Evolution of systemic therapy of advanced ovarian cancer:

A historical review

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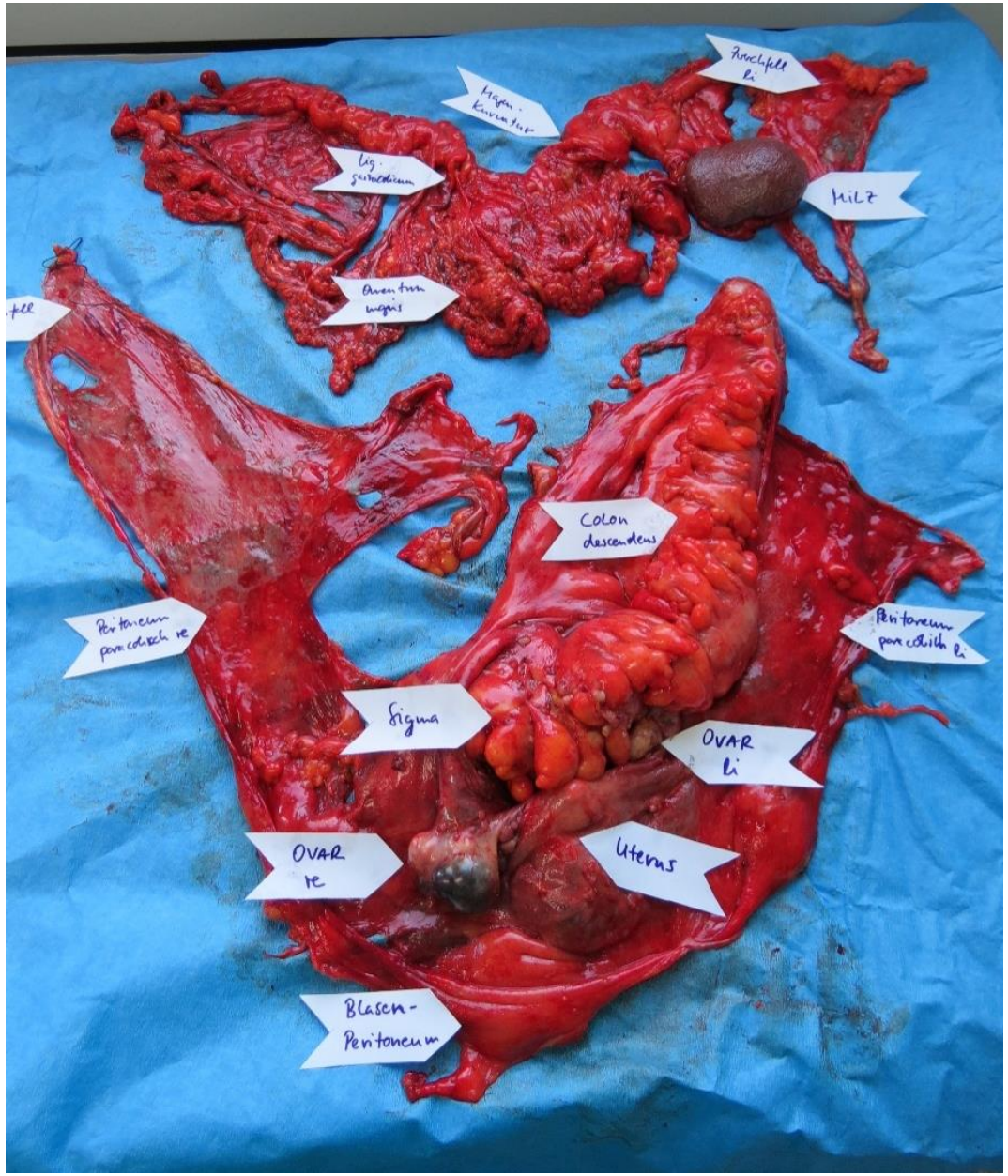
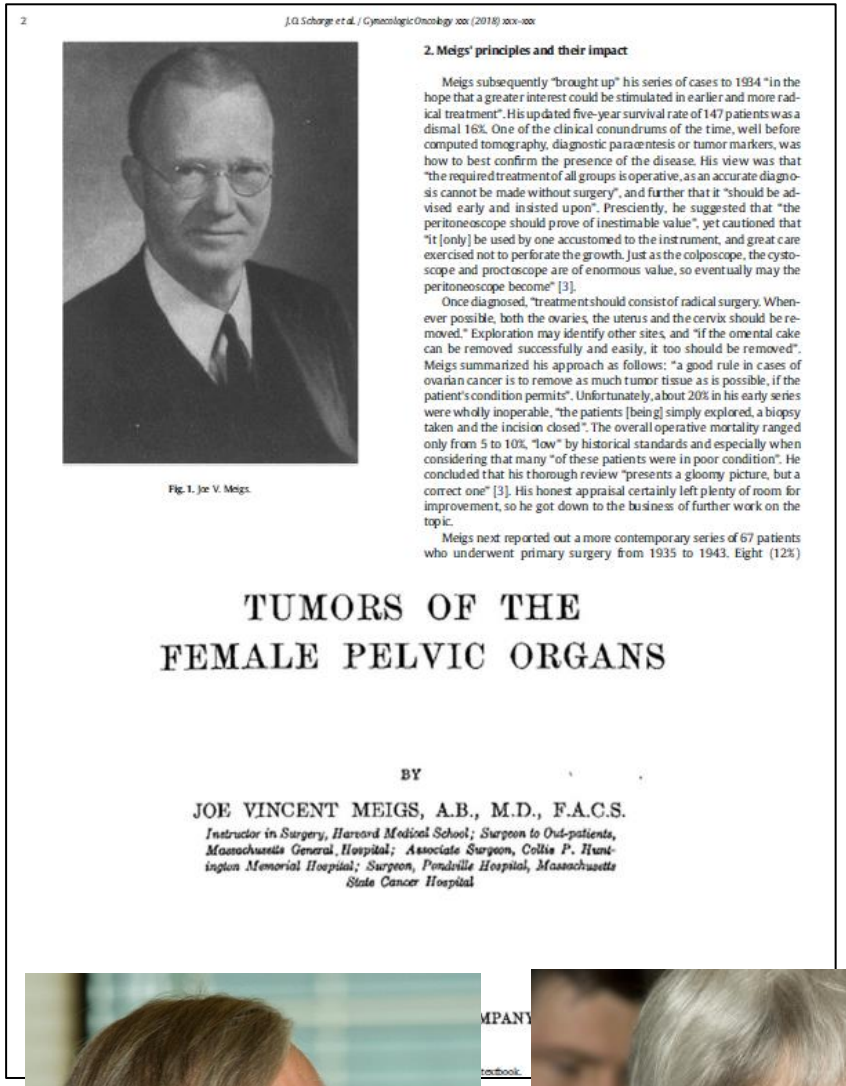
AGO Study Group



Disclosure Andreas du Bois

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*
AMGEN	x	x
Astra Zeneca	x	x
BIOCAD	x	x
Clovis	x	x
Esai		x
Genmab/Seattle Genetics		x
GSK/Tesaro	x	x
MSD	x	x
Roche	x	x
Pfizer		x
Zodiac	x	



2 J.O. Schorge et al. / Gynecologic Oncology xxx (2018) xxx–xxx

Fig. 1. Joe V. Meigs.

2. Meigs' principles and their impact

Meigs subsequently "brought up" his series of cases to 1934 "in the hope that a greater interest could be stimulated in earlier and more radical treatment". His updated five-year survival rate of 147 patients was a dismal 16%. One of the clinical conundrums of the time, well before computed tomography, diagnostic paracentesis or tumor markers, was how to best confirm the presence of the disease. His view was that "the required treatment of all groups is operative, as an accurate diagnosis cannot be made without surgery", and further that it "should be advised early and insisted upon". Presciently, he suggested that "the peritoneoscope should prove of inestimable value", yet cautioned that "it [only] be used by one accustomed to the instrument, and great care exercised not to perforate the growth. Just as the colposcope, the cystoscope and proctoscope are of enormous value, so eventually may the peritoneoscope become" [3].

Once diagnosed, "treatment should consist of radical surgery. Whenever possible, both the ovaries, the uterus and the cervix should be removed." Exploration may identify other sites, and "if the omental cake can be removed successfully and easily, it too should be removed". Meigs summarized his approach as follows: "a good rule in cases of ovarian cancer is to remove as much tumor tissue as is possible, if the patient's condition permits". Unfortunately, about 20% in his early series were wholly inoperable, "the patients [being] simply explored, a biopsy taken and the incision closed". The overall operative mortality ranged only from 5 to 10%, "low" by historical standards and especially when considering that many "of these patients were in poor condition". He concluded that his thorough review "presents a gloomy picture, but a correct one" [3]. His honest appraisal certainly left plenty of room for improvement, so he got down to the business of further work on the topic.

Meigs next reported out a more contemporary series of 67 patients who underwent primary surgery from 1935 to 1943. Eight (12%)

TUMORS OF THE
FEMALE PELVIC ORGANS

BY

JOE VINCENT MEIGS, A.B., M.D., F.A.C.S.

Instructor in Surgery, Harvard Medical School; Surgeon to Out-patients, Massachusetts General Hospital; Associate Surgeon, Collis P. Huntington Memorial Hospital; Surgeon, Pondville Hospital, Massachusetts State Cancer Hospital

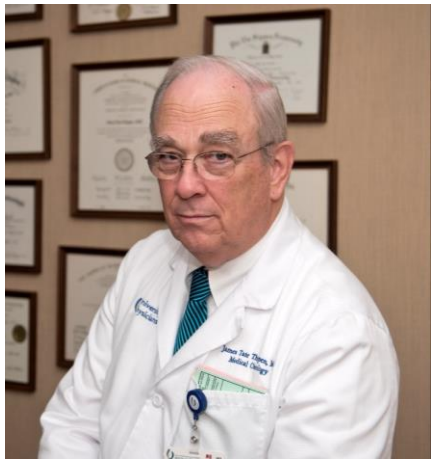
The dinosaurs

1934 Meigs reported a benefit of tumor resection before initiation of **radiotherapy**

1950s alcylating agents like melphalan, cyclophosphamide

1970s first reports of **Cisplatin** in ovarian cancer
- 40% response, no effective antiemetics
- **Cisplatin combinations became standard** (eg. PC, PAC)
- mainly GOG: RC Young et al, T Thigpen et al. F Muggia et al.

1980s first reports on **Carboplatin** in ovarian cancer
- 1982 Hilary Calvert et al., 1983 Eve Wiltshaw et al.



Introduction of Paclitaxel

This coop later led to initiation of GCIG

	GOG 111 (McGuire NEJM 1996)		Intergroup (Piccart JNCI 2000)	
	PC (75/750)	PT (75/135 24 h)	PT (75/175 3 h)	PC (75/750)
Patientinnen	410		688	
CR (%) *	31	51	50	36
CR / PR (%) *	60	73	77	66
PFI (months) *	13	18	16	11
OS (months) *	24	38	35	25
5-JÜR (%)*	16	27		

* p<0,05 PFI: median progression-free Intervall OS: median overall survival

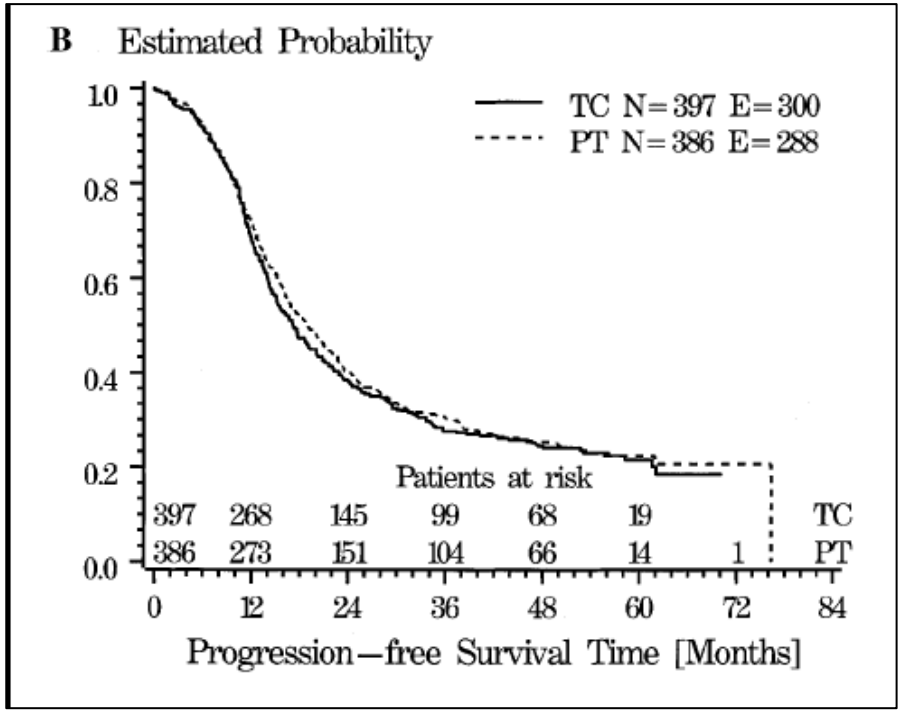
Carboplatin/Paclitaxel: New standard of care – same activity but less toxicity

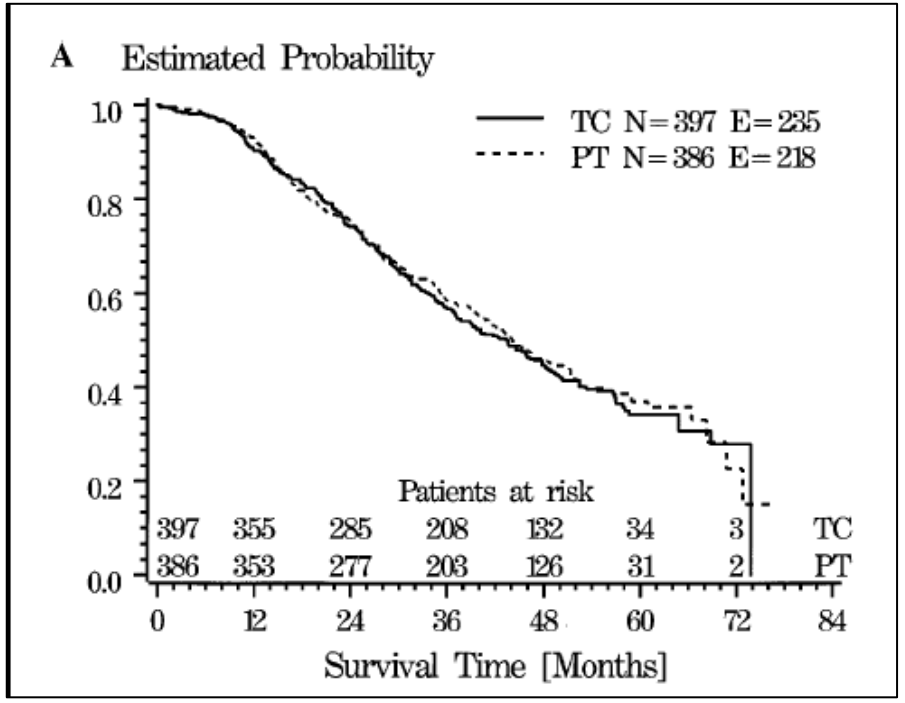
A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer

