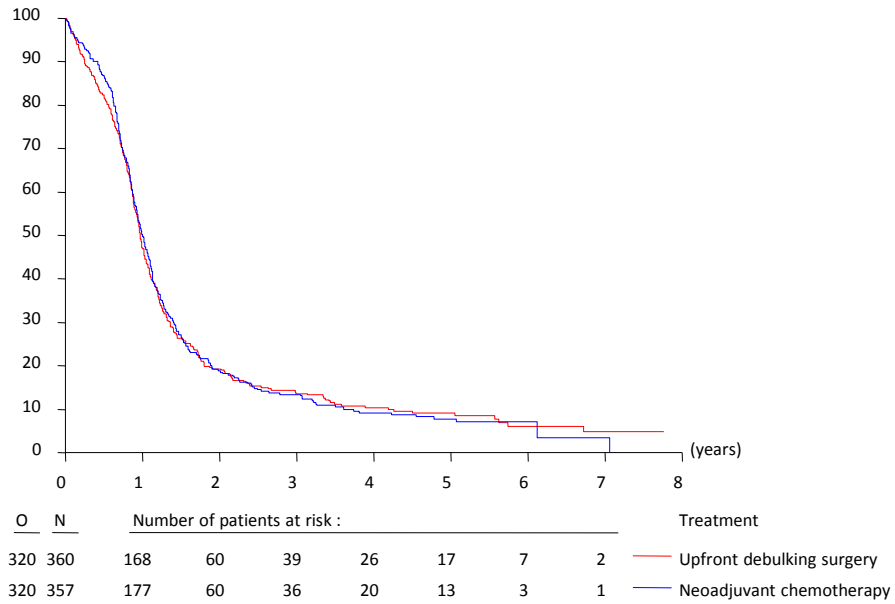
- Consider if radical debulking is not possible
- Is it safe to defer surgery by primary chemotherapy?



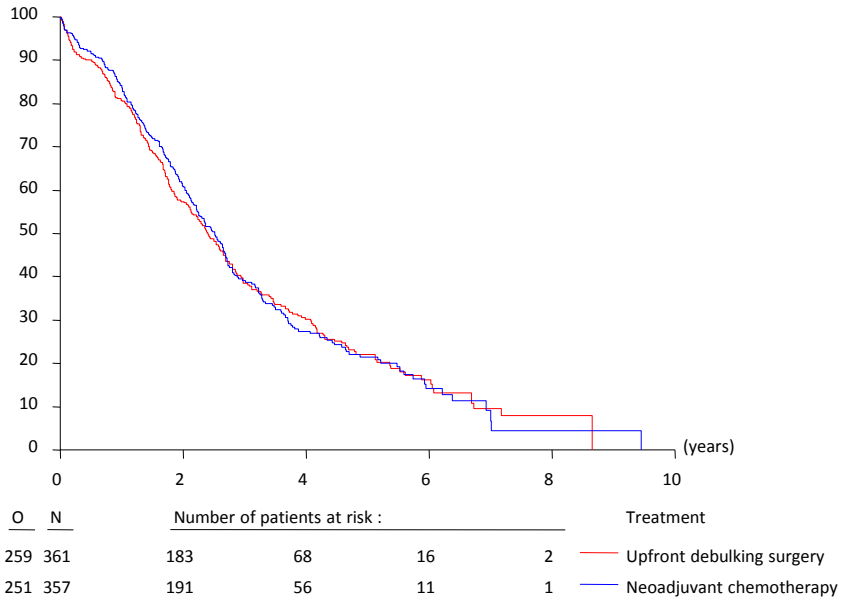
Vergote I et al. *New Engl J Med.* 2010; 363:943–953

Neoadjuvant chemotherapy
EORTC 55971

Progression-free survival



Overall survival



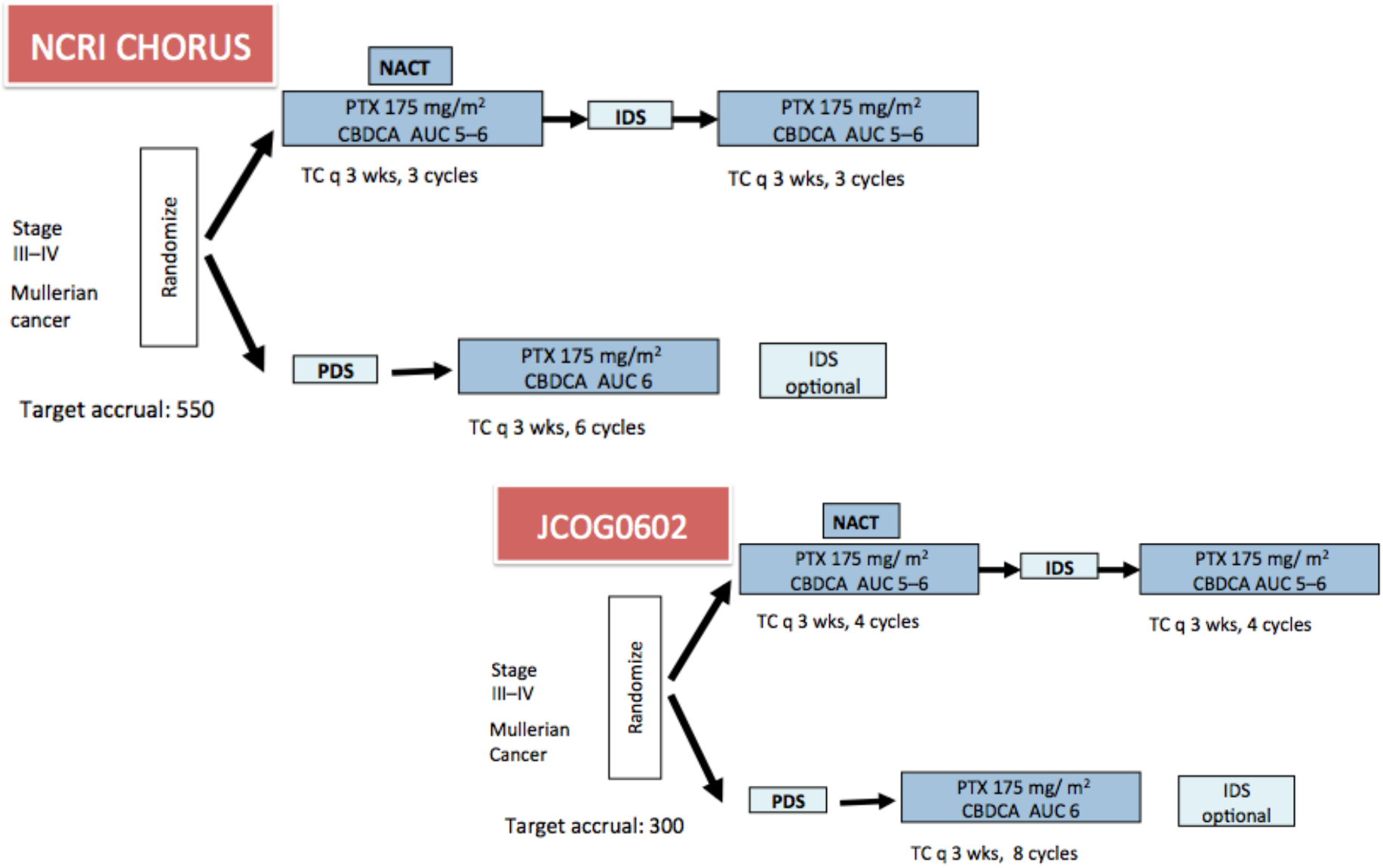
Vergote I et al. *New Engl J Med.* 2010; 363:943–953

Multivariate analysis for OS EORTC 55971

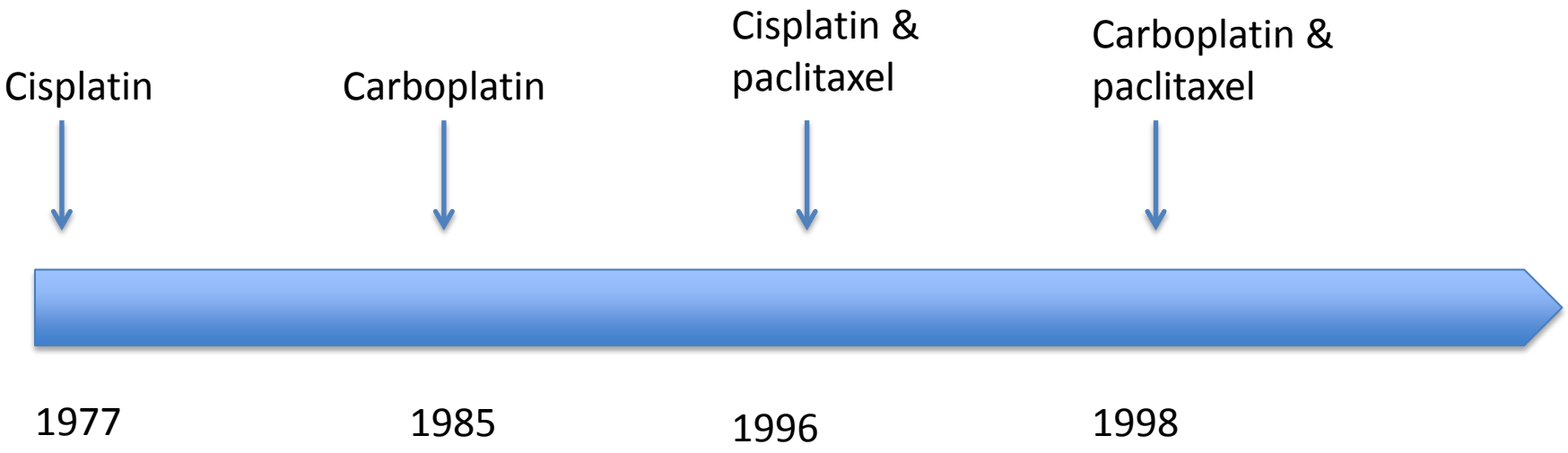
	P-value
Optimal debulking	0.0001
Histological type (nine categories)	0.0003
Largest tumour size at randomization	0.0008
FIGO stage (IIIc vs. IC)	0.0008
Country (14 categories)	0.0014
Age	0.0020
WHO PS	NS
Differentiation grade	NS
Treatment arm	NS

Vergote I et al. *New Engl J Med.* 2010; 363:943–953

International Trials of neoadjuvant chemotherapy



Chemotherapy



2000-2009

Carboplatin/paclitaxel + third drug

Carboplatin/paclitaxel sequential doublets

No improvement in PFS

Maintenance chemotherapy

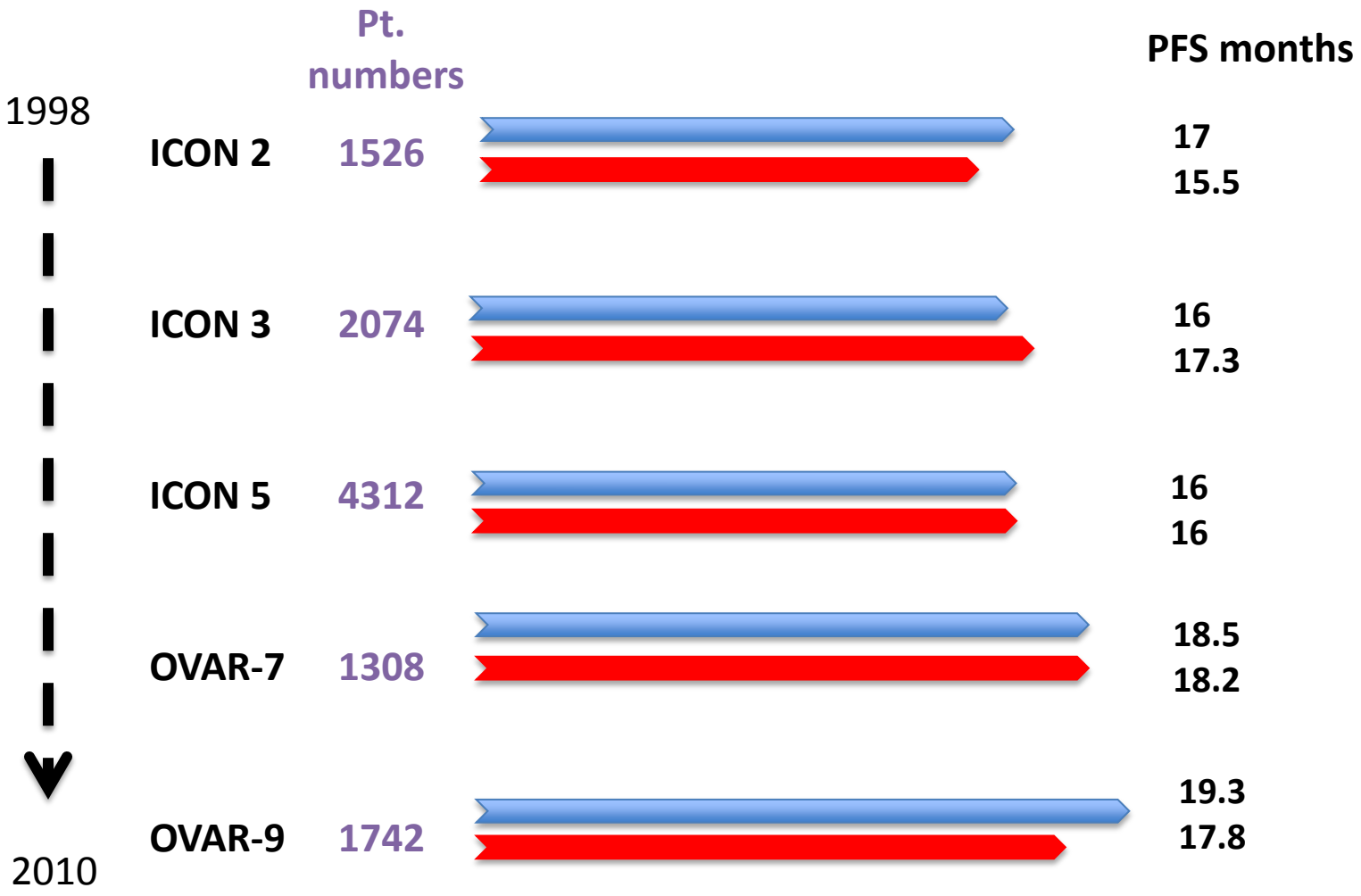
No improvement in PFS

1 trial with 12 cycles paclitaxel led ↑PFS but no ↑OS

High dose chemotherapy

No improvement in PFS

Progression-free survival in first-line trials



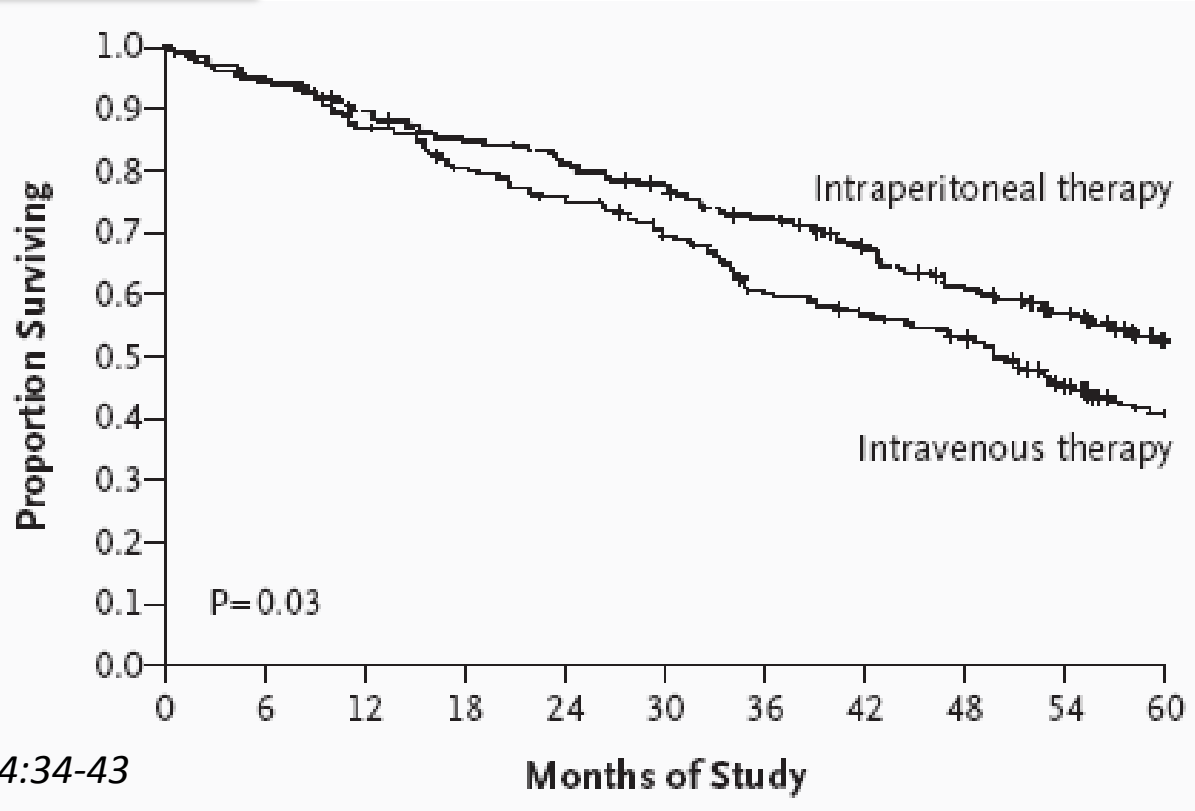
Moving Forward

- Intraperitoneal chemotherapy
- Dose-dense chemotherapy
- Molecular Targeted therapies

Intraperitoneal Therapy

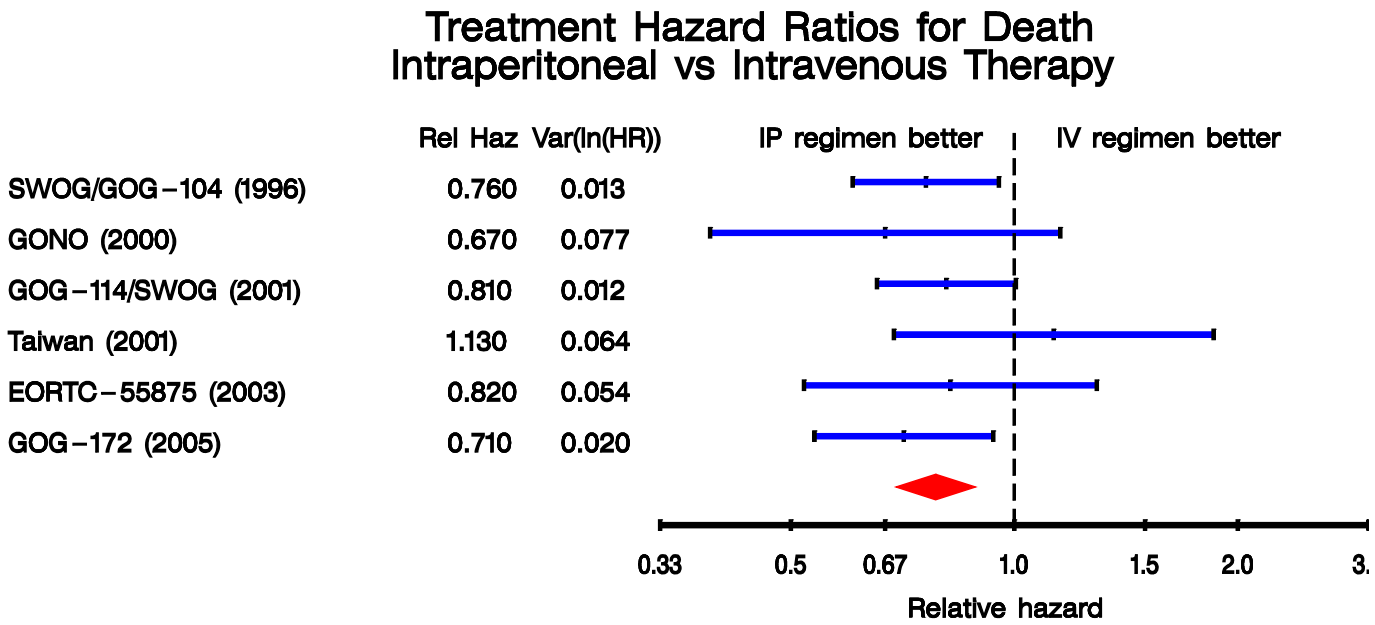
GOG-172

Cisplatin 75 mg/m^2 Paclitaxel 135 mg/m^2	Day1: IV Paclitaxel 135 mg/m^2 Day 2: IP Cisplatin 100mg/m^2 Day 8: IP Paclitaxel 60 mg/m^2



Armstrong et.al. N Engl J Med 2006;354:34-43

Intraperitoneal therapy



X^2 heterogeneity (5 d.f.)= 3.1, p=0.68

- Is the observed effect real?
- Do carboplatin and cisplatin have an equivalent effect when given i.p.?
- What is the contribution of weekly paclitaxel?

Ongoing intraperitoneal therapy studies

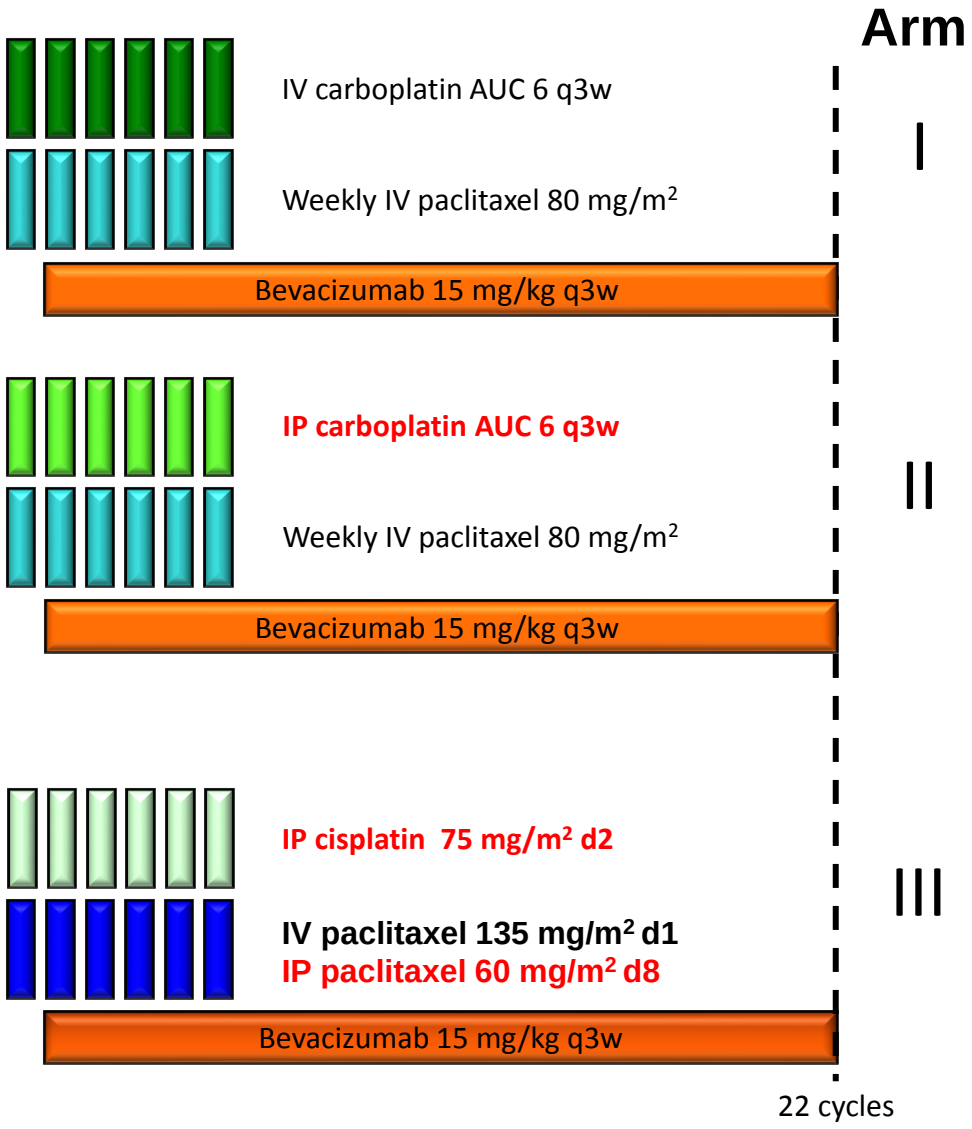
GOG 252

Ovarian (epithelial), primary peritoneal, or fallopian tube cancer

Stage II–IV optimal
No prior anti-VEGF therapy

n=1250 (target)