Andreas du Bois, Hans-Joachim Lück, Werner Meier, Hans-Peter Adams, Volker Möbus, Serban Costa, Thomas Bauknecht, Barbara Richter, Matthias Warm, Willibald Schröder, Sigrid Olbricht, Ulrike Nitz, Christian Jackisch, Günther Emons, Uwe Wagner, Walther Kuhn, Jacobus Pfisterer

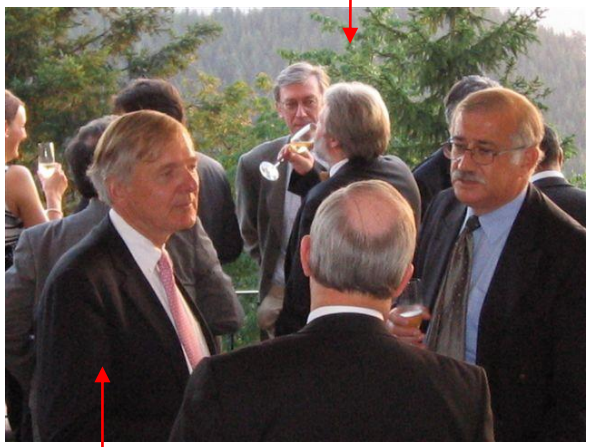
For the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group

[J Natl Cancer Inst 2003;95:1320–30]





3rd OCCC 2004
…once upon a time in the black forrest



+ confirmatory trial GOG 158, but Carbo AUC 7,5 and only in „optimal FIGO III patients“: B. Ozols et al., JCO 2003

3rd International Ovarian Cancer Consensus Conference

3rd - 5th September 2004, Black Forest, Germany

4-A4:

Which regimen / kind of regimens can be regarded as standard comparator for future first-line trials?

- Within a given trial the chemotherapy regimen should be standardised and consistent with respect to drugs, dose, and schedule
- **The recommended standard comparator for trials of medical treatment in advanced ovarian cancer (FIGO IIB-IV) is carboplatin-paclitaxel**
- The recommended regimen is carboplatin with a dose of AUC 5 - 7.5 and paclitaxel 175 mg/m²/ 3h given every three weeks for 6 courses
- The recommended standard in early stage (FIGO I-IIA) ovarian cancer patients in whom adjuvant chemotherapy is indicated should contain at least carboplatin AUC 5 - 7.5

Level of Acceptance: 13 / 13

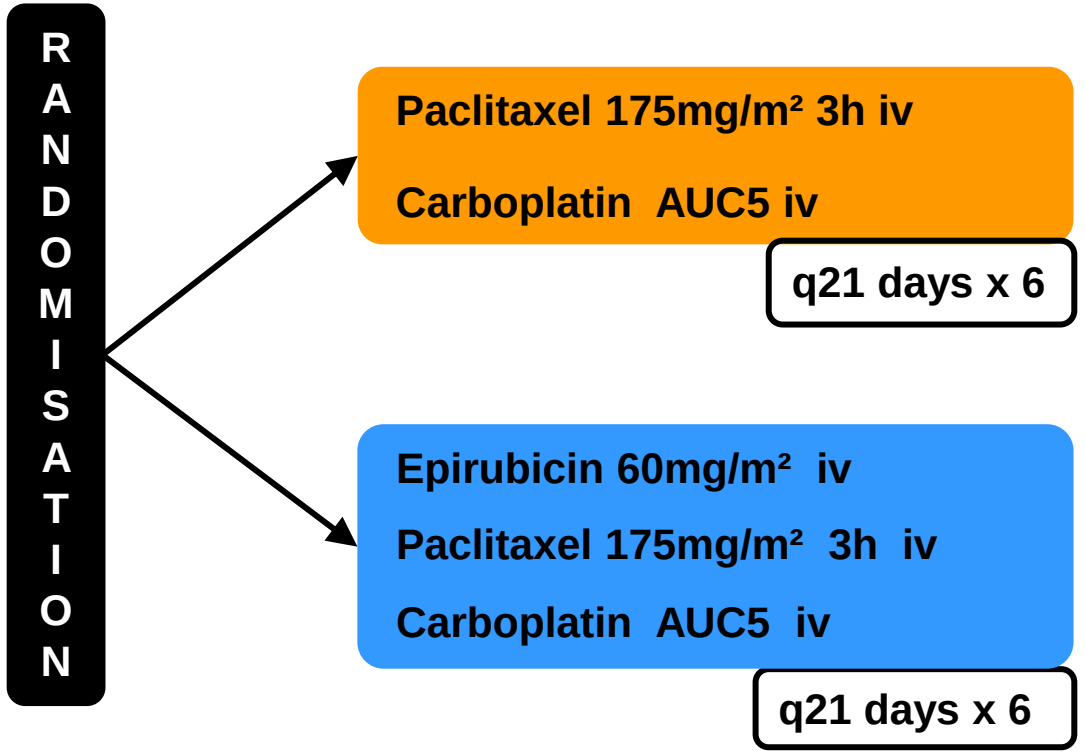
du Bois A et al. for the Gynecological Cancer Intergroup (GCIG) and its member organizations. 2004 Consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004), Ann Oncol, 16 (suppl 8): viii7-viii12, 2005

Is more better I (eg. more cytostatic drugs) ?

AGO-OVAR 5: prospective, randomised trial adding 3rd drug

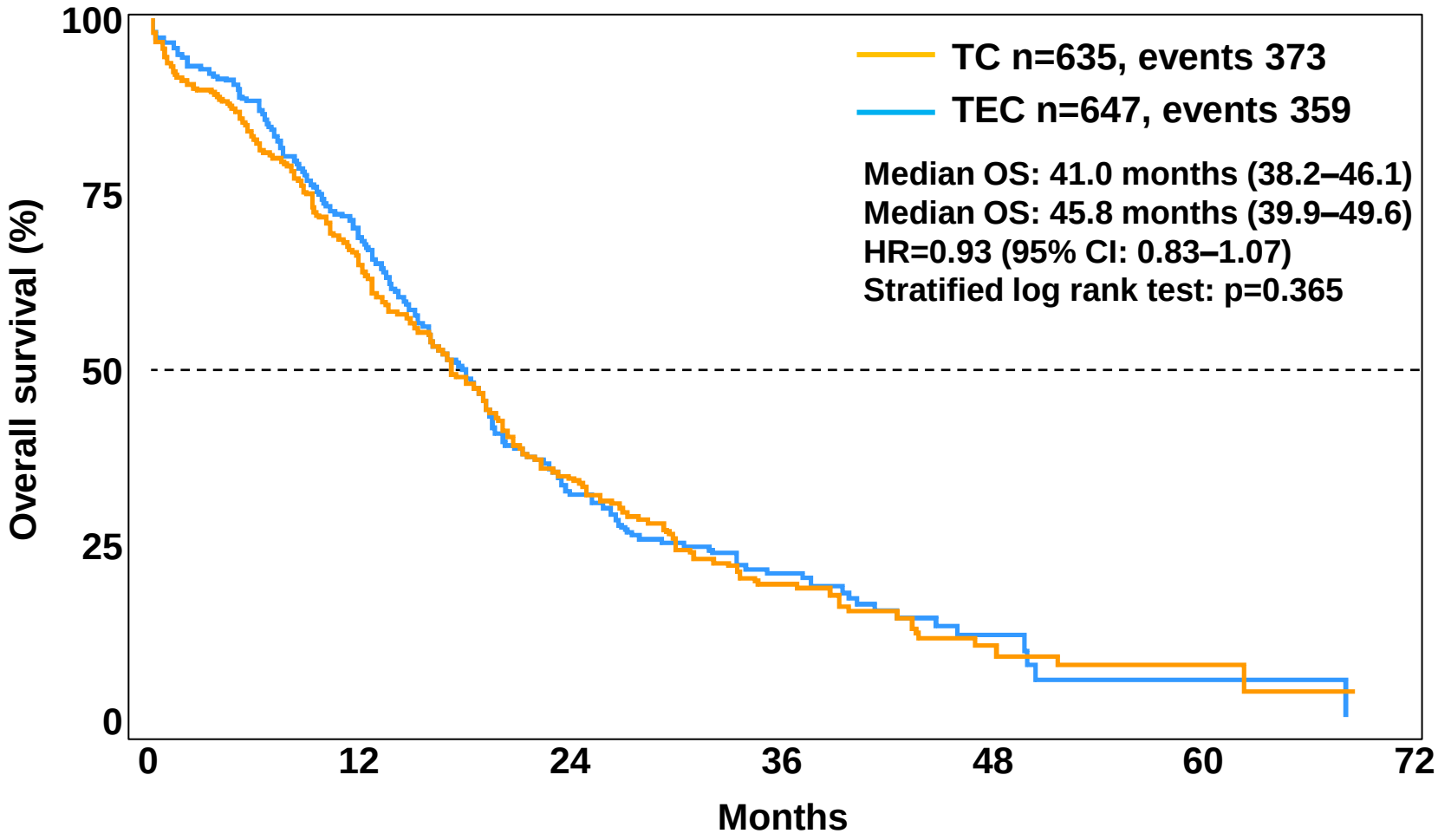
Stratification:

- FIGO stage IIB–III + tumour ≤1cm
- FIGO stage IV or tumour >1 cm
- centre



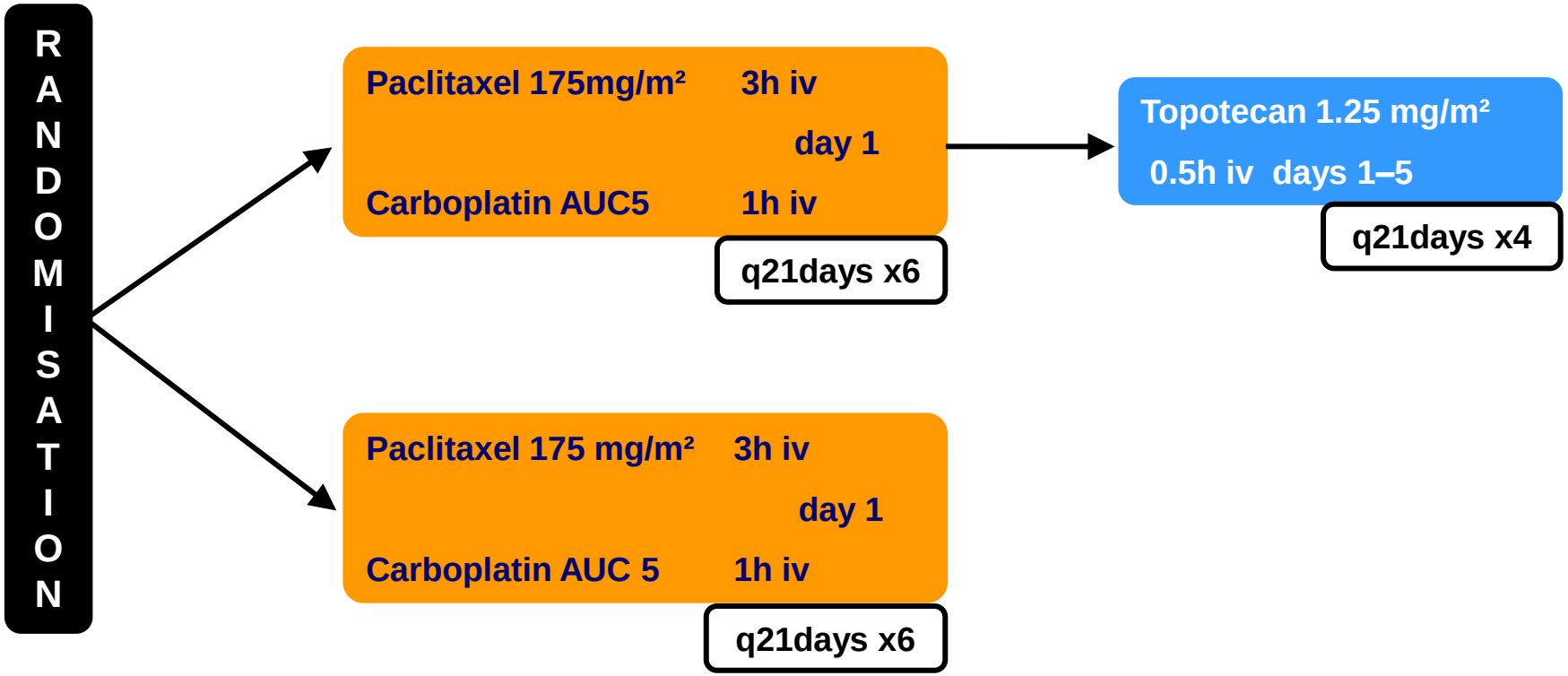
du Bois, et al. JCO 2006

GCIG trial of TEC vs TC (AGO-OVAR 5): overall survival by arm



du Bois, et al. JCO 2006

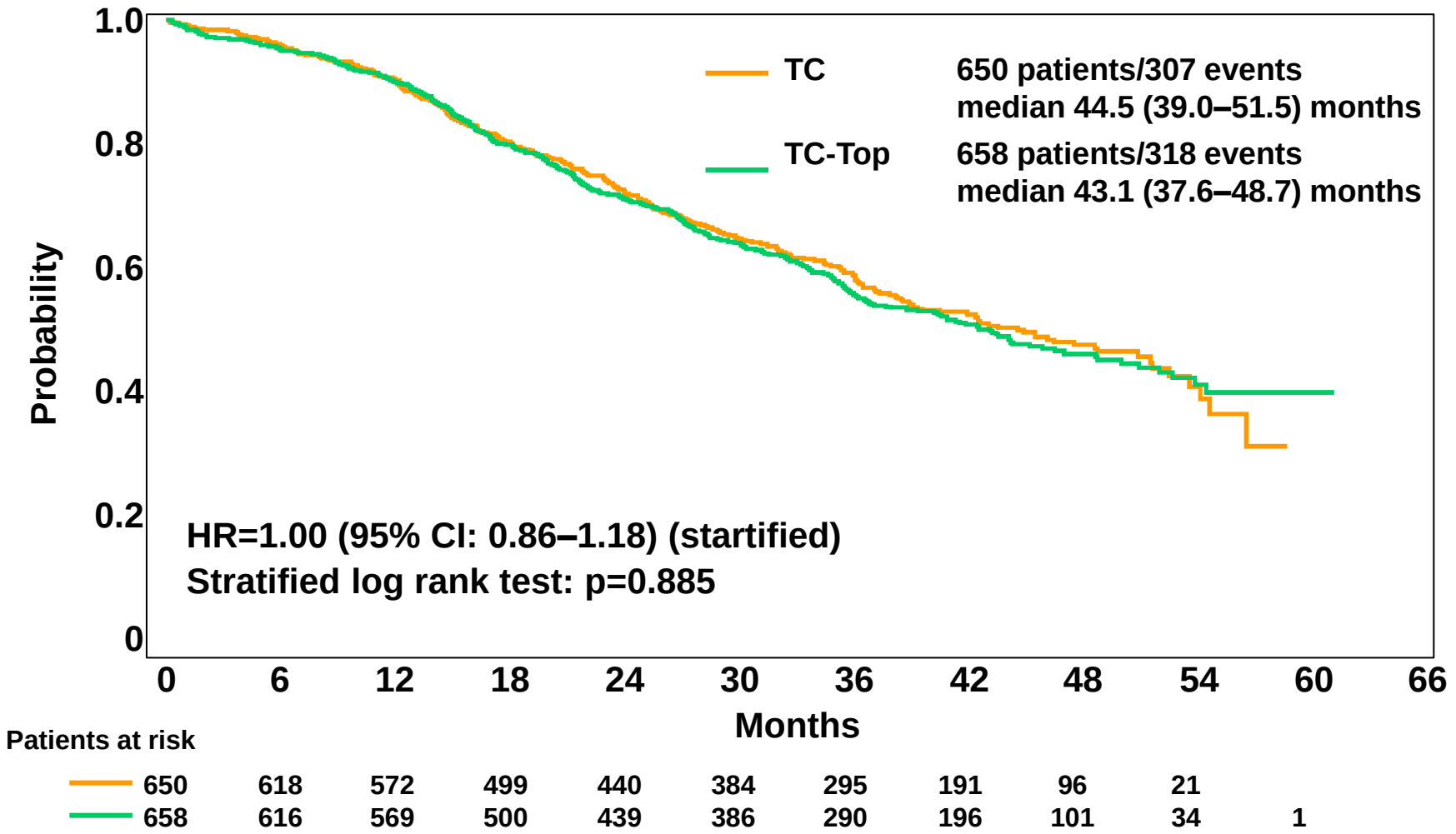
TC vs TC-Top (AGO-OVAR 7) (AGO-OVAR & GINECO): study design



- Stratification
  - centre
  - FIGO stage IIB–IIIc + ≤1cm tumour (Stratum 1)
  - FIGO IV or >1cm tumour (Stratum 2)

Pfisterer, et al. JNCI 2006

TC vs TC-Top (AGO-OVAR 7): overall survival

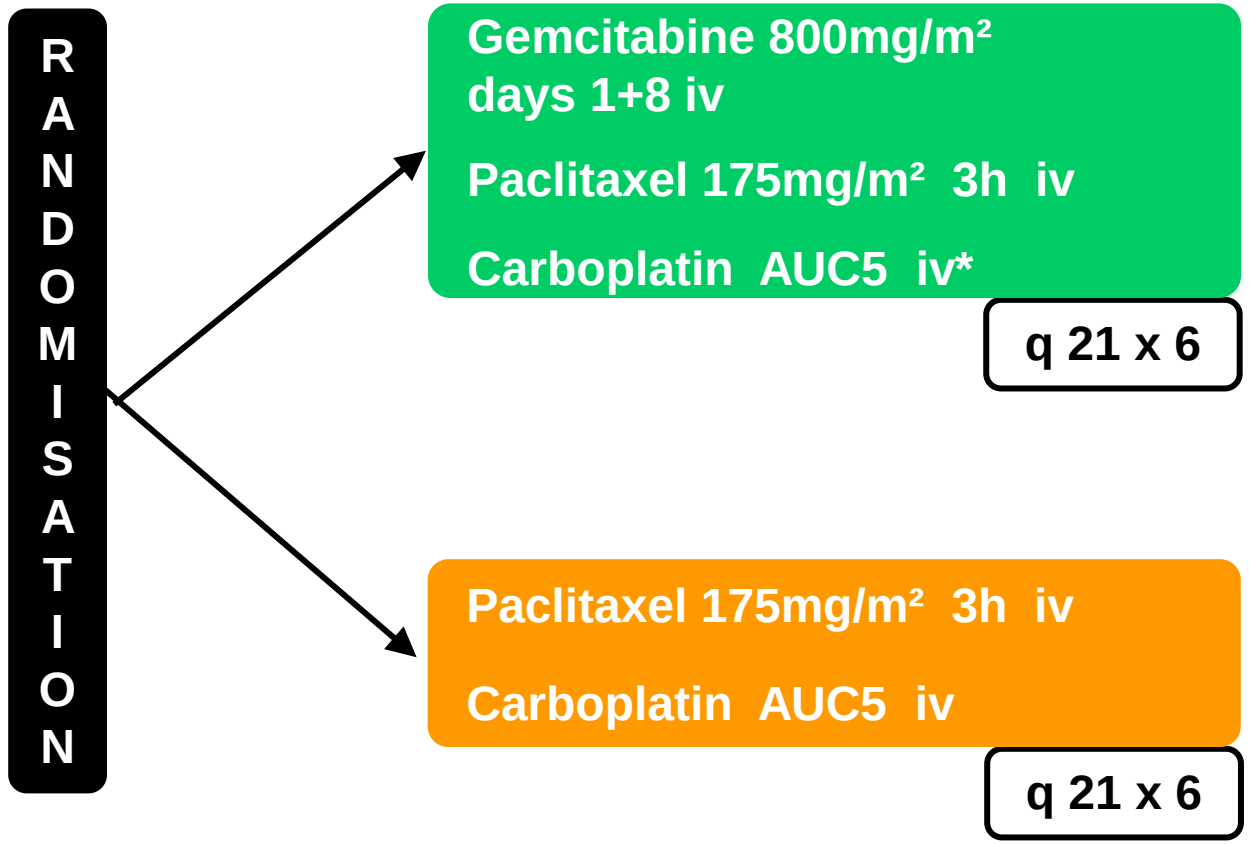


Pfisterer, et al. JNCI 2006

TC vs TCG (AGO-OVAR 9; AGO-OVAR/GINECO/NSGO: study design

Stratification:

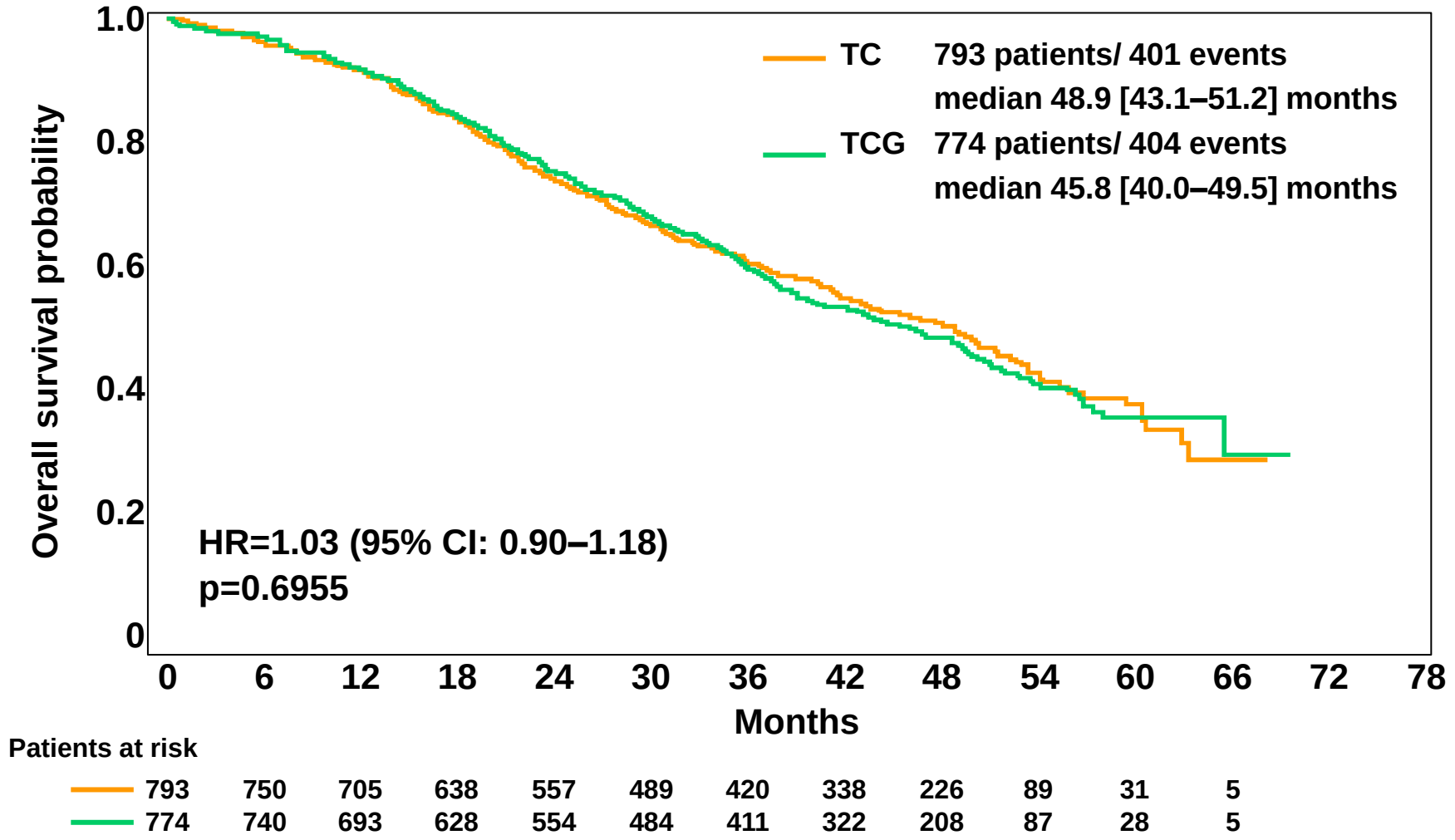
- FIGO stage
- post-operative residual tumour
- surgery
  - interval surgery y/n
- centre



***Evaluated in preceding phase II study protocol AGO-OVAR 8**

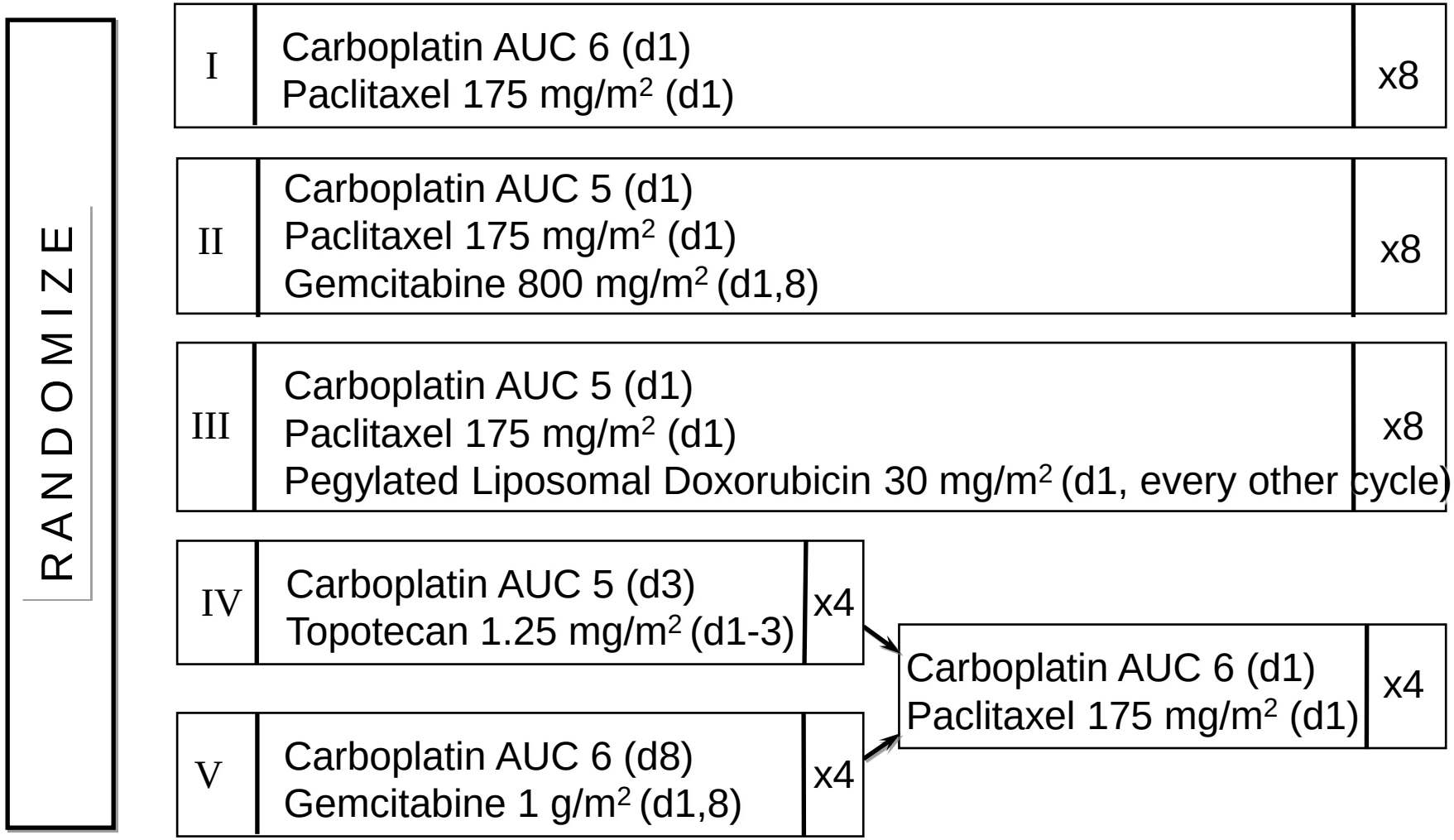
du Bois, et al. JCO 2010

TC vs TCG (AGO-OVAR 9): overall survival (FIGO IIB-IV)