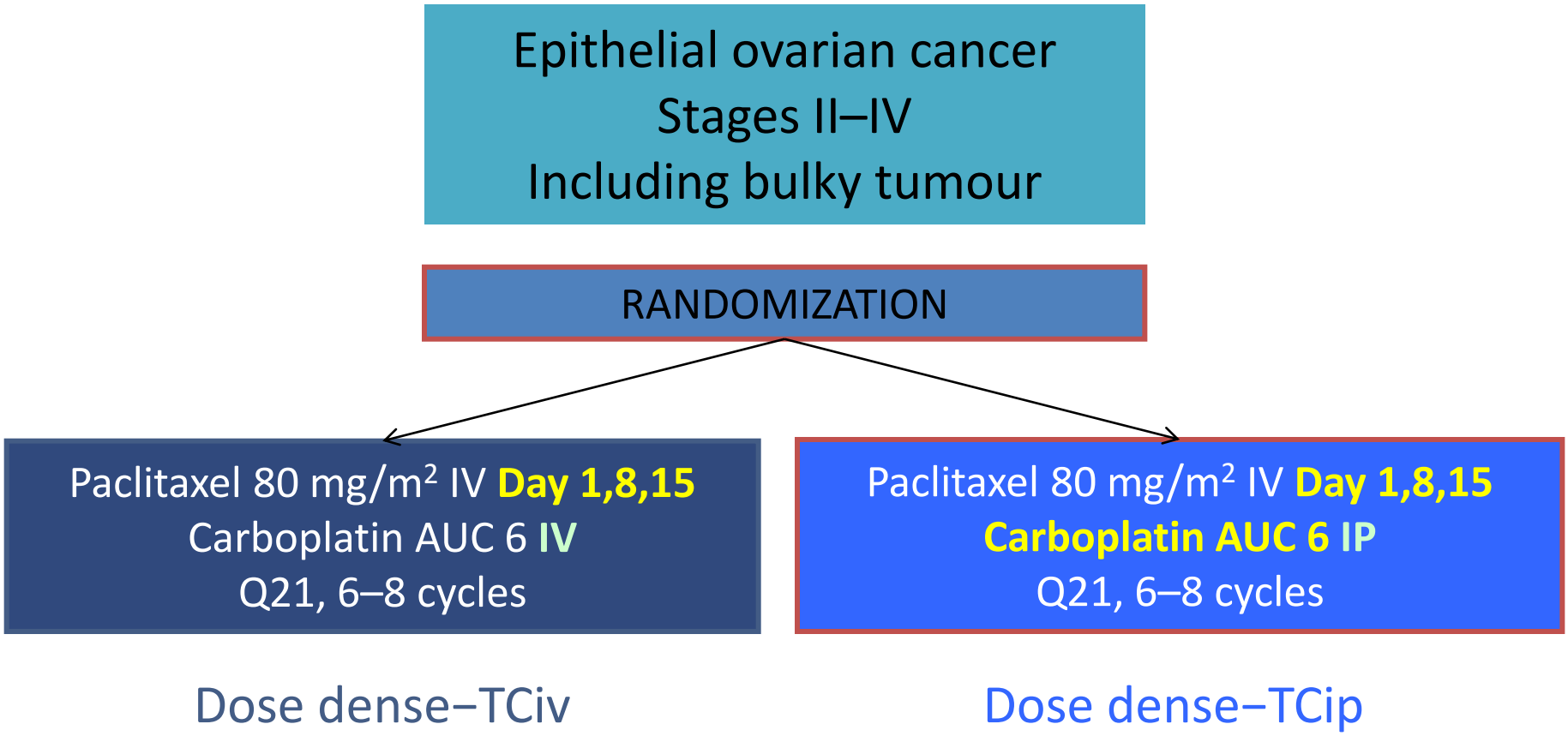
RANDOMISE



Primary endpoint: PFS

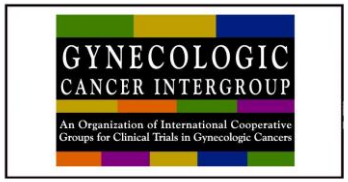
Secondary endpoints:
OS, QoL, safety

iPocc JGOG trial



Primary endpoint: PFS
Secondary endpoints: OS, toxicity, QoL
Accrual goal: 746 patients / 511 events