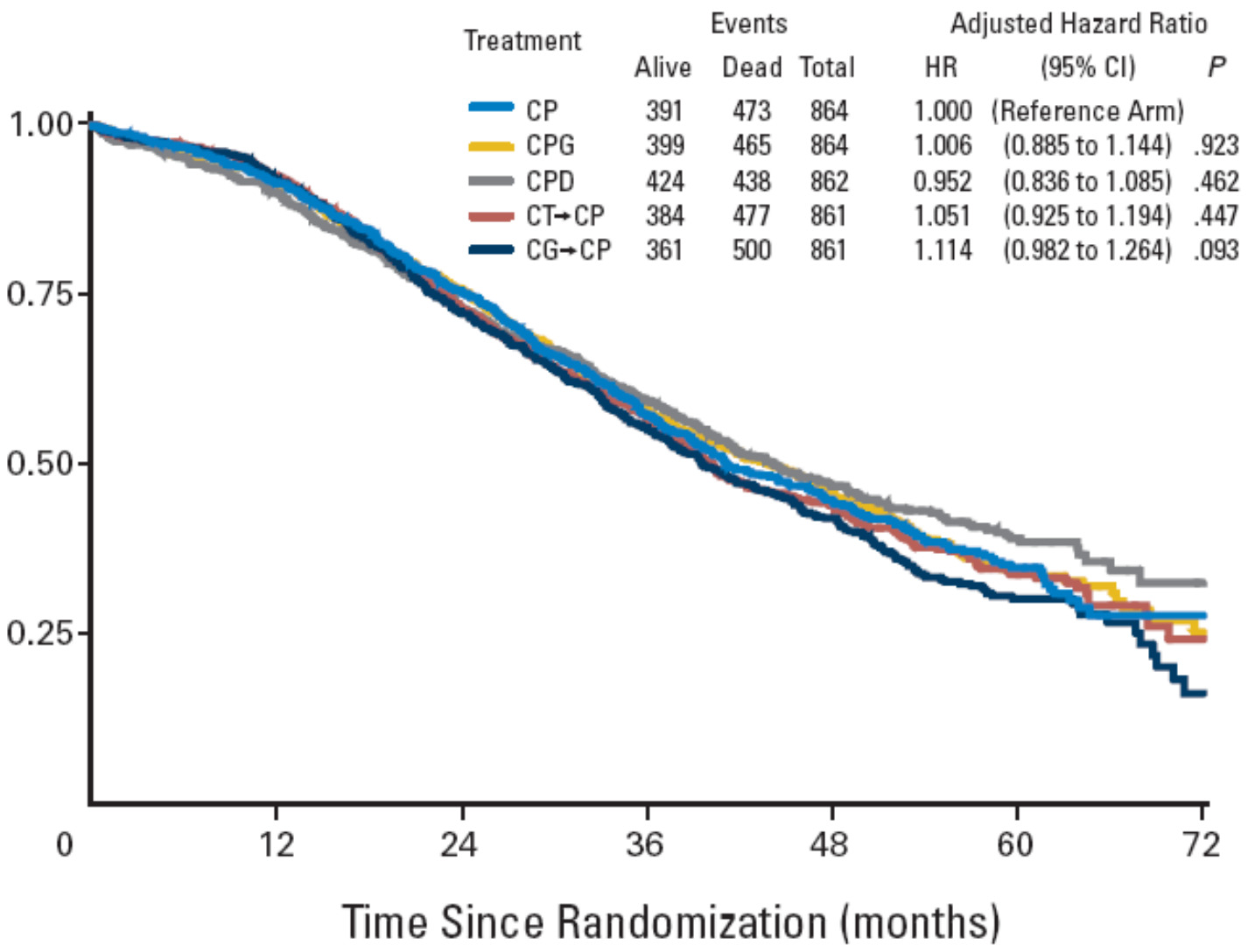
du Bois, et al. JCO 2010

GOG0182-ICON5-ANZGOG



Bookman M et al: J Clin Oncol 2009

GOG0182-ICON5-ANZGOG: overall survival



Bookman MA, et al. *J Clin Oncol* 27:1419-25, 2009

International Phase 3 experience with TC based triple drug regimens or TC modifications:

	TC	TCG	C-PLD	TC + Top	CG	CDoc	TEC	Total	outcome
GOG0182-ICON5	864	864	862	861	861			4312	**Negative**
SCOTROC	538					539		1077	**Negative**
AGO-GINECO	635						647	1282	**Negative**
NSGO-EORTC-NCIC-GEICO	444						443	887	**Negative**
Bolis, et al	170			156				326	**Negative**
AGO-GINECO-NSGO	882	860						1742	**Negative**
AGO-GINECO	650			658				1308	**Negative**
NCIC-EORTC-GEICO OV16	410			409				819	**Negative**
MITO-2	410		410					820	**Negative**
Regimen Total:	5003	**1724**	**1272**	**2084**	**861**	**539**	**1090**	**12,573**	**patients**

Triple drug regimens

Is more better II (eg. high-dose chemotherapy) ?

VOLUME 25 · NUMBER 27 · SEPTEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of High-Dose Sequential Chemotherapy With Peripheral Blood Stem Cell Support Compared With Standard Dose Chemotherapy for First-Line Treatment of Advanced Ovarian Cancer: Intergroup Trial of the AGO-Ovar/AIO and EBMT

Volker Möbus, Hannes Wandt, Norbert Frickhofen, Carmelo Bengala, Kim Champion, Rainer Kimmig, Helmut Ostermann, Axel Hinke, and Jonathan A. Ledermann

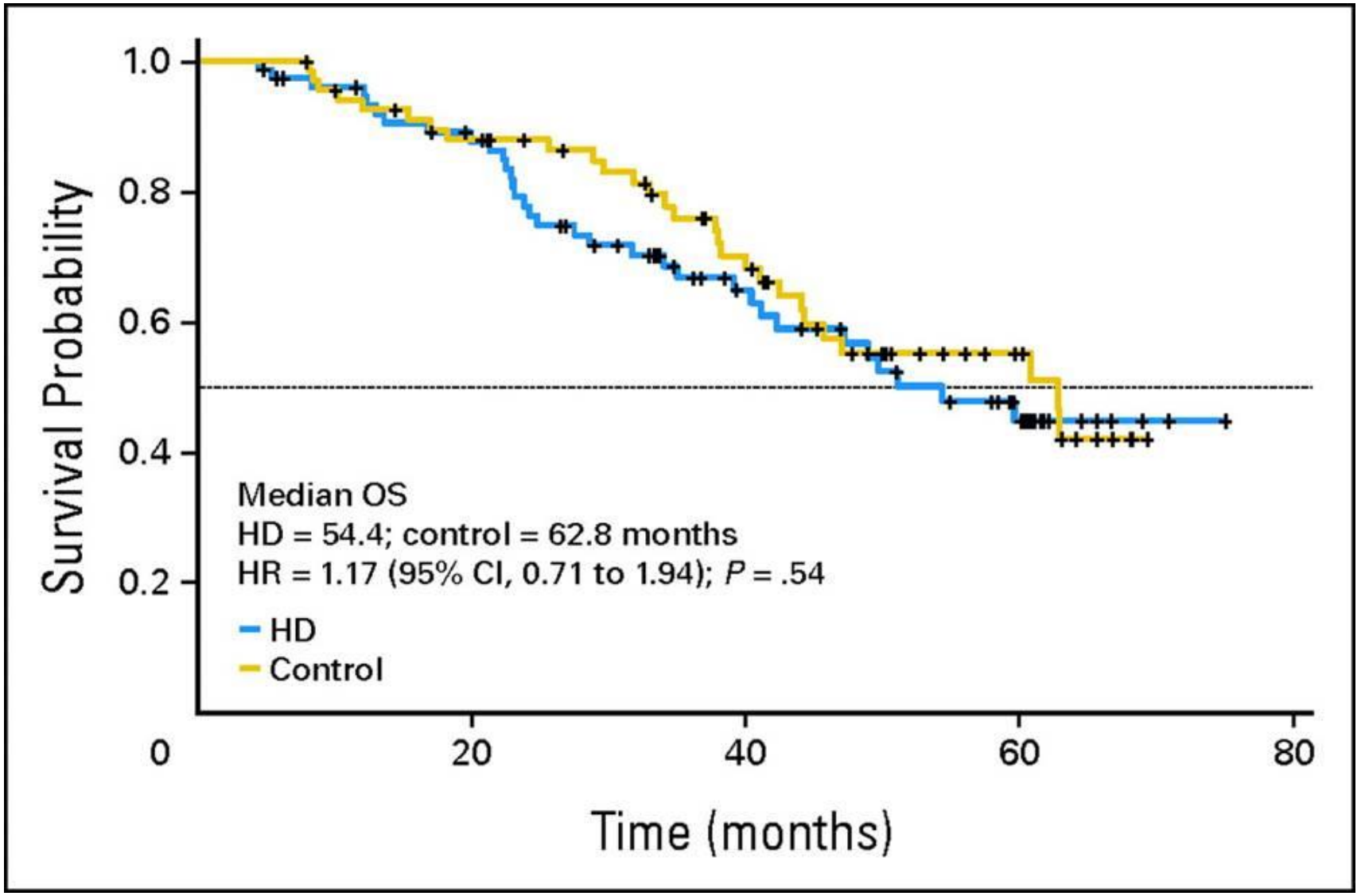
Epithelial ovarian cancer
Surgical debulking
FIGO IIB/III – IV
≤65 years

Surgery

Arm A
Multicycle high dose chemotherapy + PBSC Support

Arm B
Standard dose platin chemotherapy

AGO/AIO + EBMT Intergroup: Results



High-dose without any benefit in advanced ovarian cancer

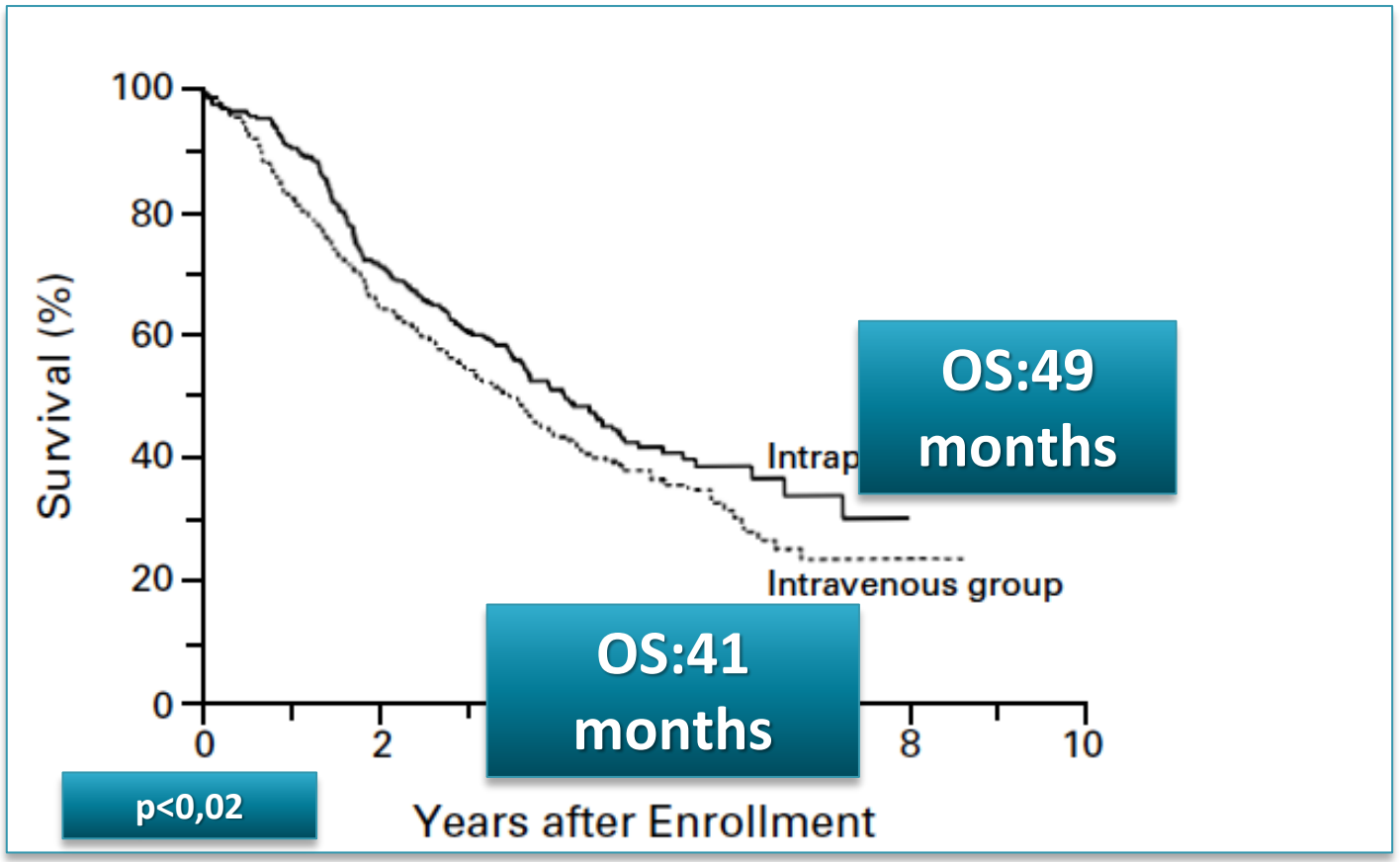
Möbus V, et al. *J Clin Oncol*. 2007;25(27):4187-4193.

Is more better III (eg. regional high dose chemotherapy) ?

The New England Journal of Medicine

INTRAPERITONEAL CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE VERSUS INTRAVENOUS CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE FOR STAGE III OVARIAN CANCER

DAVID S. ALBERTS, M.D., P.Y. LIU, PH.D., EDWARD V. HANNIGAN, M.D., ROBERT O'TOOLE, M.D., STEPHEN D. WILLIAMS, M.D., JAMES A. YOUNG, M.D., ERNEST W. FRANKLIN, M.D., DANIEL L. CLARKE-PEARSON, M.D., VINAY K. MALVIYA, M.D., BRENT DUBESHTER, M.D., MARK D. ADELSON, M.D., AND WILLIAM J. HOSKINS, M.D.



Year 1996, GOG # 104

Residual tumor <2 cm

N=564

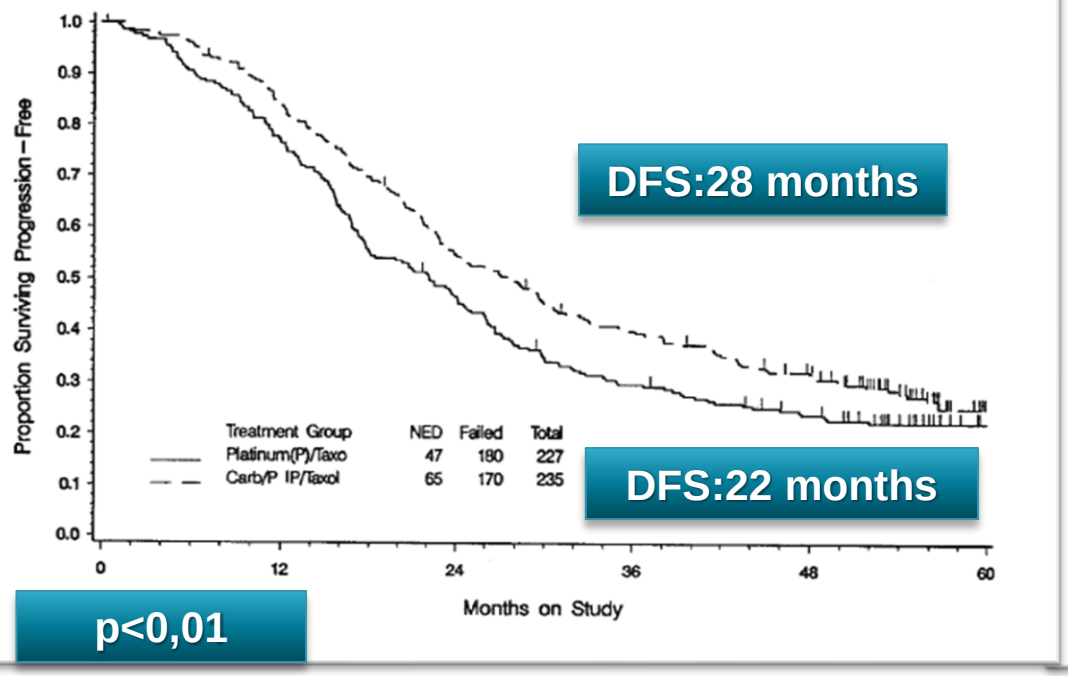
Critics:

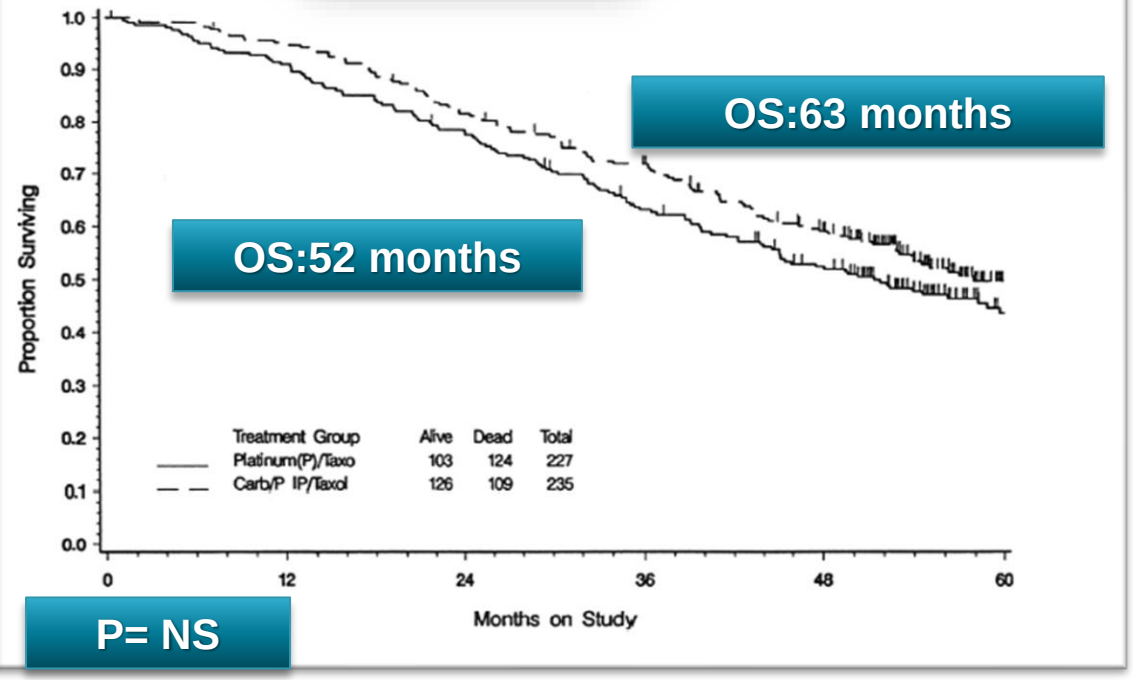
1. Outdated control arm
2. Was only rendered significant after ex-panding recruitment in one subgroup

Phase III Trial of Standard-Dose Intravenous Cisplatin Plus Paclitaxel Versus Moderately High-Dose Carboplatin Followed by Intravenous Paclitaxel and Intraperitoneal Cisplatin in Small-Volume Stage III Ovarian Carcinoma: An Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group

By Maurie Markman, Brian N. Bundy, David S. Alberts, Jeffrey M. Fowler, Daniel L. Clark-Pearson, Linda F. Carson, Scott Wadler, and Joshua Sickel

JOURNAL OF CLINICAL ONCOLOGY





Year 2001, GOG # 114, Residuals <1 cm, N=462;
« **it is not appropriate to suggest that this regime should be used in standard clinical practice** »

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*

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

GOG 172

FIGO III
tumour ≤1cm

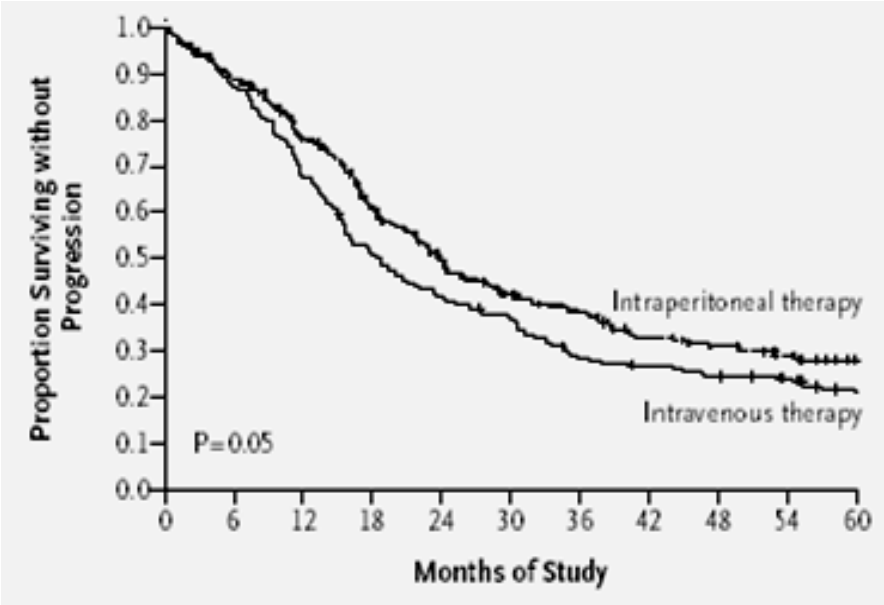
n=210

Cisplatin 75mg/m² iv q21 days x6
Paclitaxel 135mg/m² 24h iv|

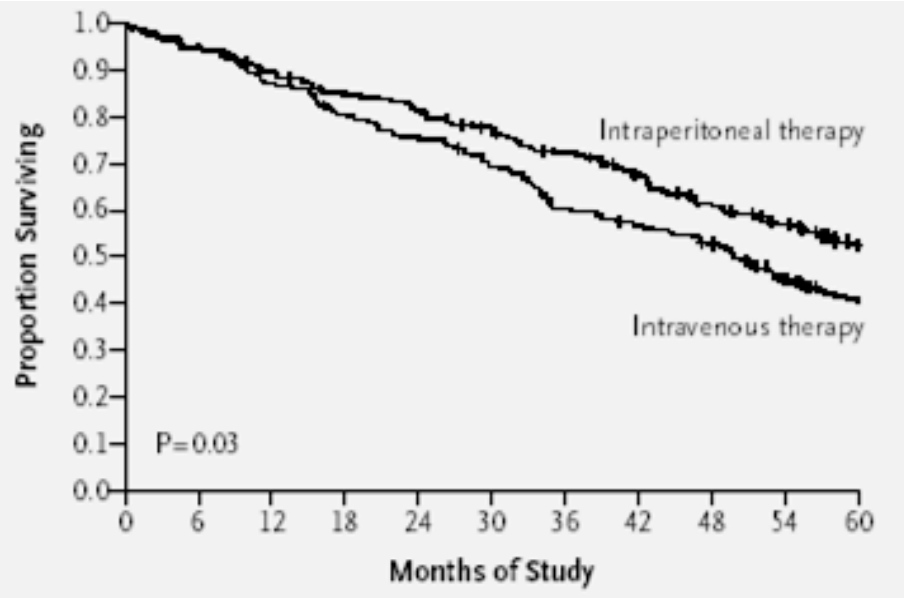
n=205

Paclitaxel 135mg/m² 24h iv day 1
Cisplatin 100mg/m² ip day 2
Paclitaxel 60mg/m² ip day 8 q21 days x6

GOG 172 results:



not significant, 18,3 vs. 23,8 months



significant, 49,7 vs. 65,6 months (median +15.9 mos.)

205 eligible patients

170 received 6 cycles of therapy

86 received all cycles of assigned intraperitoneal treatment **42%**

84 received intravenous treatment for some cycles

47 intravenous cisplatin and paclitaxel

37 intravenous carboplatin and paclitaxel

Number of intraperitoneal cycles completed (n = 205)

48%

No. of IP cycles	No. of patients	% of patients
0	16	8
I	38	19
2	30	15
3	14	7
4	10	5
5	11	5
Failed: <6 cycles	119	58
Success: 6 cycles	86	42
Total	205	100

Armstrong, et al. NEJM 2006

However, facts can be interpreted in different ways:

The US Perspective

1/5/06
NCI Clinical Announcement
Intraperitoneal chemotherapy for ovarian cancer

After primary surgery, women with optimally-debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with combined IB and IP administration of chemotherapy. Based on the most recent trials, strong consideration should be given to a regimen containing IP cisplatin (100 mg/m2) and a taxane, whether given by an IV only or IV plus IP.

National Cancer Institute (NCI) Clinical Announcement.
URL:https://ctep.cancer.gov/highlights/docs/clin_annc_010506.pdf

An European Perspective

….some years before Brexit

VOLUME 24 · NUMBER 28 · OCTOBER 1 2006
JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Intraperitoneal Chemotherapy in Ovarian Cancer Remains Experimental

Martin Gore, *Department of Medicine, Royal Marsden Hospital, London, United Kingdom*
Andreas du Bois, *Department of Gynecology and Gynecologic Oncology, Dr Horst-Schmidt-Klinik, Wiesbaden, Germany*
Ignace Vergote, *Division of Gynecologic Oncology, University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium*

Women should not be subjected to intraperitoneal chemotherapy outside the context of properly designed clinical trials. These trials must either assess IP therapy in comparison to standard treatment or address the issue of route of administration for equivalent doses and schedules of the same drugs, not a mosaic of these questions.

GOG 252:
a study designed to finally establish ip-therapy (or not)

Careful Strategic Planning

GOG Protocol 252:
Stage II/III Disease: Small Volume Residual

- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy

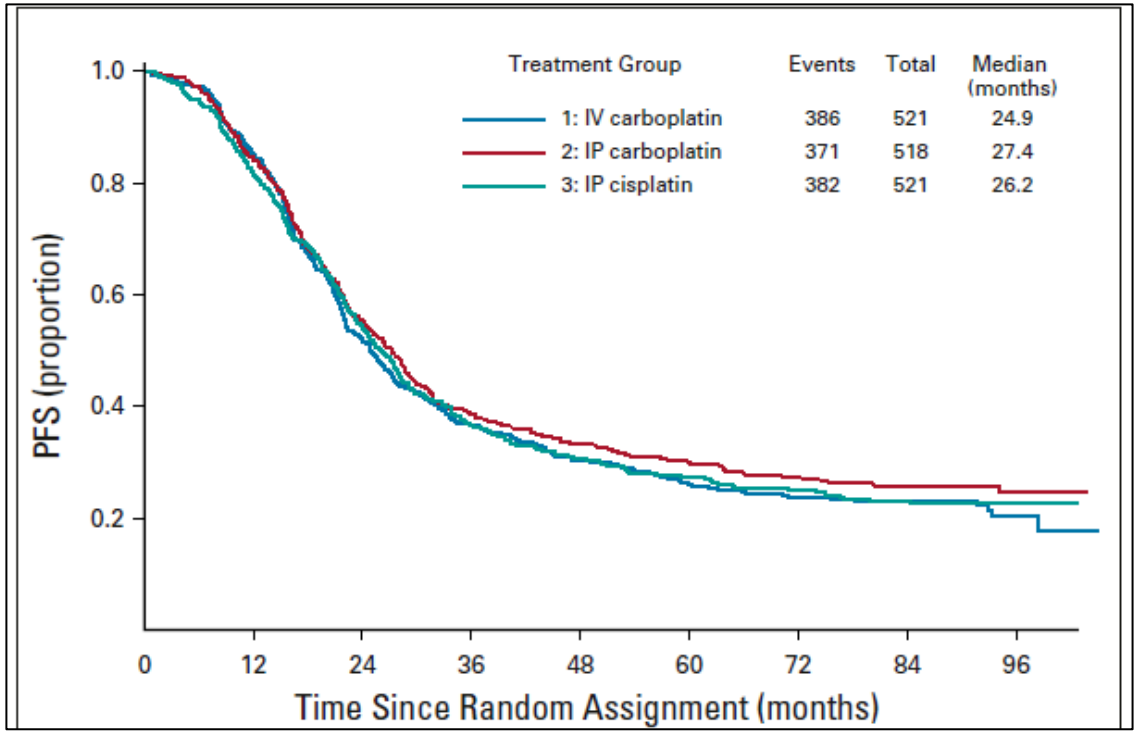
I	Carboplatin AUC=6 (IV) Paclitaxel 80 mg/m² (d1, 8, 15 3h) Bevacizumab (C2+ C22) x 21 days
II	Carboplatin AUC=6 (IP) Paclitaxel 80 mg/m2 (d1, 8, 15 3h) Bevacizumab (C2+ C22) x 21 days
III	Cisplatin 75 mg/m² (IP d2) Paclitaxel 135 mg/m² (d1, 3h) Paclitaxel 60 mg/m² (d8, IP) Bevacizumab (C2+ C22) x 21 days