Intrapertioneal therapy after interval debulking surgery



NCIC- OV21 & NCRI – GEICO[PETROC] - SWOG

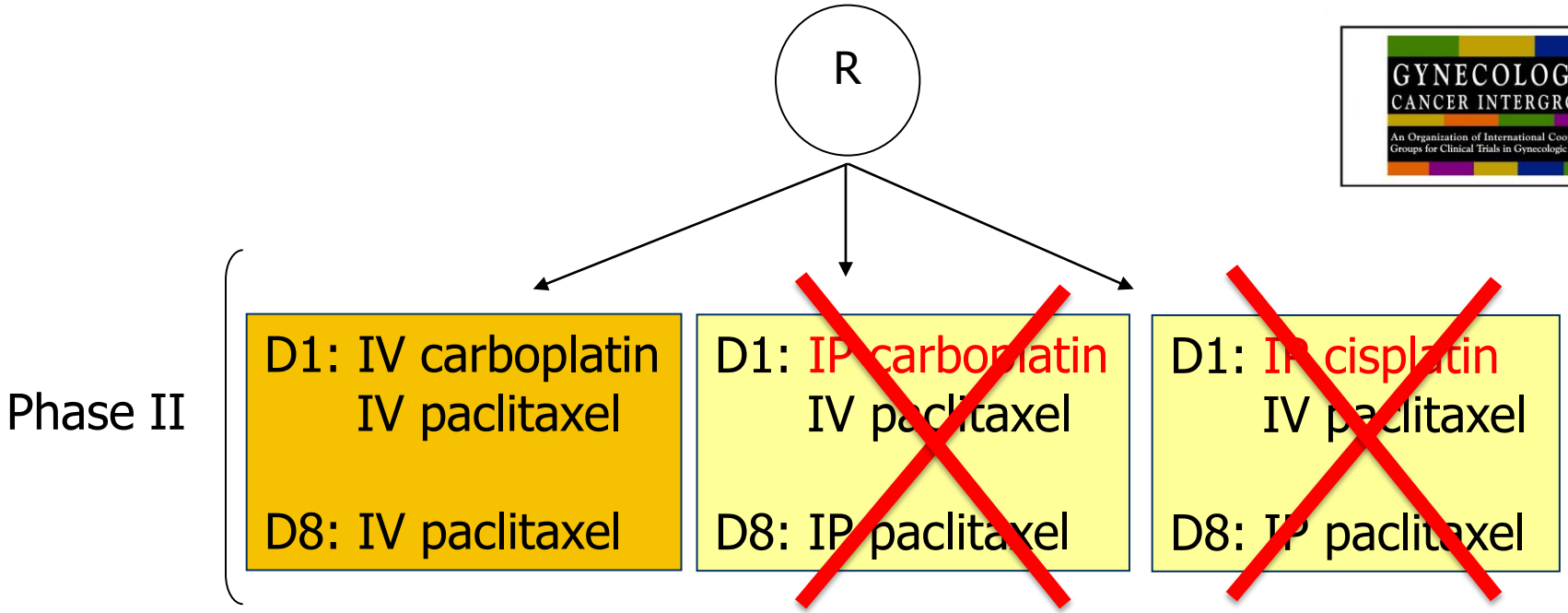
Patients with EOC

3-4 cycles neoadjuvant chemotherapy

Initial surgery: ≤ 1 cm residual

3 cycles standard
IV carboplatin/paclitaxel

3 cycles **IP/IV**
platinum and paclitaxel

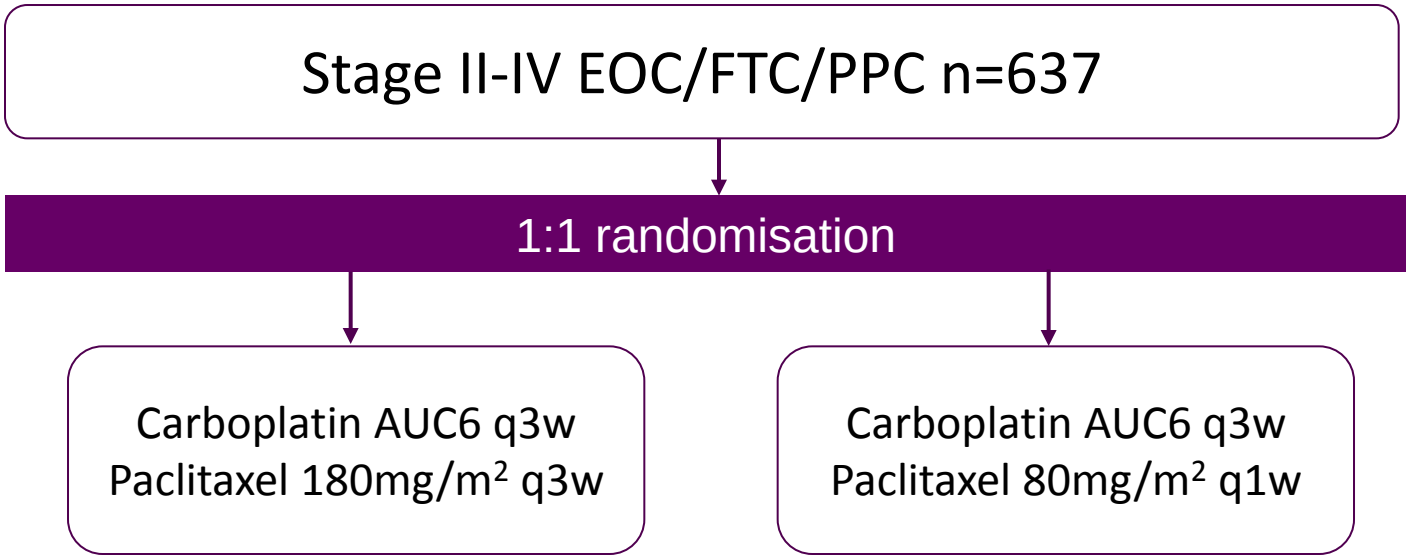


First phase- 50 patients per arm, assessing PD rate at 9 months and tolerability

Part II will drop one of the ip arms

Endpoints: PFS and OS

Dose-dense paclitaxel

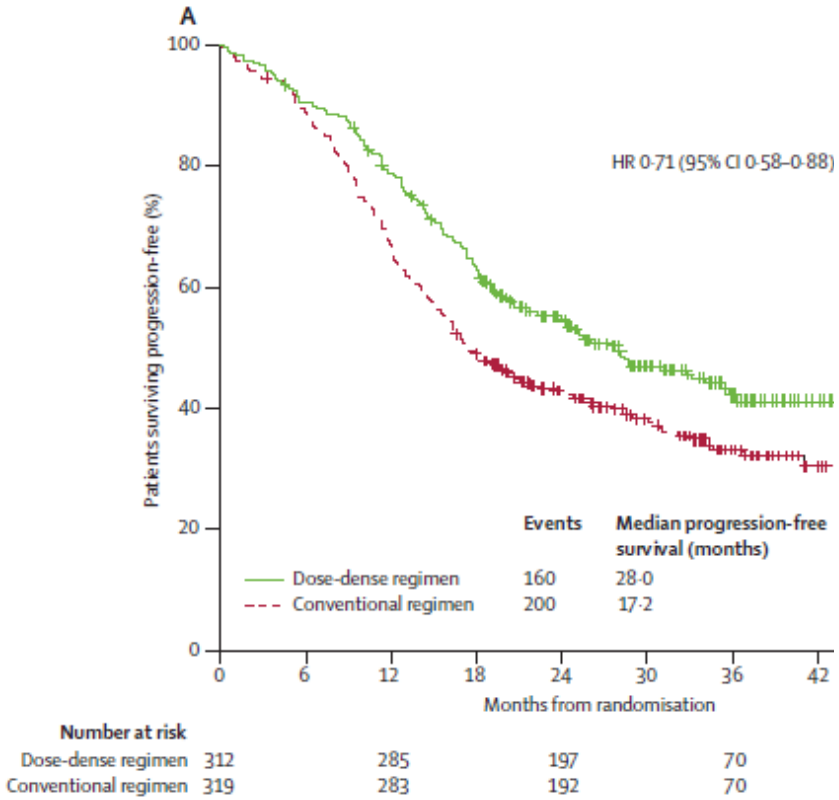


- 66% stage III
- 98% ECOG PS 0-2
- 89% primary debulking, 10% delayed debulking
- 55% residual disease >1cm
- 56% serous, 12% endometrioid, 11% clear cell, 5% mucinous

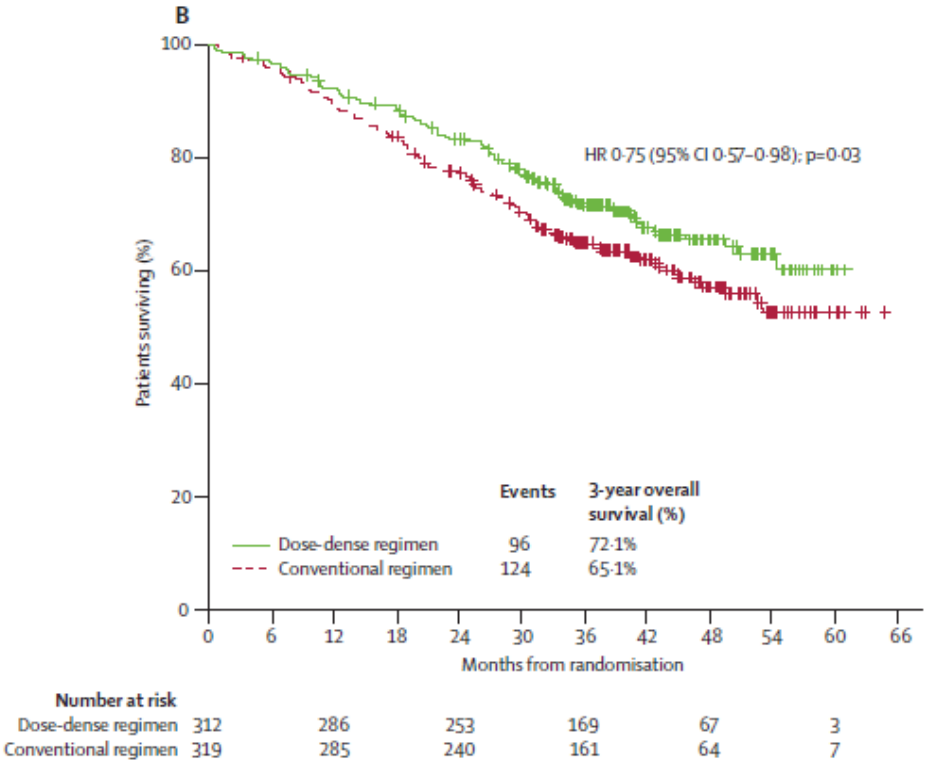
JGOG 3016

Katsumata et al; Lancet 2009

JGOG 3016- Outcome



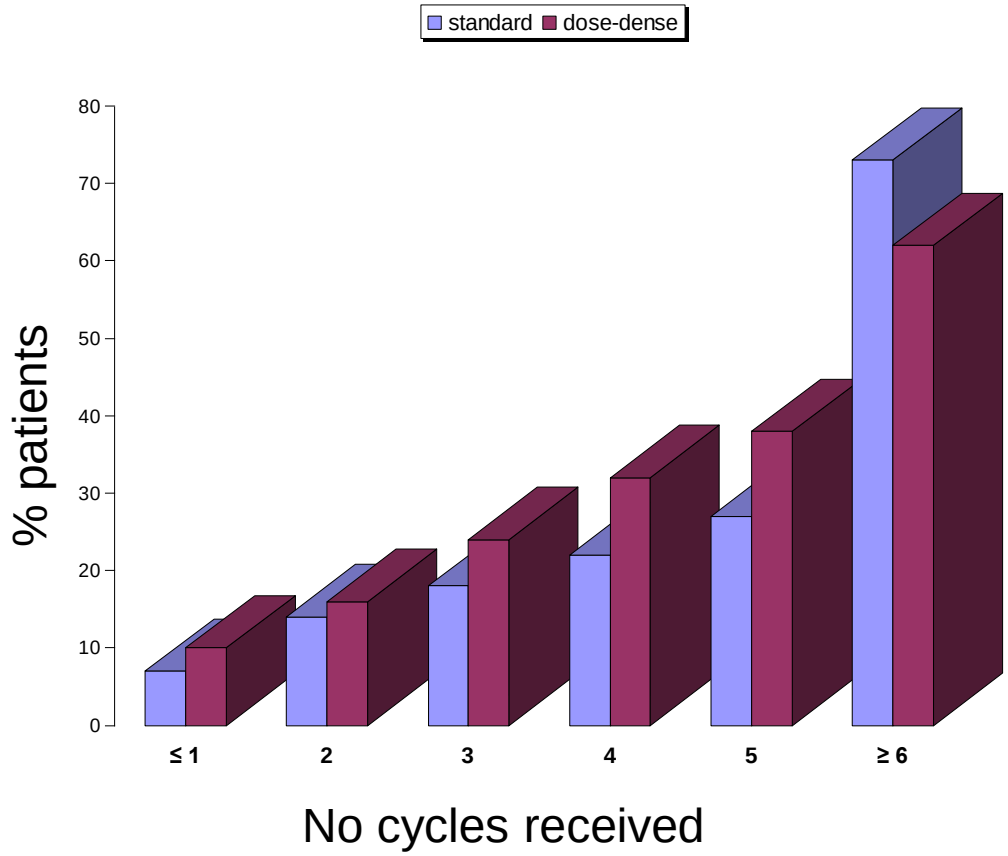
Progression-free survival



Overall survival

Katsumata et al; Lancet 2009

JGOG treatment delivery



- Discontinuation due to toxicity

  113 vs 69

  - Haematological 60 vs 43%
- Cycle delayed 76% vs 67%
- Dose intensity
  - Carboplatin

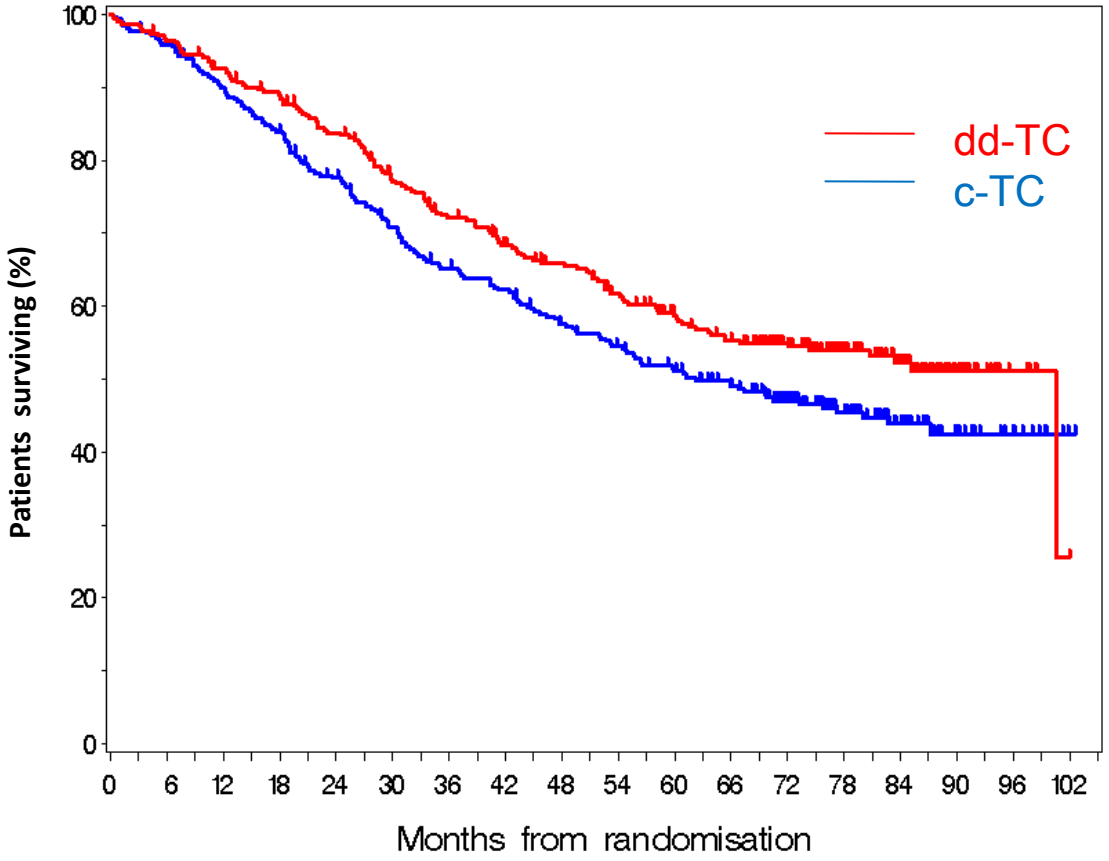
    (AUC/wk 1.54 vs 1.71)
  - Paclitaxel

    (mg/m^2/wk 63 vs 52)