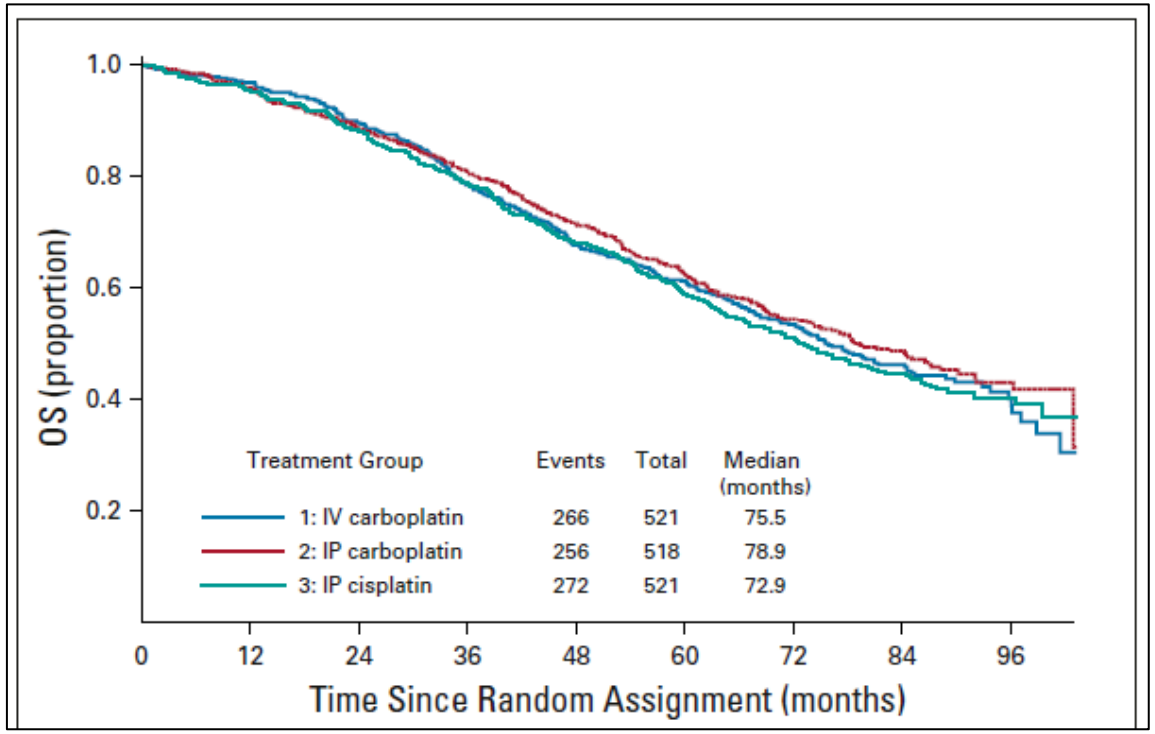
- Phase III
- PFS primary endpoint

Open: 27 Jul 2009
Closed: 30 Nov 2011
Accrual: 1100
Study Chair: J Walker

ClinicalTrials.gov Identifier: NCT00951496

GOG252 (TC Bev vs T weekly Carbo ip Bev vs GOG 172 Bev) …and the winner was…





more toxicity in IP arms

Walker JL et al. J Clin Oncol 2019.

…in the meantime another negative trial: PETROC. IP ->

..and I was so self assure…

..but then,
out of the blue and unexspected,
came another „higher-dose" trial…

Is more better IV (eg. Dose-dense chemotherapy) ?

Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial

Noriyuki Katsumata, Makoto Yasuda, Fumiaki Takahashi, Seiji Isonishi, Toshiko Jobo, Daisuke Aoki, Hiroshi Tsuda, Toru Sugiyama, Shoji Kodama, Eizo Kimura, Kazunori Ochiai, Kiichiro Noda, for the Japanese Gynecologic Oncology Group*

Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube cancer FIGO Stage II-IV

N = 631

Randomization

Stratification;
- Residual disease: ≤1cm, > 1cm
- FIGO Stage II vs. III vs. IV
- Histology clear cell/mucinous vs.serous/others

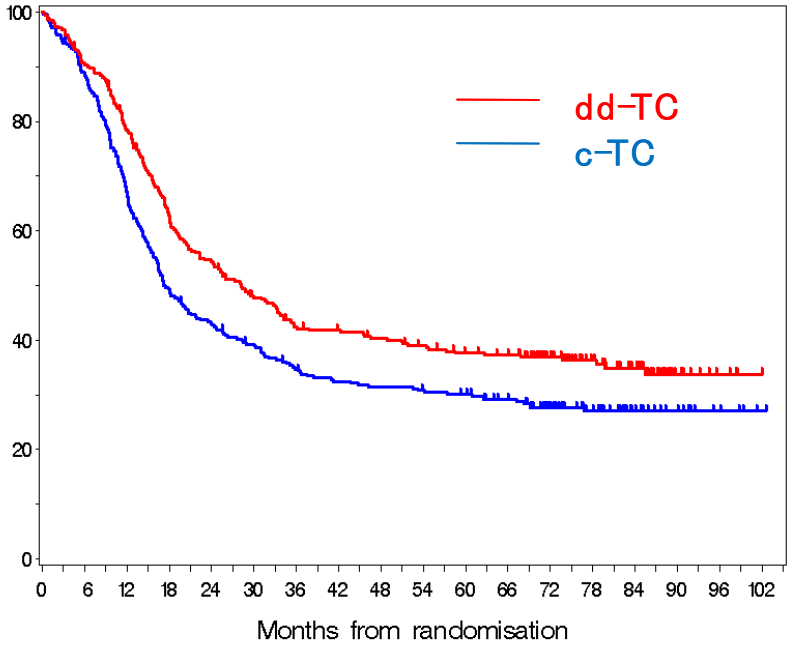
Conventional TC (c-TC)
Paclitaxel 180mg/m², day 1
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

Dose-dense weekly TC (dd-TC)
Paclitaxel 80mg/m², days 1,8,15
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

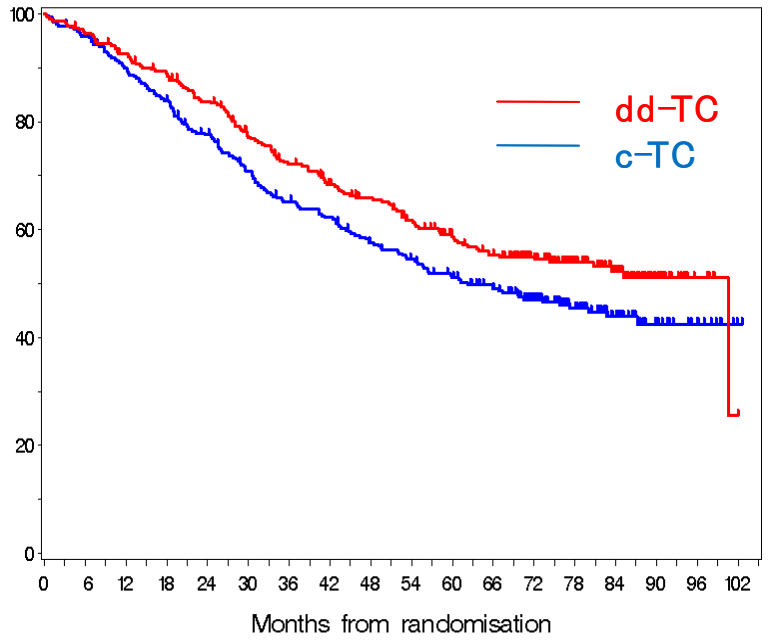
Katsumata N et al.: Lancet 2009; 374:1331-8

Update after median follow-up: 6.4 years

PFS



OS



Treatment	n	Event, n (%)	Median PFS	*P* value	HR	95% CI
dd-TC	312	197 (63)	28.2 mos.	0.0037	0.76	0.62-0.91
c-TC	319	229 (72)	17.5 mos.			

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 N et al. Lancet Oncol 2014

A run started to confirm: 1st was MITO 7 study

Random

1:1

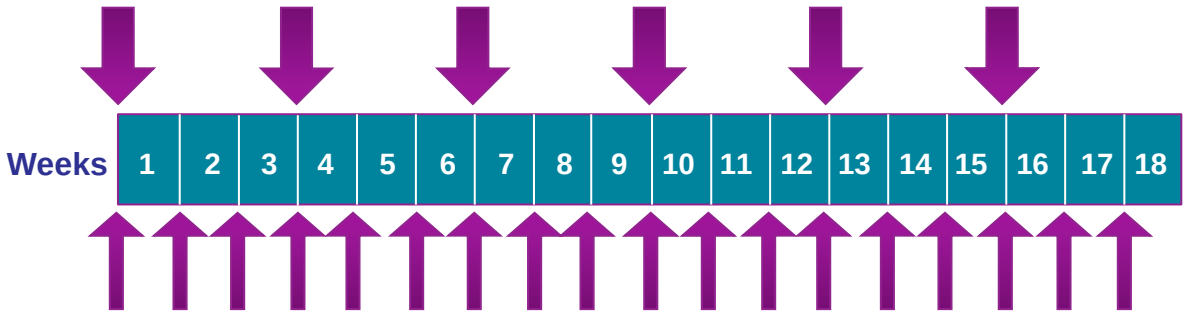
N= 403

Control arm

Carboplatin AUC 6, d1 q21

Paclitaxel 175 mg/m^2, d1 q21

Treatment repeated for 6 cycles



N= 405

Experimental arm

Carboplatin AUC 2, d1, 8, 15 q21

Paclitaxel 60 mg/m^2, d1, 8, 15 q21

Treatment repeated for 6 cycles

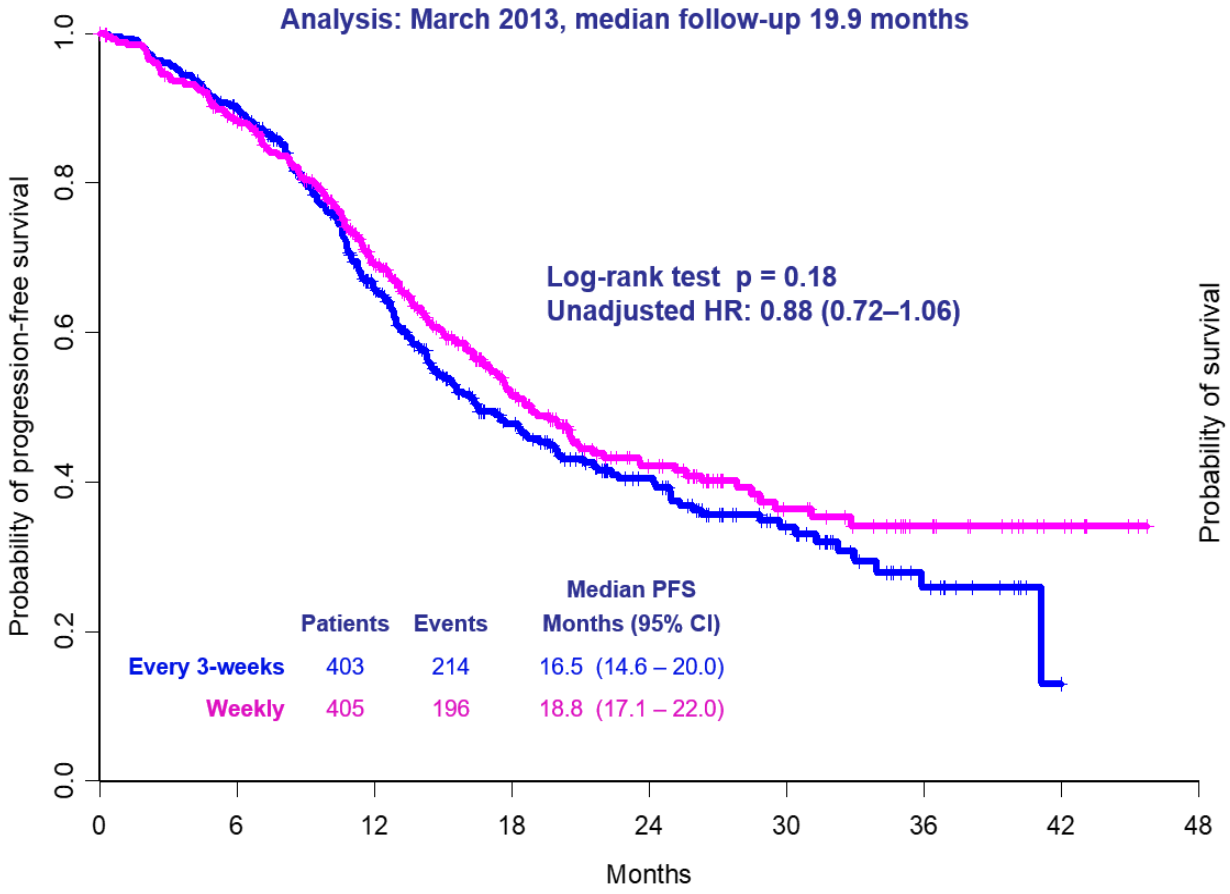
Strata:

- **Centre**
- **PS (0, 1, 2)**
- **Residual disease after surgery (absent, ≤1 cm, >1 cm, no surgery)**

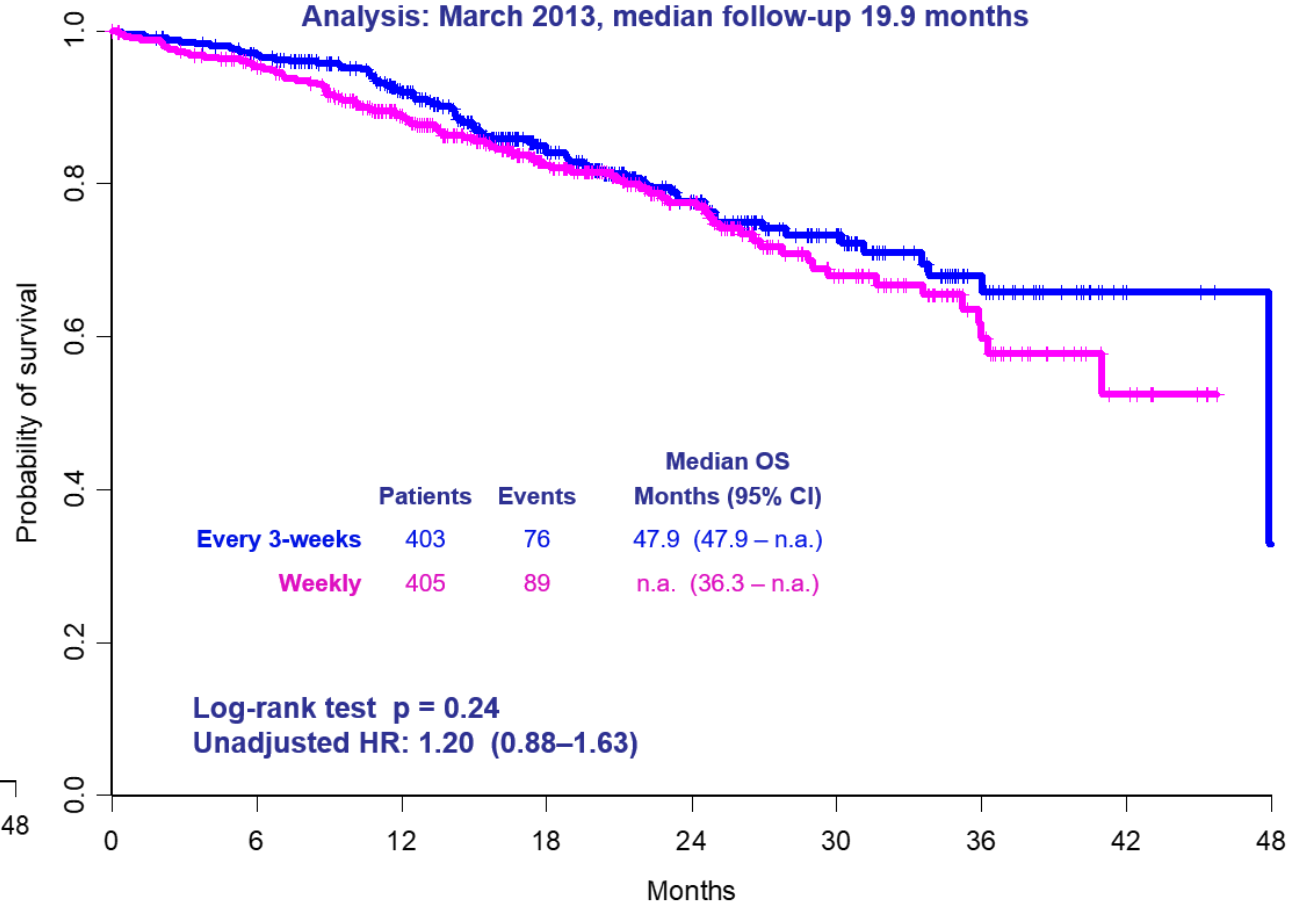
ClinicalTrials.gov NCT00660842

MITO 7 results: dose-dense *not* superior

Progression-free survival

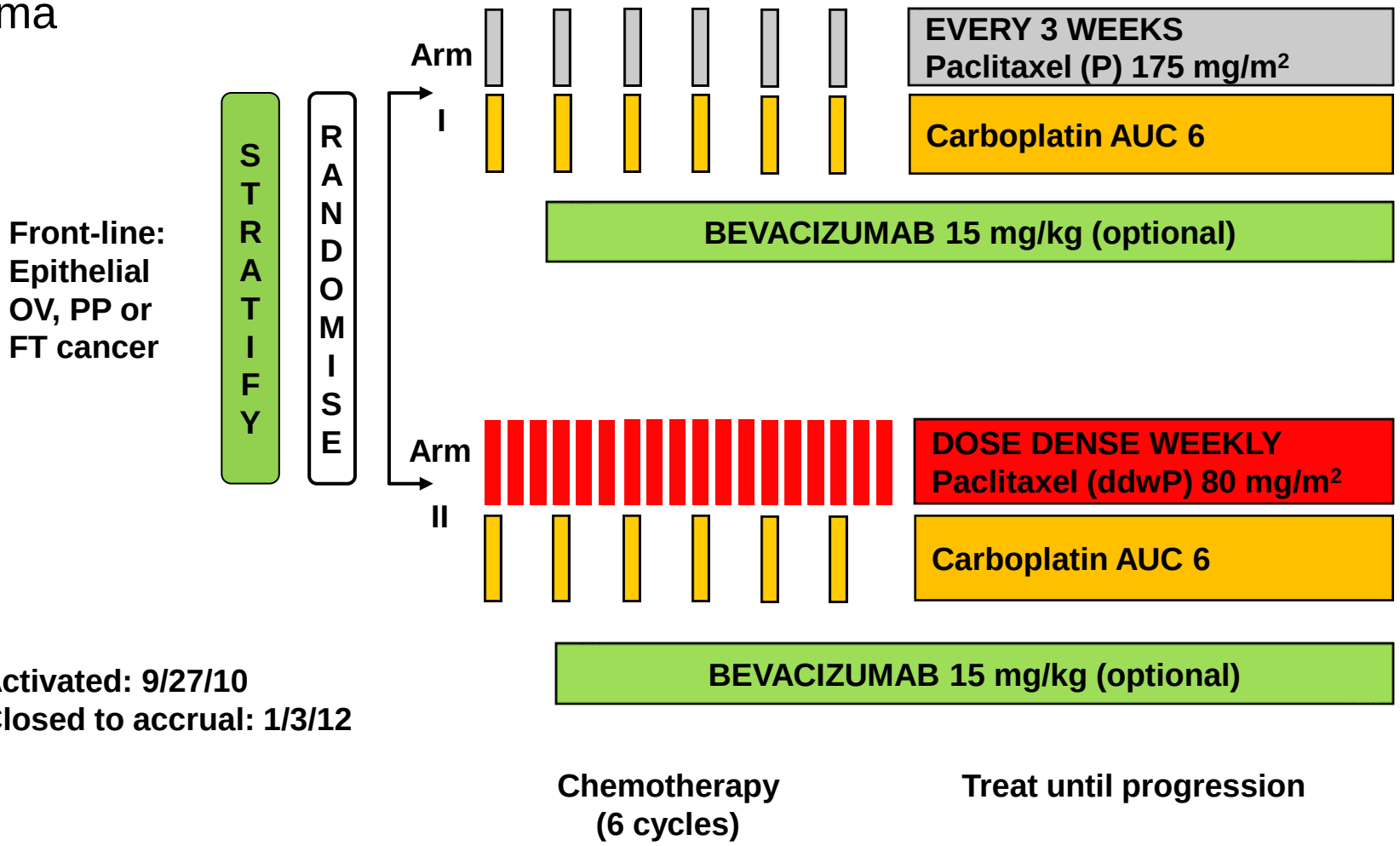


Overall survival



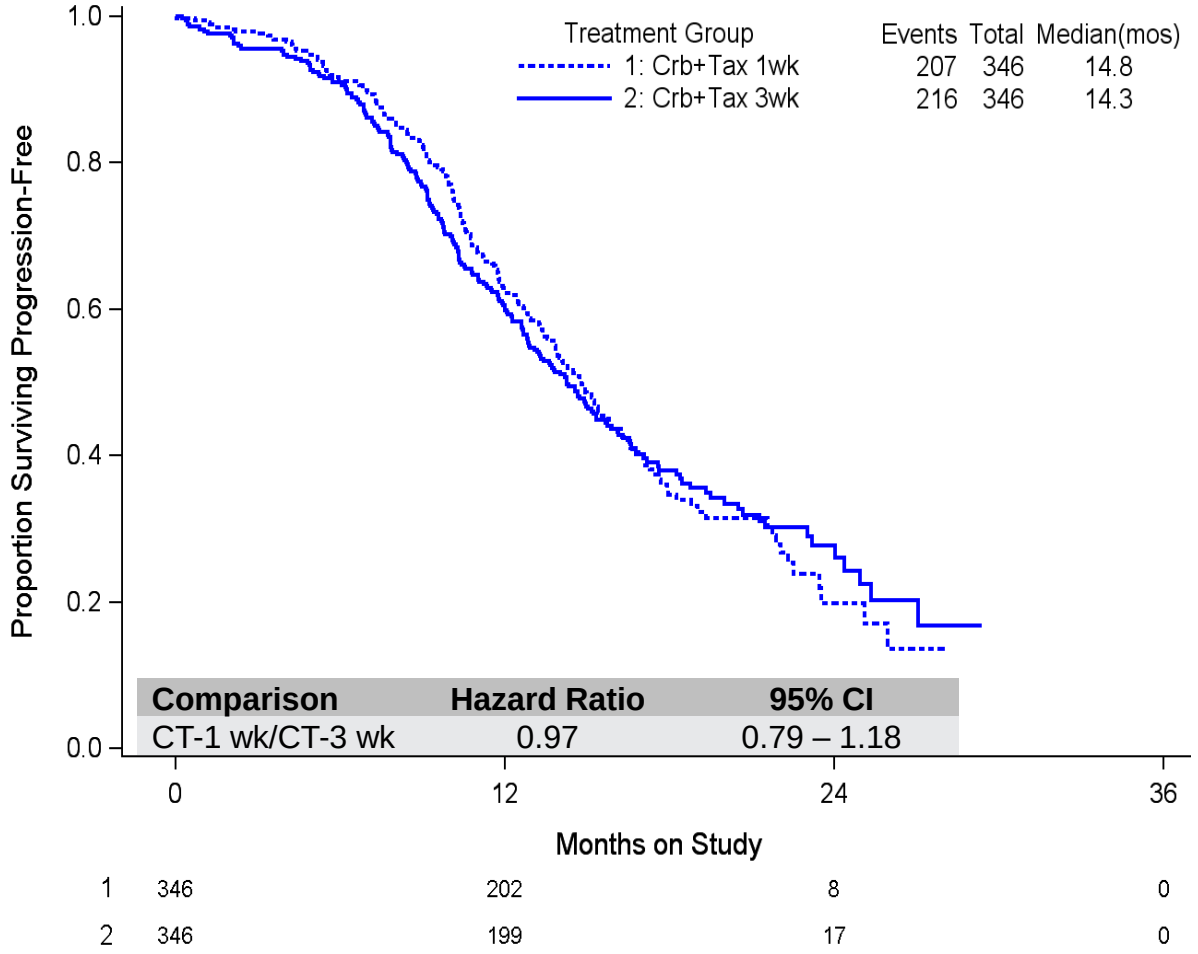
A run started to confirm: 2nd was GOG #262 study

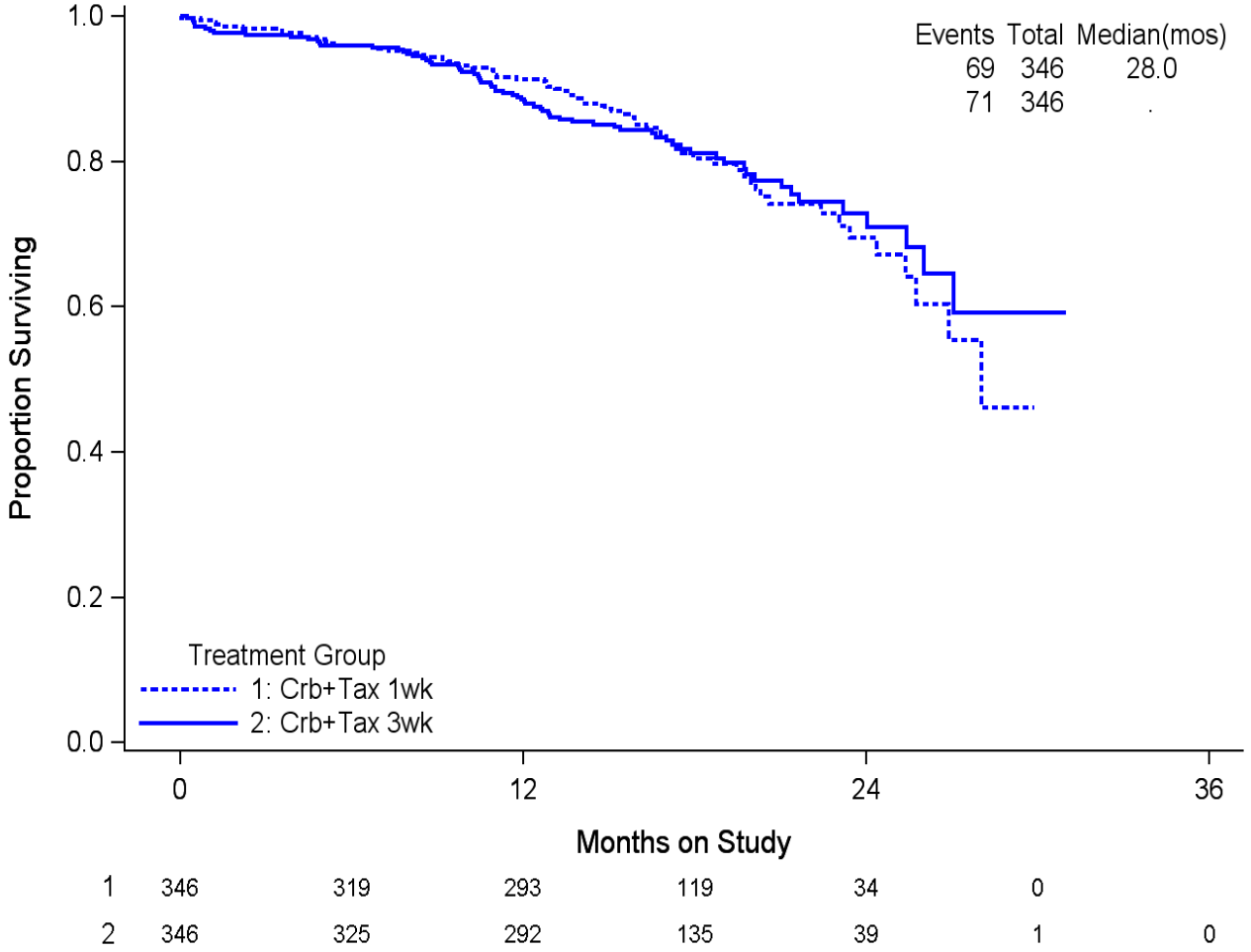
GOG-262: Schema



JK Chan et al. N Engl J Med 2016;374:738-48.