Katsumata et al; Lancet 2009

JGOG3016: Updated Overall Survival

median follow-up period: 6.4 years

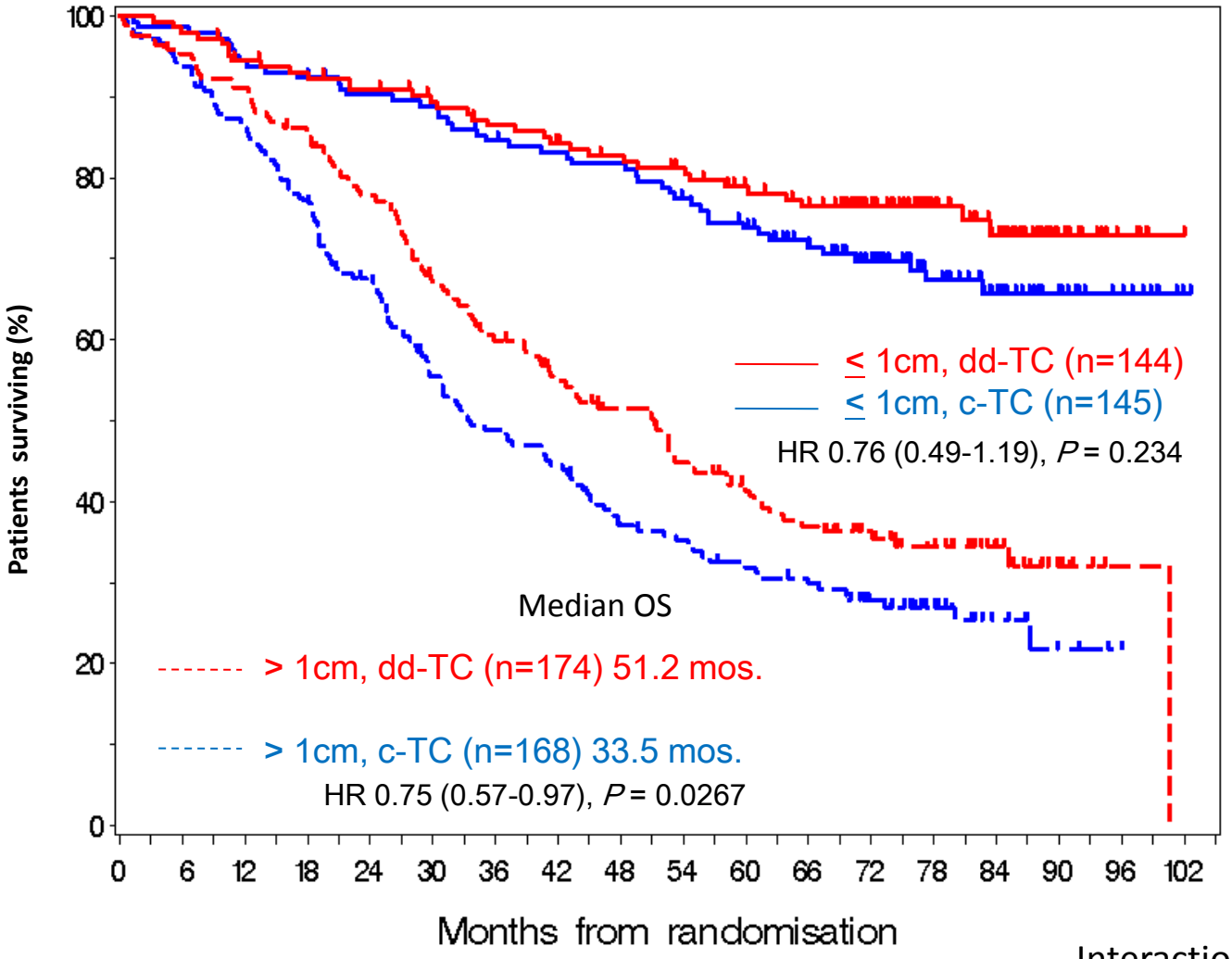


Treatment	n	Deaths, n (%)	Median OS	5-yr survival	*P* value	HR	95%CI
dd-TC	312	139 (45)	not reached	58.7%	0.039	0.79	0.63-0.99
c-TC	319	168 (53)	62.2 mos.	51.1%			

Katsumata et al ASCO 2012

JGOG 3016 – NOVEL trial

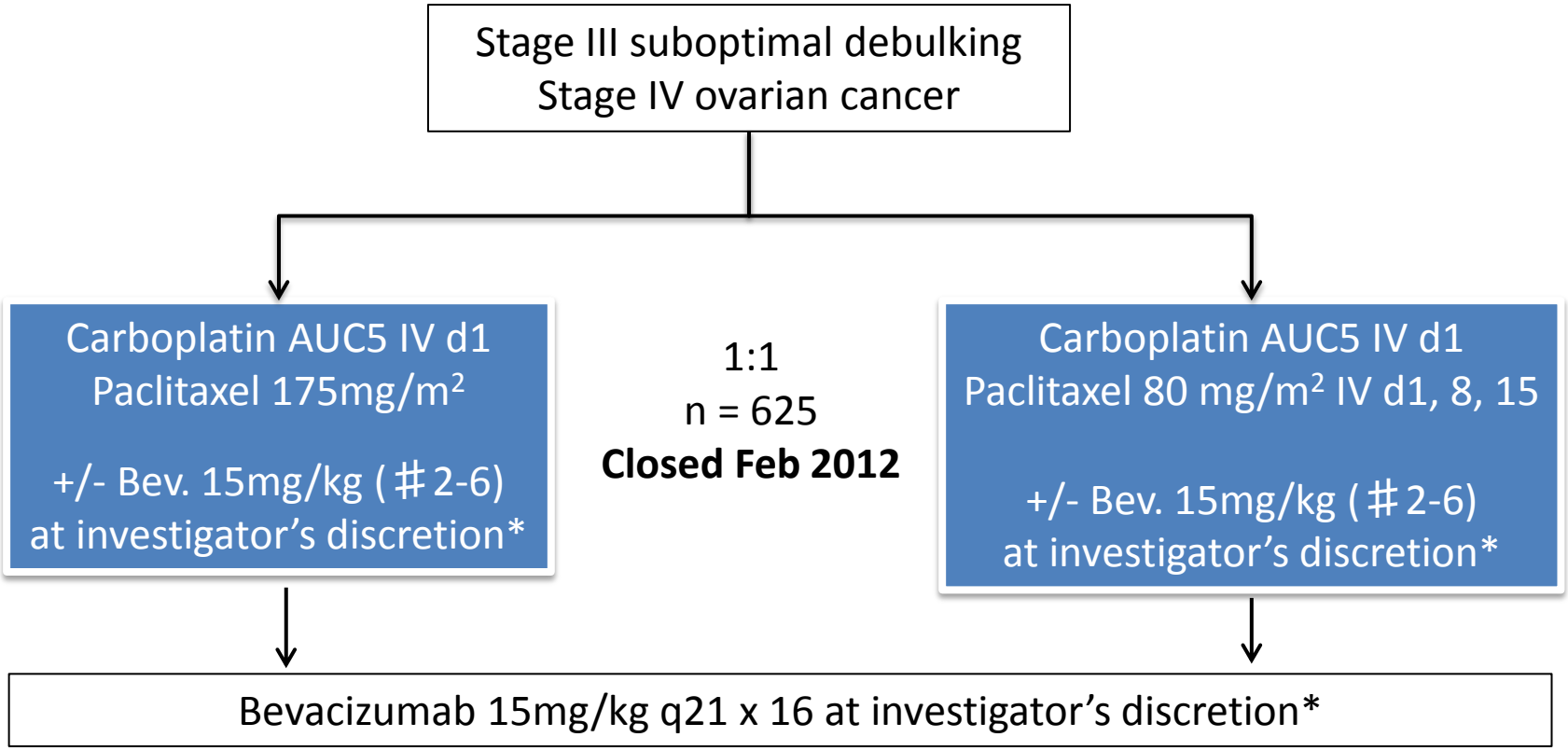
OS: by residual disease



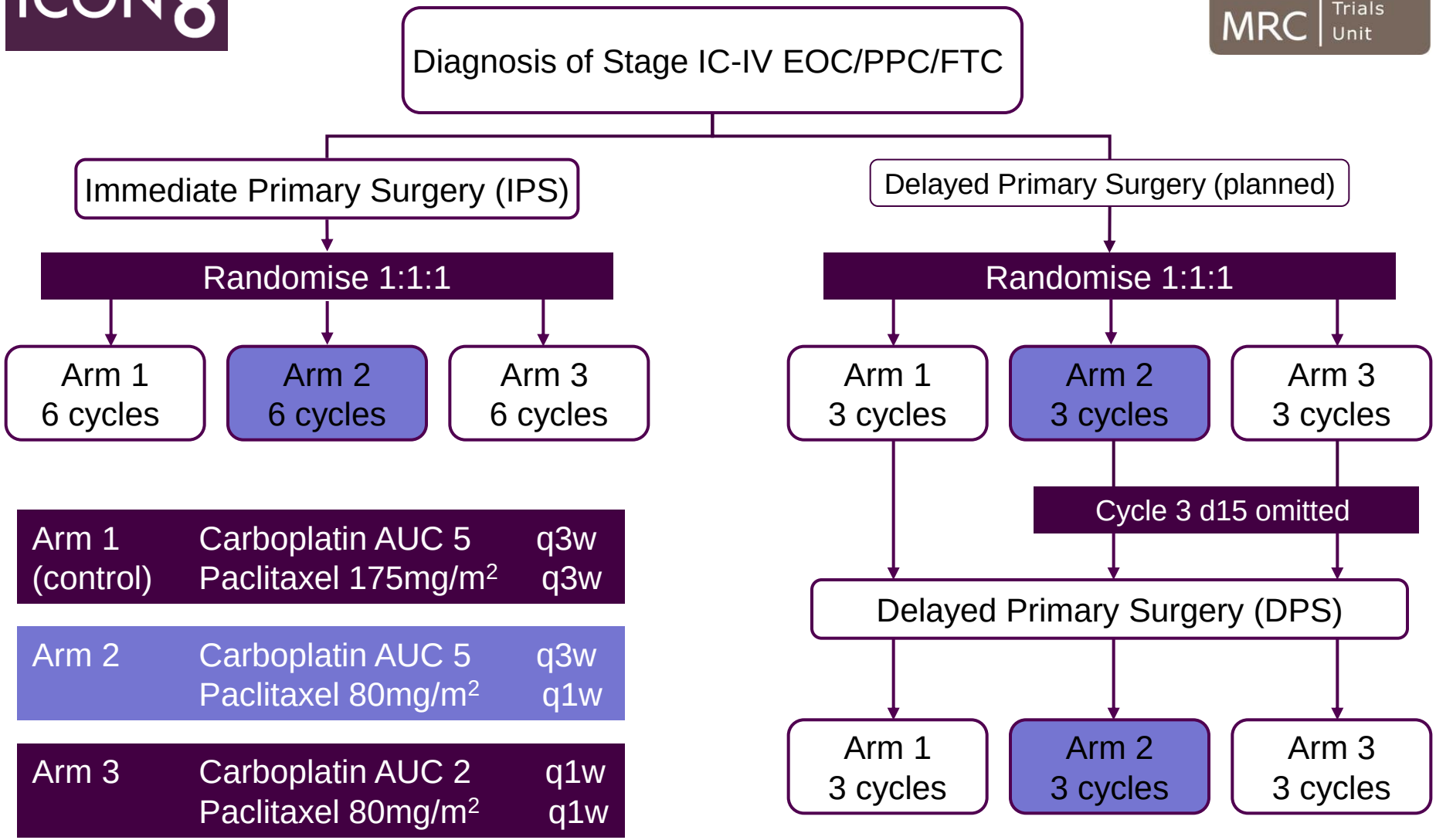
Interaction: $P = 0.925$

Katsumata et al ASCO 2012

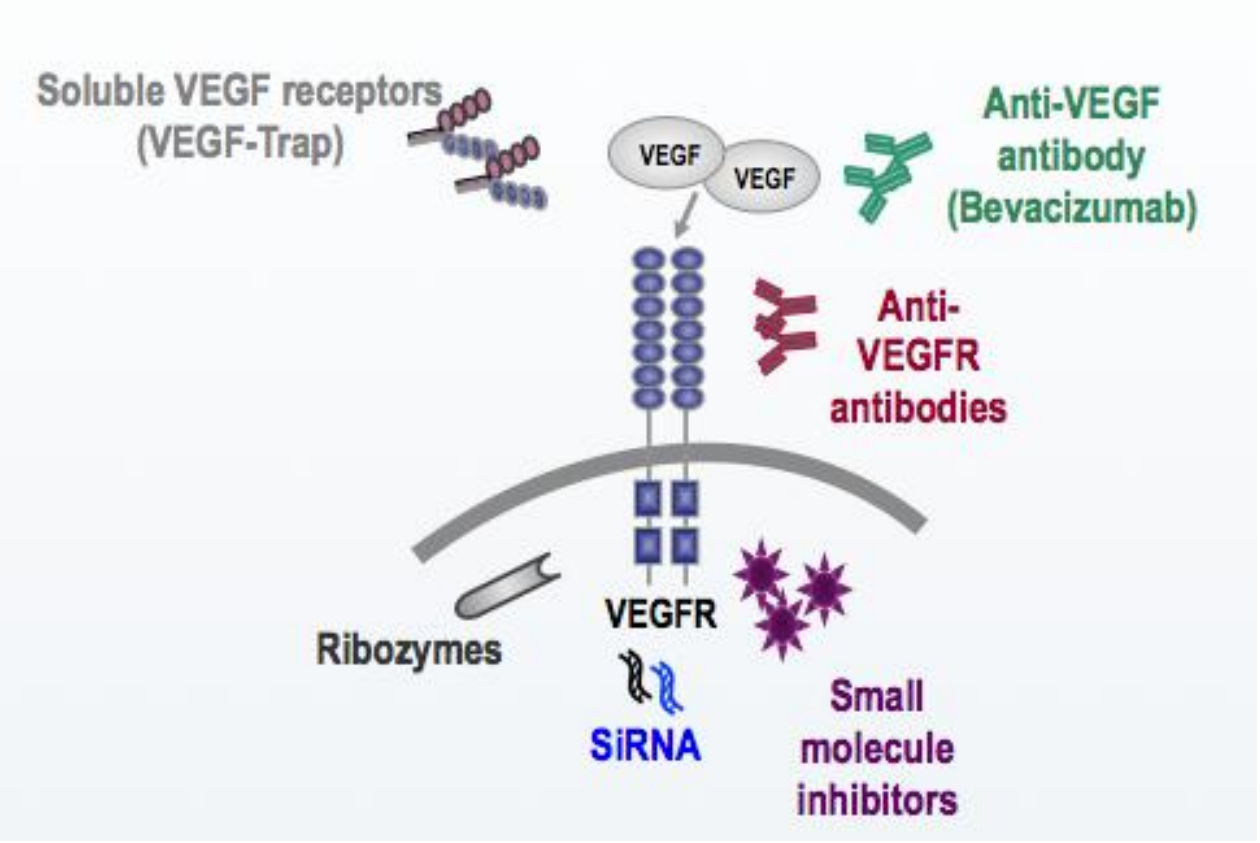
GOG 262- Dose dense chemotherapy



* 85% of patients received bevacizumab

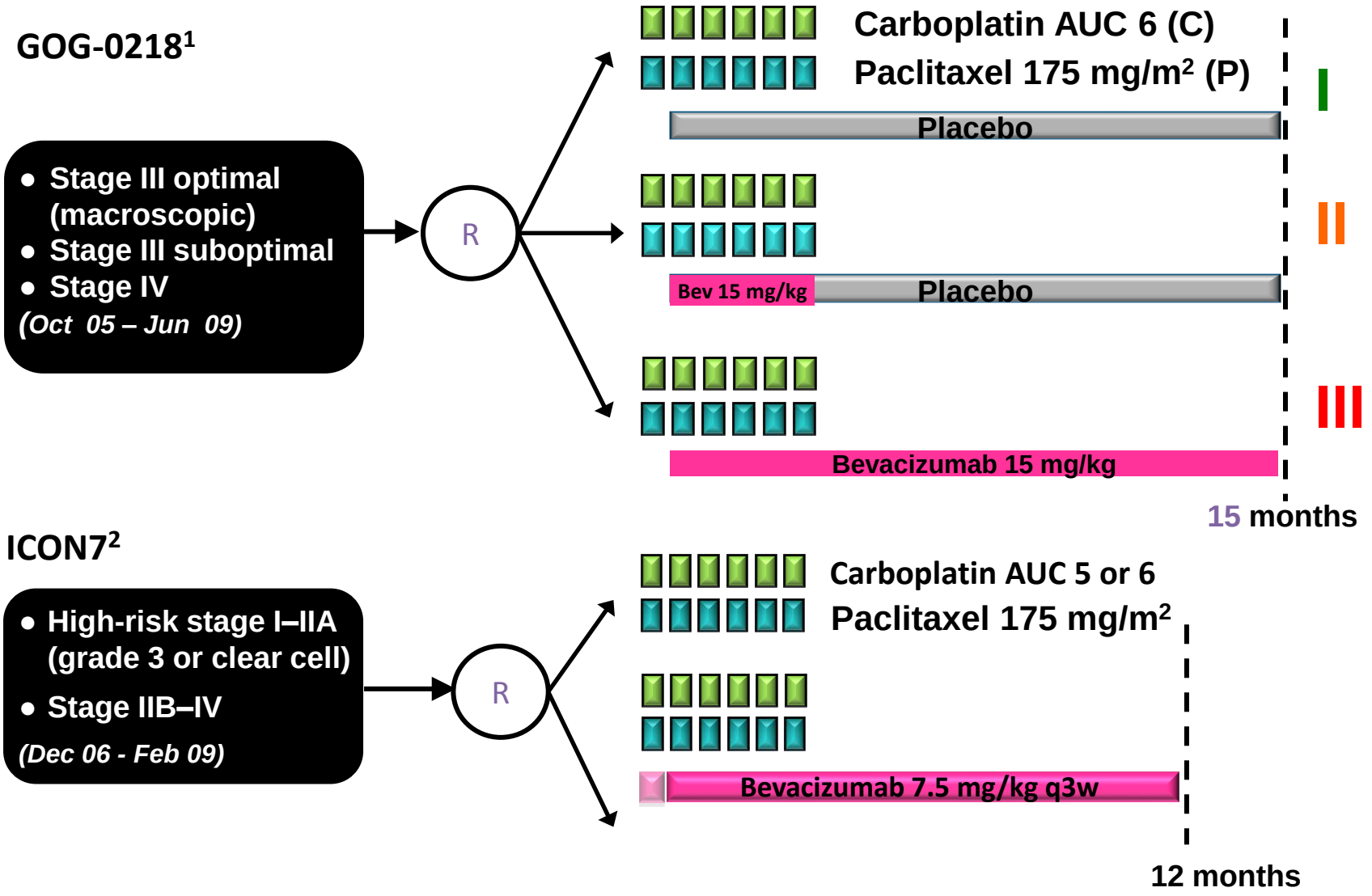

ICON8
MRC Clinical Trials Unit
Diagnosis of Stage IC-IV EOC/PPC/FTC
Immediate Primary Surgery (IPS)
Delayed Primary Surgery (planned)
Randomise 1:1:1
Randomise 1:1:1
Arm 1 6 cycles
Arm 2 6 cycles
Arm 3 6 cycles
Arm 1 3 cycles
Arm 2 3 cycles
Arm 3 3 cycles
Cycle 3 d15 omitted
Arm 1 (control) Carboplatin AUC 5 q3w Paclitaxel 175mg/m2 q3w
Arm 2 Carboplatin AUC 5 q3w Paclitaxel 80mg/m2 q1w
Arm 3 Carboplatin AUC 2 q1w Paclitaxel 80mg/m2 q1w
Delayed Primary Surgery (DPS)
Arm 1 3 cycles
Arm 2 3 cycles
Arm 3 3 cycles
NCRI National Cancer Research Institute
CANCER RESEARCH UK
Single trial with a pre-specified stratification for IPS vs. DPS
1590 patients
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Anti-angiogenic therapy of ovarian cancer



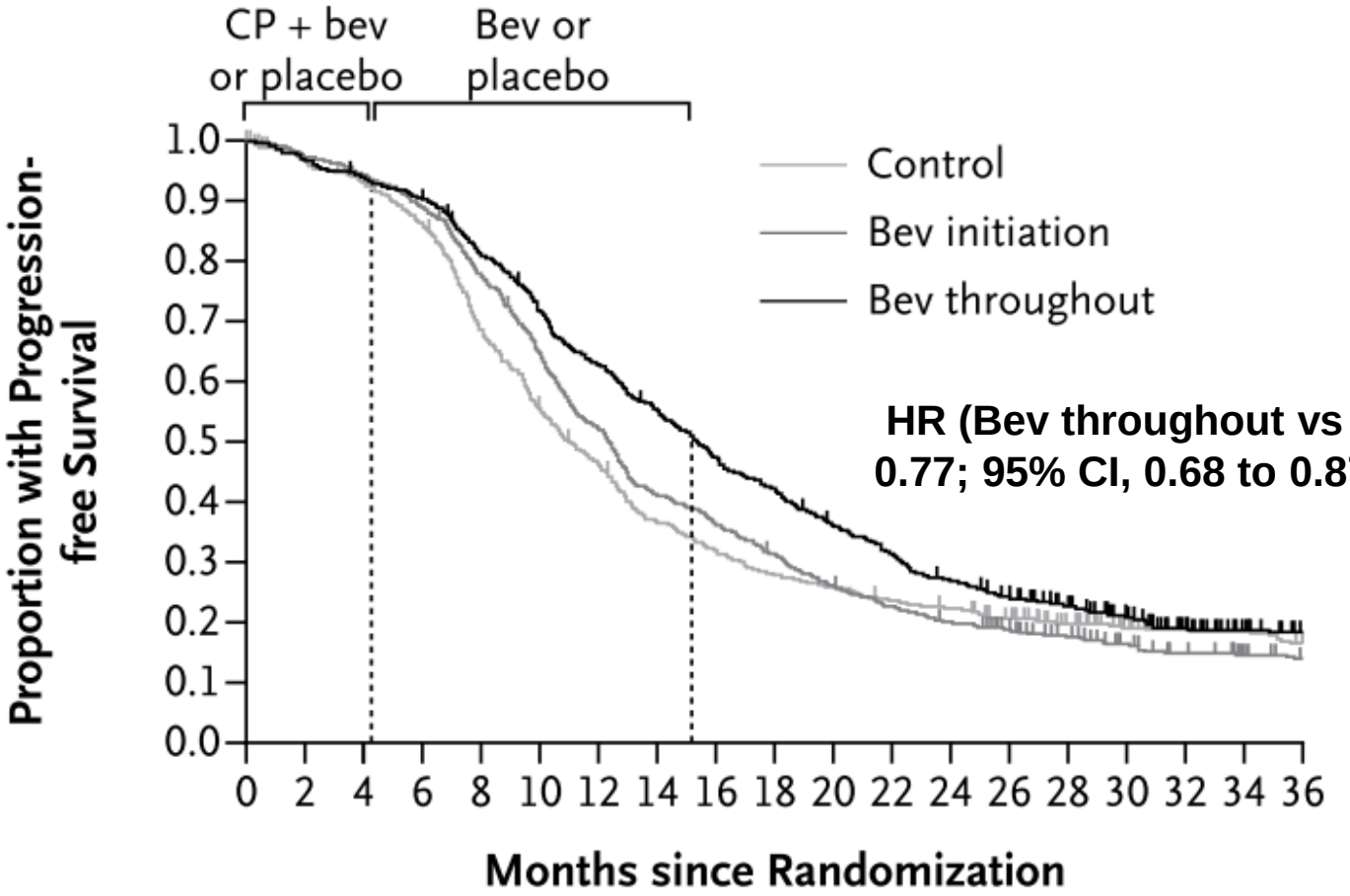
- Increased expression of angiogenic cytokines and receptors
- Associated with development of ascites
- High expression associated with poor prognosis