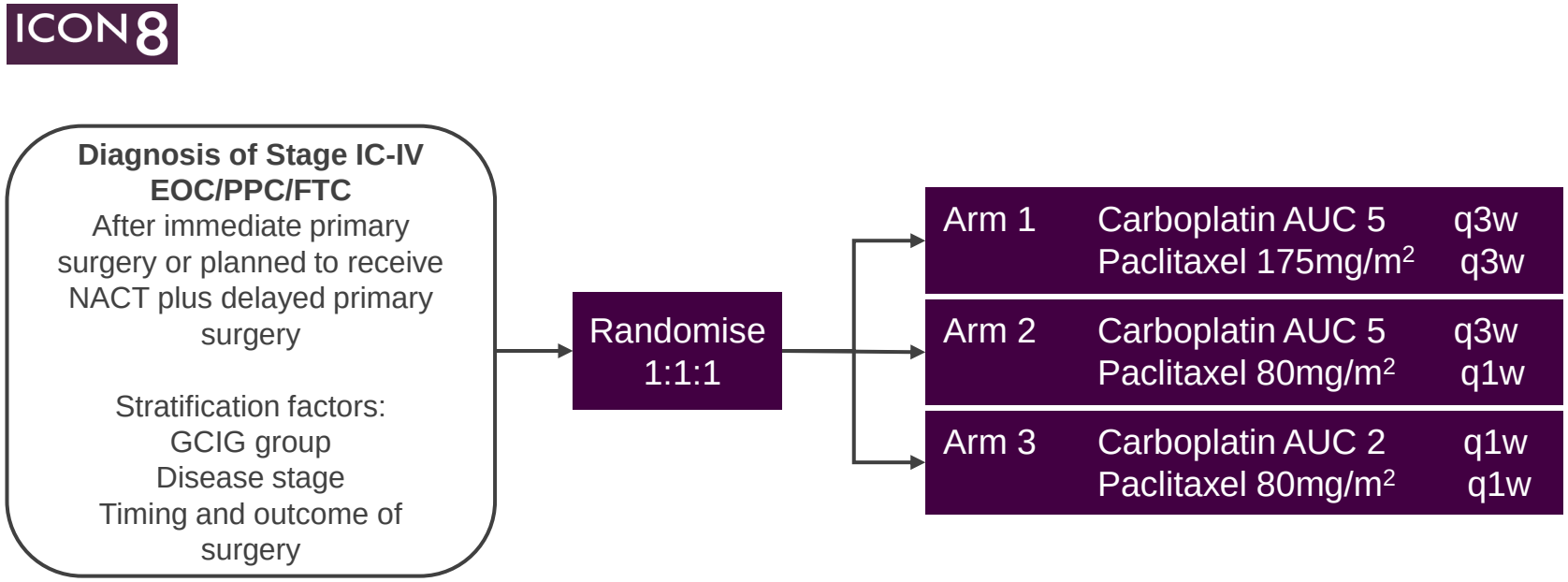
GOG #162 results: again, dose-dense *not* superior





JK Chan et al. N Engl J Med 2016;374:738-48.

and almost last but not least: 3rd was ICON 8

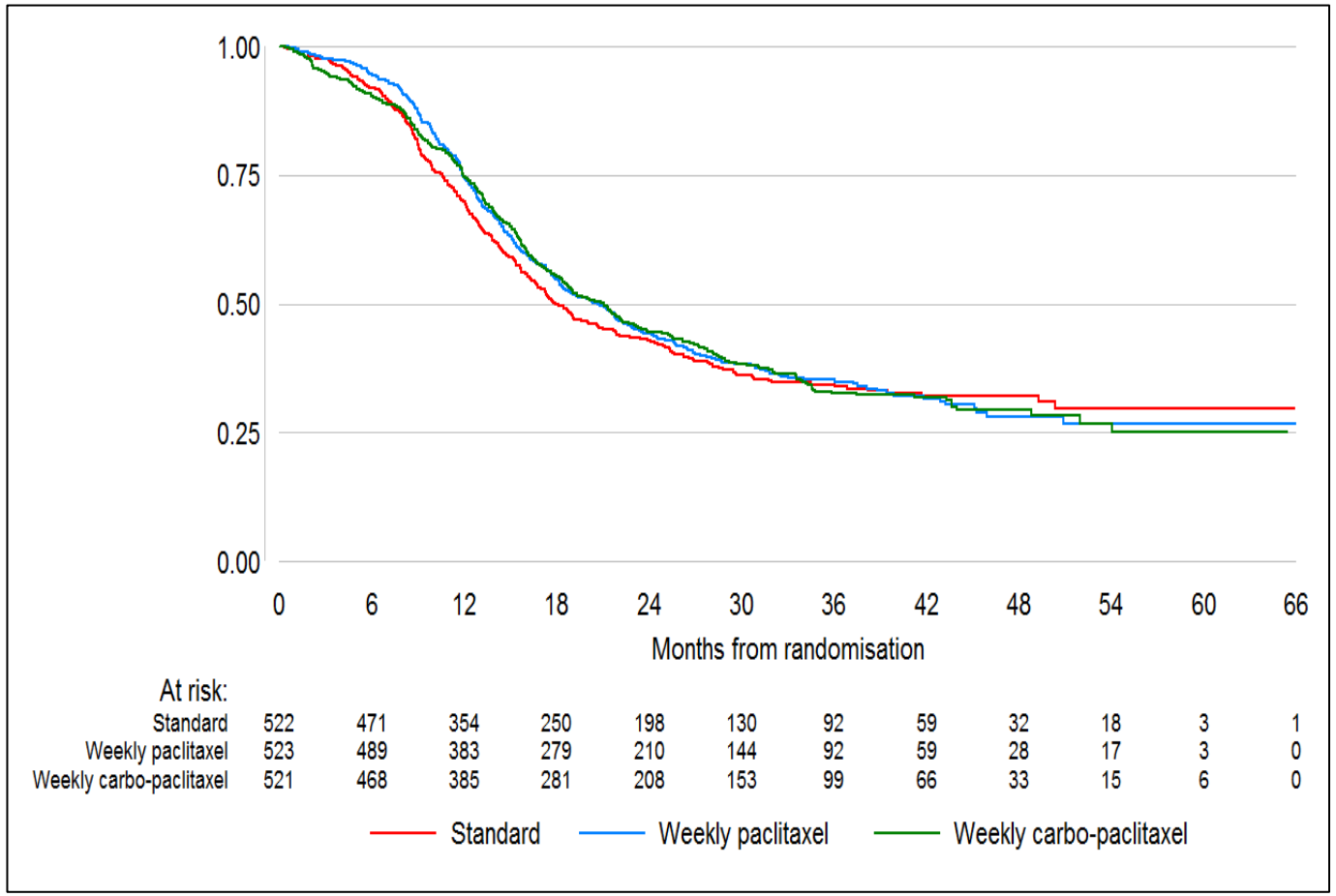


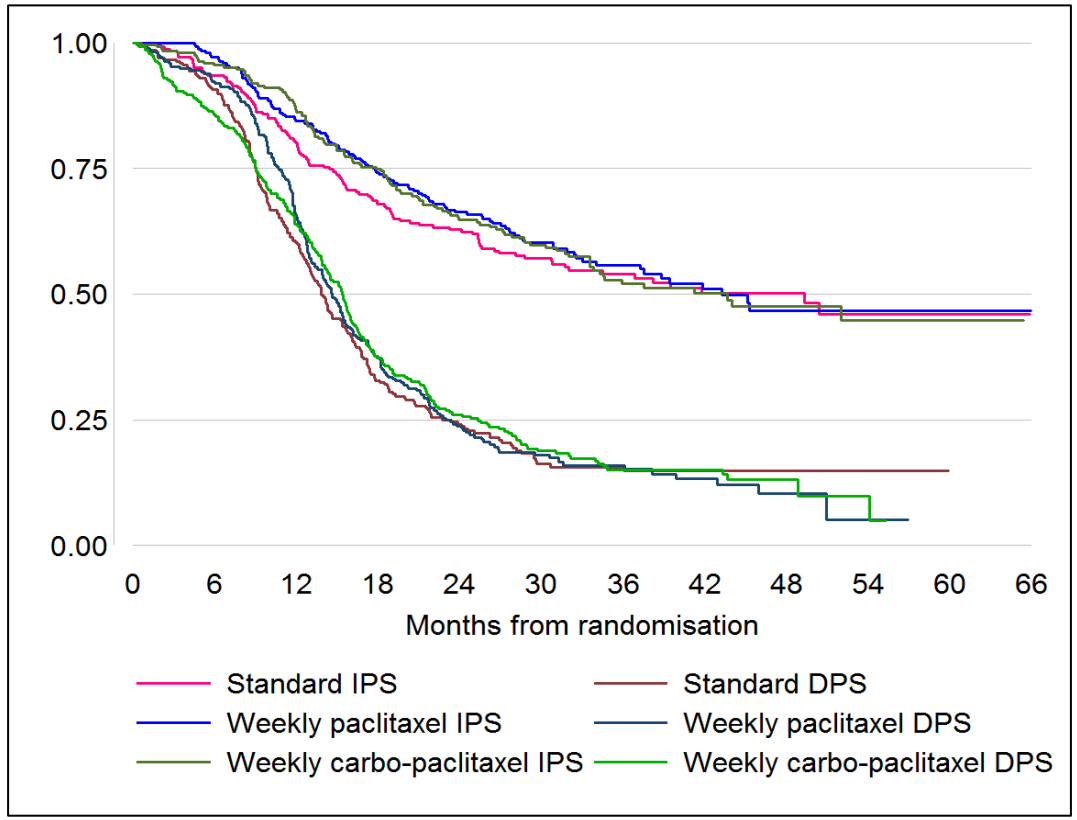
- Six cycles chemotherapy mandated

Delayed Primary Surgery cohort

- Cytoreductive surgery strongly advised after 3 cycles of chemotherapy
- Cycle 3 day 15 treatment omitted in arms 2 and 3

ICON 8 results: again, dose-dense *not* superior

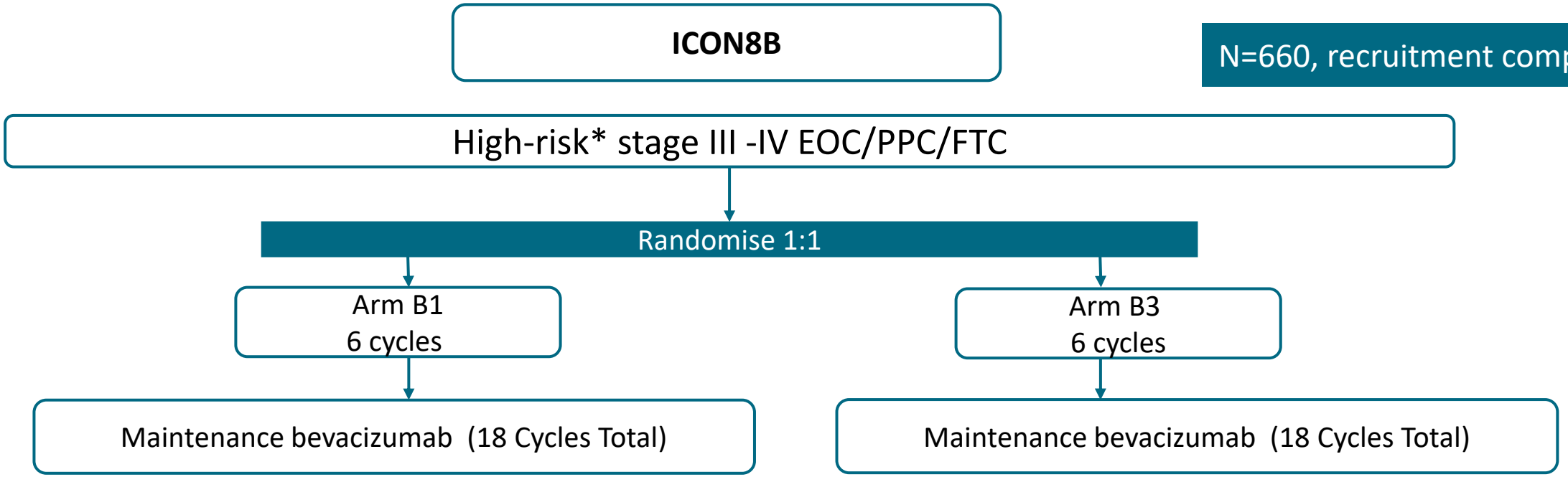




…but standard TC showed less toxicity and better quality of life ->

Clamp A, et al. Lancet 2019

However, dose-dense seems to be very attractive to gyne oncologists: so the story continues with ICON 8B



Arm B1	Carboplatin AUC 5	q3w
	Paclitaxel 175mg/m^2	q3w
	Bevacizumab 7.5 mg/kg	q3w

Arm B3	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
	Bevacizumab 7.5 mg/kg	q3w

…and why Bevacizumab?

So I end up here

I started my career as PI of my first phase III study:

We started recruitment on 23rd OCT 1995

and later defined a new standard: **TC**

…which is still the backbone

A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer

Andreas du Bois, Hans-Joachim Lück, Werner Meier, Hans-Peter Adams, Volker Möbus, Serban Costa, Thomas Bauknecht, Barbara Richter, Matthias Warm, Willibald Schröder, Sigrid Olbricht, Ulrike Nitz, Christian Jackisch, Günther Emons, Uwe Wagner, Walther Kuhn, Jacobus Pfisterer

For the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group

Background: **Despite considerable improvement in the treatment of advanced ovarian cancer, the optimization of efficacy and tolerability remains an important issue. Therefore, we performed a randomized, phase III non-inferiority trial comparing paclitaxel plus cisplatin (PT) with paclitaxel plus carboplatin (TC) in patients with advanced ovarian cancer.** ***Methods:*** **A total of 798 patients with International Federation of Gynecology and Obstetrics stage IIB–IV were randomly assigned to receive six courses of either PT or TC at 3-week intervals. The primary endpoint was the proportion of patients without progression at 2 years. Secondary endpoints included toxicity, response to treatment, quality of life, and overall and progression-free survival time. Quality of life was evaluated using the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ)-C30, version 2.0. Survival curves were calculated using the Kaplan–Meier method, and hazard ratios were estimated using the Cox proportional hazards model.** ***Results:*** **The proportion of patients without progression at 2 years was not statistically significantly different between the two treatment arms (40.0% for PT versus 37.5% for TC, difference = 2.5%, one-sided 95% confidence interval [CI] = −∞ to 8.2%). Median progression-free survival time in the TC arm (17.2 months, 95% CI = 15.2 to 19.3 months) and the PT arm (19.1 months, 95% CI = 16.7 to 21.5 months) were also not statistically significantly different; the same was true of median overall survival time (43.3 months, 95% CI = 37.2 to 47.8 months versus 44.1 months, 95% CI = 40.2 to 49.4 months, for the TC and PT arms, respectively). The TC regimen was associated with a higher frequency of hematologic toxicity, but a lower frequency of gastrointestinal and neurologic toxicity, than the PT regimen. Mean global quality-of-life scores at the end of treatment were statistically significantly better in the TC arm than in the PT arm (65.25 versus 51.97, respectively; difference = −13.28, 95% CI = −18.88 to −7.68).** ***Conclusion:*** **The TC regimen achieved comparable efficacy to the PT regimen but was associated with better tolerability and quality of life, and should, therefore, be considered as an important alternative for standard first-line chemotherapy in patients with advanced ovarian cancer. [J Natl Cancer Inst 2003;95:1320–30]**

During the past two decades, the chemotherapy regimens used to treat advanced ovarian cancer have undergone two major advances in efficacy, the first being the introduction of platinum-based agents and the second the introduction of taxanes. In the mid-1980s, two studies *(1,2)* demonstrated that the addition of cisplatin to the combination of doxorubicin and cyclophosphamide (CAP) statistically significantly increased response rates and progression-free and overall survival times. Subsequent studies *(3,4)* have not shown any clinically relevant differences in efficacy between two-drug combinations (predominantly cisplatin and cyclophosphamide) and multidrug combinations, which for the most part included anthracyclines. As a result, the combination of cisplatin and cyclophosphamide was considered standard therapy for the first-line treatment of patients with advanced ovarian cancer for approximately the next 10 years.

The replacement of cyclophosphamide with paclitaxel in first-line therapy marked the next major advance in treatment efficacy for advanced ovarian cancer, as first reported in a study by the Gynecologic Oncology Group (GOG) *(5)* and confirmed by a European–Canadian intergroup study *(6)*. The paclitaxel-

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See "Notes" following "References."

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Jonathan Lederman will tell the story of

PARPine, BEVman & -the new heroes

BEVman PRIMAtor **PARPi**ne RUCAboy Mr. PAOLA the triple SOLO