Two front-line trials with similar but not identical designs



1. Burger et al. ASCO 2010; 2. Perren et al ESMO 2010;

GOG0218: Updated PFS



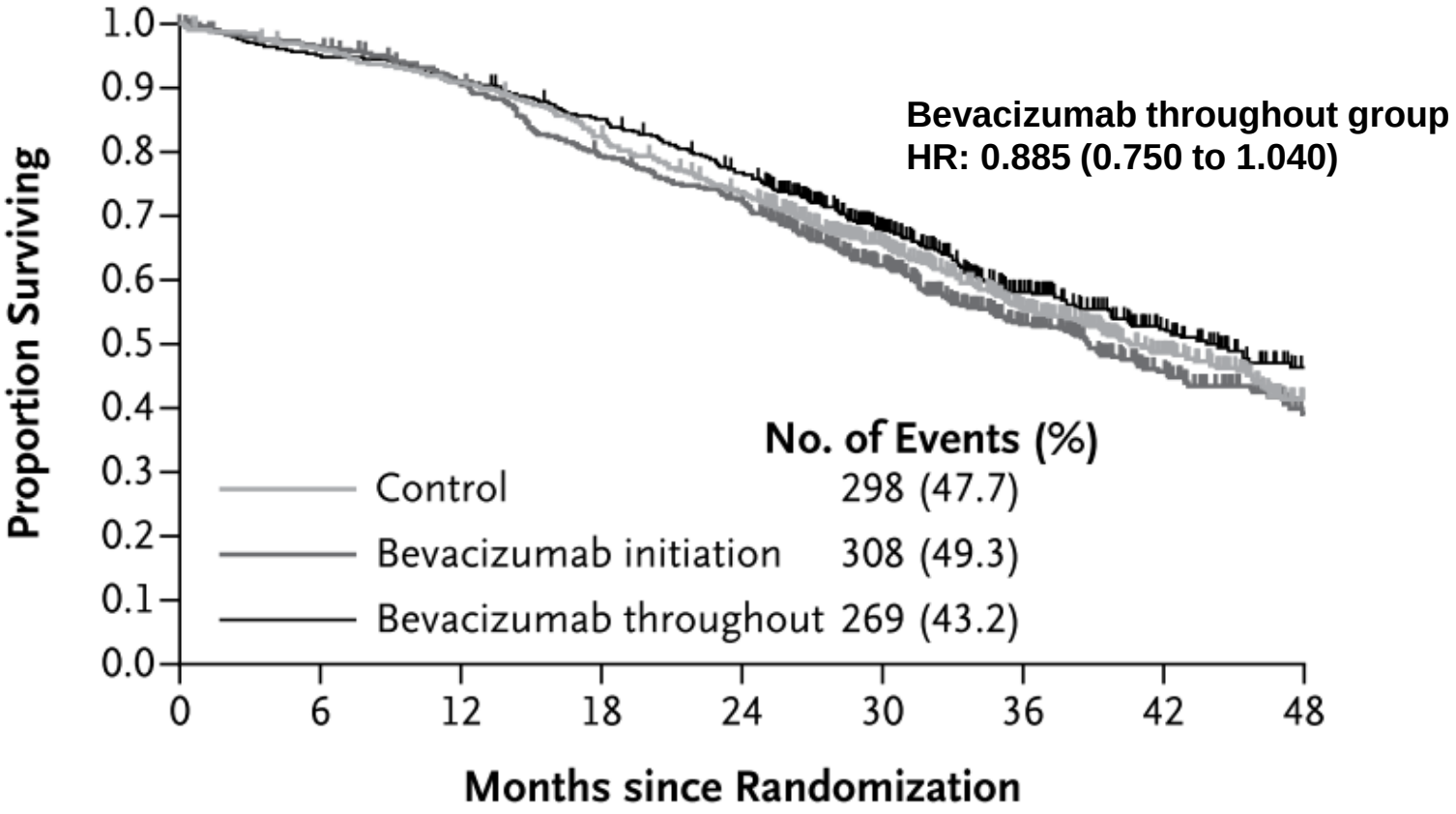
HR (Bev throughout vs Control)
0.77; 95% CI, 0.68 to 0.87

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 et al N Engl J Med (2011) 365:2473-83

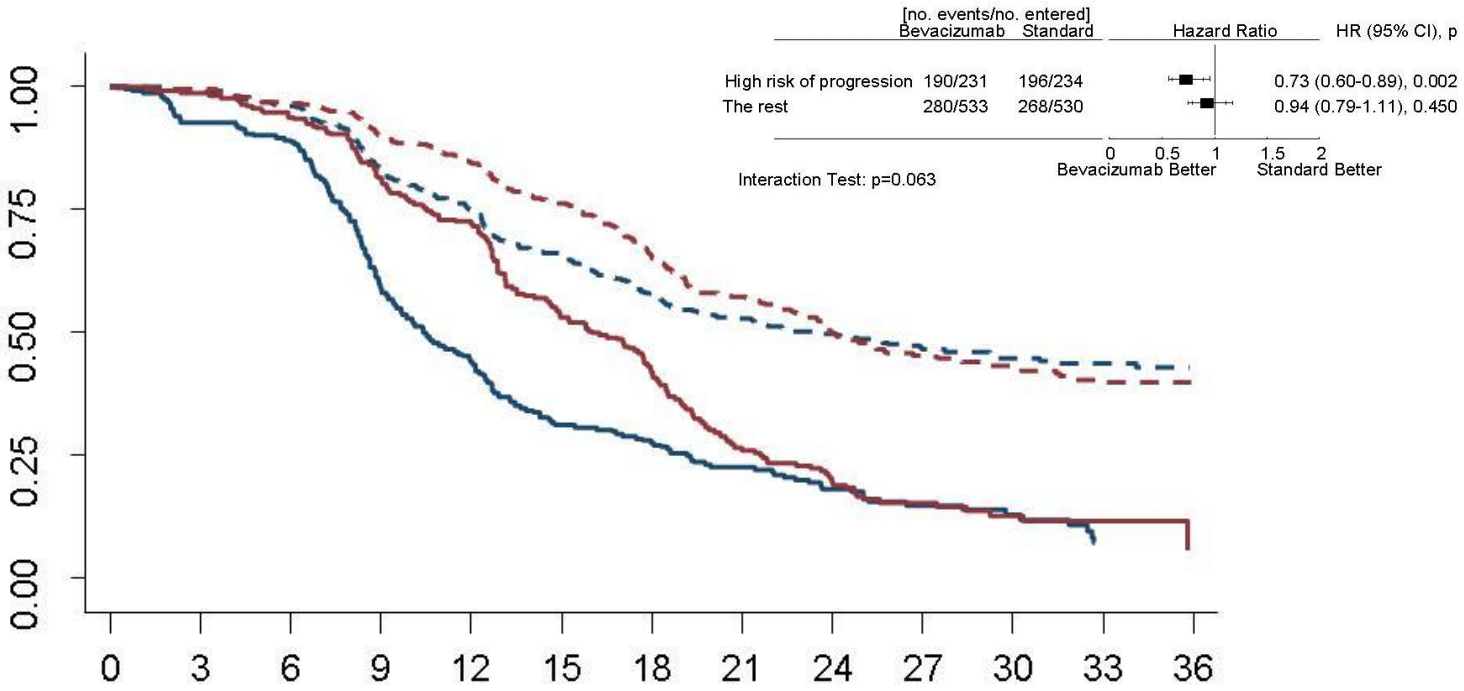
GOG0218: Updated OS



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 et al N Engl J Med (2011) 365:2473-83

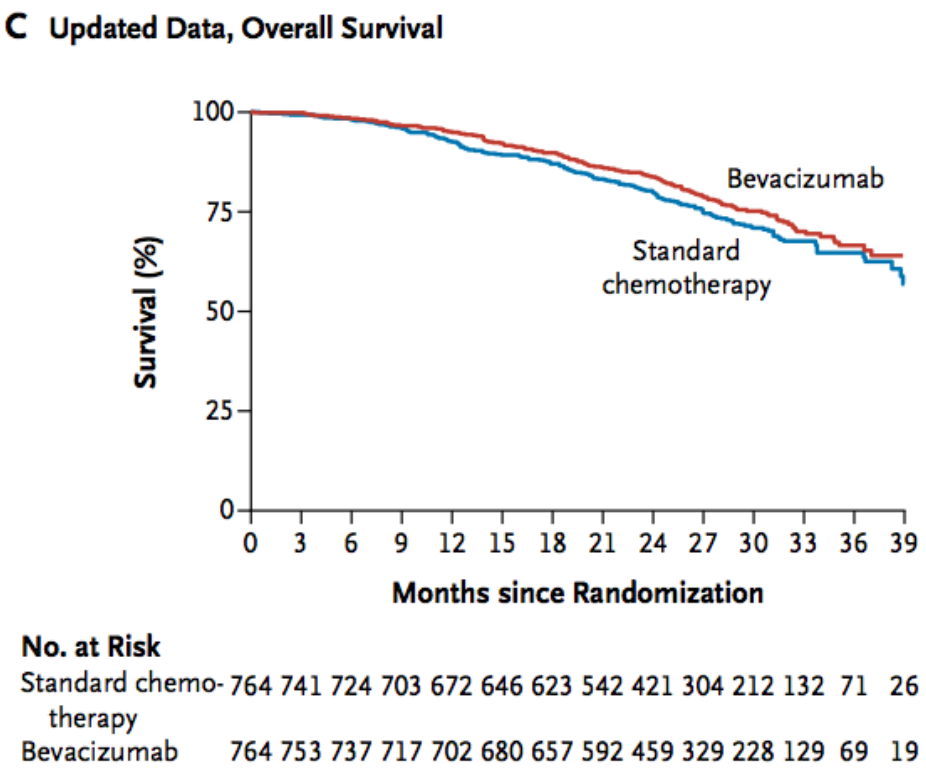
ICON7: Updated progression-free survival by risk groups

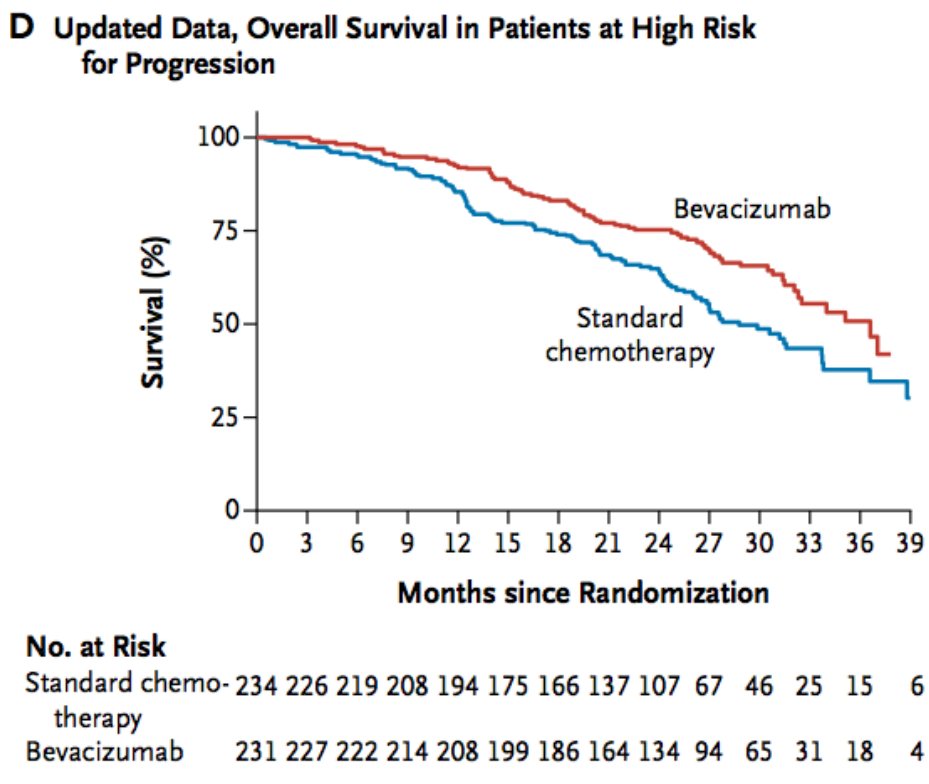


High-risk of progression							
Standard	234	205	100	63	30	13	5
Bevacizumab	231	213	163	94	35	13	1
The rest							
Standard	530	488	374	287	191	101	34
Bevacizumab	533	503	436	336	194	94	26

Perren et al N Engl J Med (2011) 365: 2484-96

ICON7: updated (interim) survival





Perren et al N Engl J Med (2011) 365: 2484-96

Questions

- Will survival benefit be confirmed in the 'high risk' subset of ICON 7
- How will this affect use?

  - bevacizumab not licensed in the USA for ovarian cancer
- What dose? 7.5 or 15 mg/kg
- For how long?
  - Boost study exploring extended use of maintenance bevacizumab
- Which group of patients?
  - First line; 'platinum sensitive' recurrence; 'platinum-resistant?
- Who?
  - No predictive markers to select patients. Can healthcare providers accept an expensive treatment that is potentially given to all with no prior knowledge?

Anti-angiogenic agents

- VEGFR Tyrosine Kinase Inhibitors - small molecules
  - Oral
  - Not pure VEGFR antagonists
  - Different spectrum of s/e: hypertension; diarrhoea, mucositis

TKI	Targets
Pazopanib	VEGFR; PDGFR; c-kit; FGFR
BIBF 1120 (nintedanib)	VEGFR; PDGFR; FGFR

- Angiopoietin Antagonist
  - Angiopoietin 1 and 2 neutralising peptibody
  - Blocks interaction with tie-2 receptor
  - AMG 386 (trebananib)- intravenous weekly

AGO-OVAR 12 (LUME-Ovar 1): a first-line Phase III study

BIBF 1120 (Nintedanib) in combination with carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer

Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer
N=1300

2:1 randomization

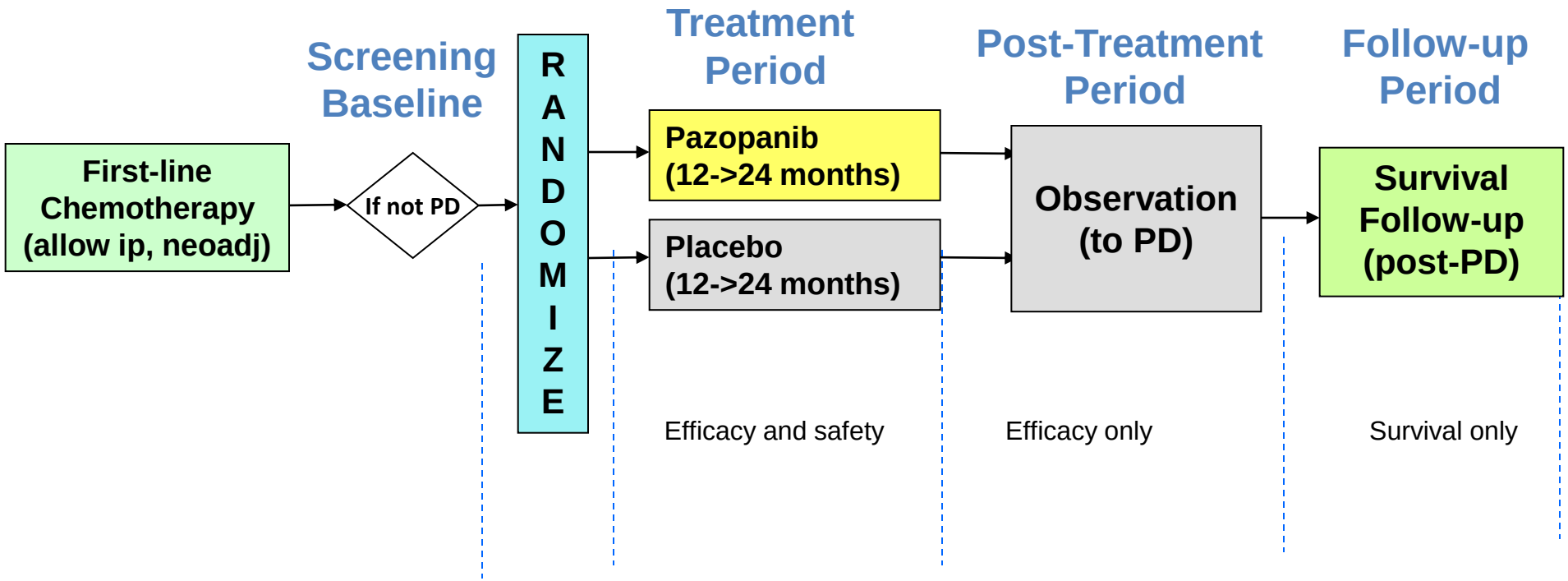
BIBF 1120 200 mg p.o. BID
PLUS
Paclitaxel 175 mg/m^2 + carboplatin AUC 5/6
Every 21 days for 6 courses

Placebo p.o. BID
PLUS
Paclitaxel 175 mg/m^2 + carboplatin AUC 5/6
Every 21 days for 6 courses

BIBF 1120/placebo monotherapy continued in patients who have not progressed until AEs, disease progression or for a maximum of 120 weeks after randomization

AGO-OVAR16/VEG110655: Study Design

- Phase III randomized, two-arm, placebo controlled, double-blind, multicentre, intergroup study
- N= 900 subjects (1:1). Pazopanib administered at 800 mg daily for 52 weeks (12 months) – extended to 104 weeks (24 months).



ENGOT-ov2/BGOG-ov7/GOG3001/Trinova-3
Trebananib (AMG 386) in first line ovarian cancer

Stratification: -
AUC 5 or 6
- PDS or IDS
- Resid Tumour,
- IIIa-B vs IIIc-IV

Ovarian, tubal or peritoneal cancer
FIGO stage III-IV (n = 2000)

Randomisation 2:1

Accrual 152/2000

6 courses
Paclitaxel 175 mg/m² q3w
Carboplatin AUC 5 or 6 q3w
Trebananib 15mg/kg qw

6 courses
Paclitaxel 175 mg/m² q3w
Carboplatin AUC 5 or 6 q3w
Placebo qw

Interval debulking allowed after 3 cycles

↓

Maintenance Trebananib qw 18 months

Interval debulking allowed after 3 cycles

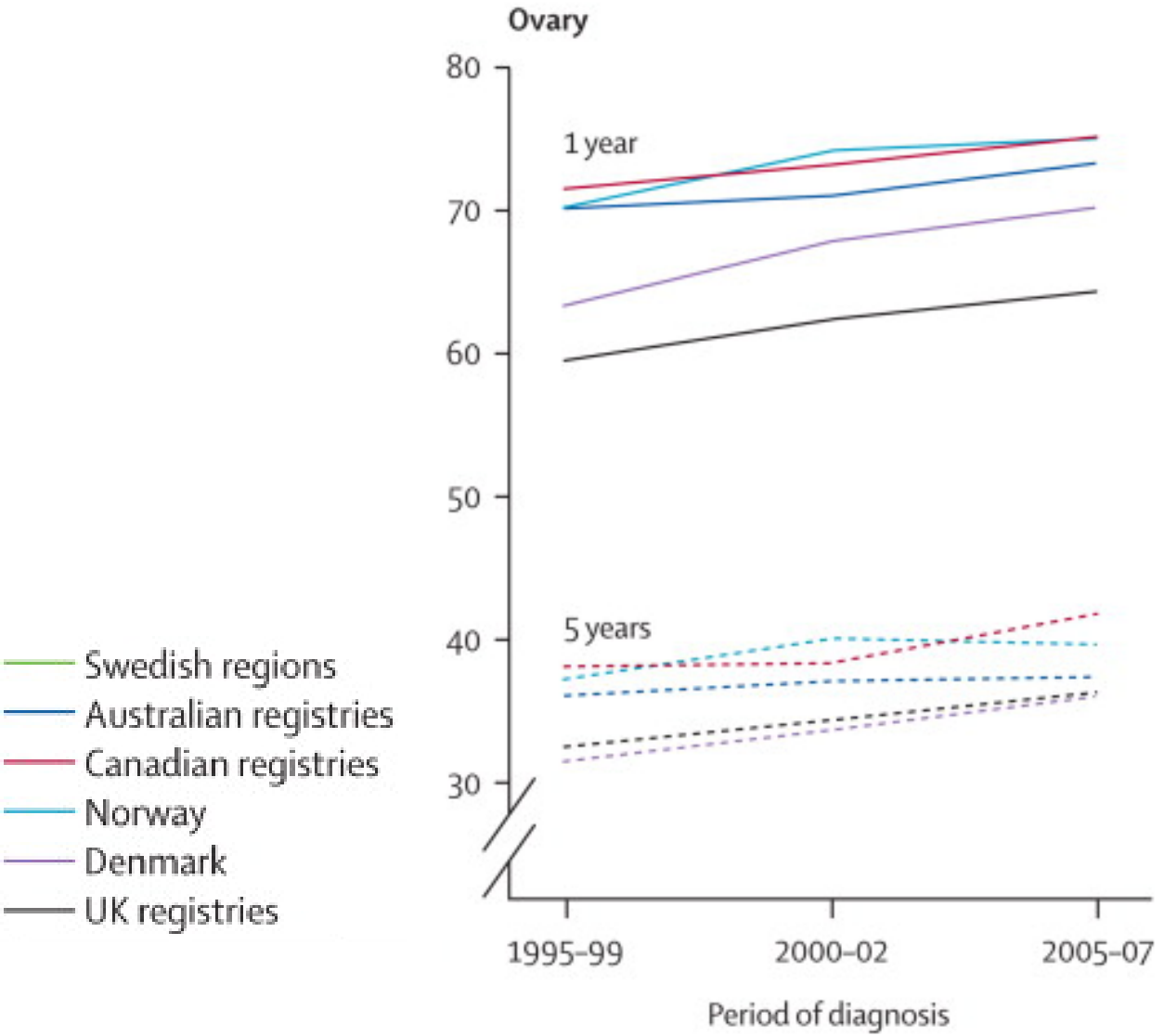
↓

Maintenance Placebo qw 18 months

Primary Endpoint: Progression-free survival

Secondary endpoints: Overall Survival, Quality of Life, Complications,PK

International Benchmarking Project



Coleman et al Lancet 2011

Conclusions

- Survival of women with advanced ovarian cancer is increasing
- Management of recurrent disease contributes significantly towards this
- Areas contributing to improvements in outcome from first-line therapy:

  Earlier diagnosis
  Specialised centres- surgery and chemotherapy
  Improvements first line treatment

- Over last 15 years little improvement in PFS from first line therapy with different combinations of cytotoxic therapy
- Early indications are that novel molecular targeted therapies and/or different dose scheduling may improve current outcome figures