TRATTAMENTO ANTIBLASTICO DELLE NEOPLASIE EPITELIALI DELL'OVAIO IN FASE AVANZATA

Paola Agnese Cassandrini

Negrar ,16 febbraio 2015

strategy	trial	Number of patients	stage	arms	results
CHT	AGO Du Bois et al JNCI 2003	776	IIB-IV	TP (185-75) vs TC (185-6)	TP=TC mPFS 18 vs 17 mesi
	GOG 158 Ozols JCO 2003	840	III (<1 cm)	TP (135-75) vs TC (175-7,5)	TP=TC mTTP 22 vs 22 mesi
	Neijt JCO2000	208	IIB - IV	TP (175-75) vs TC (175 – 5)	TP = TC mPFS 16 vs 16 mesi

T: paclitaxel P:cisplatino C :carboplatino

CARCINOMA SIEROSO DELL'OVAIO

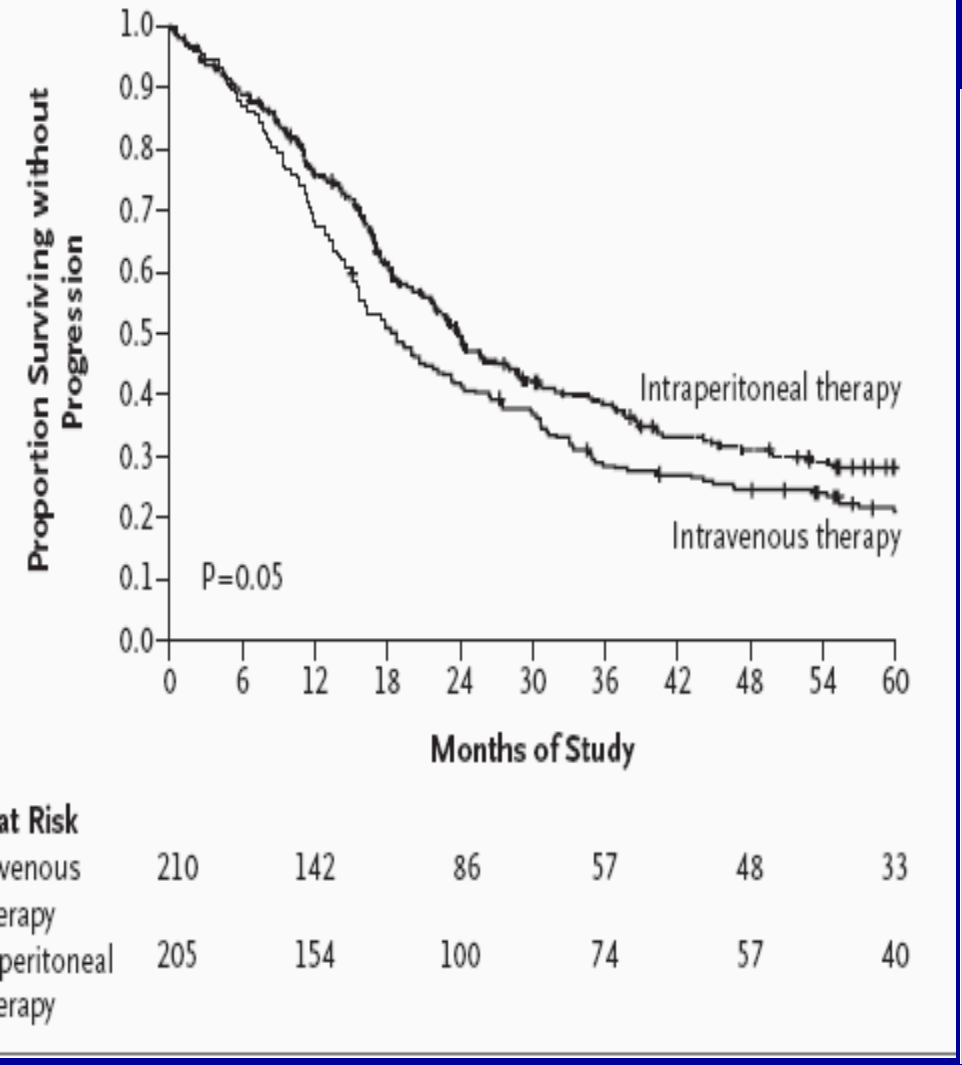
STADIO III e IV

CHEMIOTERAPIA DOPO CHIRURGIA :

CARBOPLATINO AUC 5-6 + PACLITAXEL 175 mg/mq

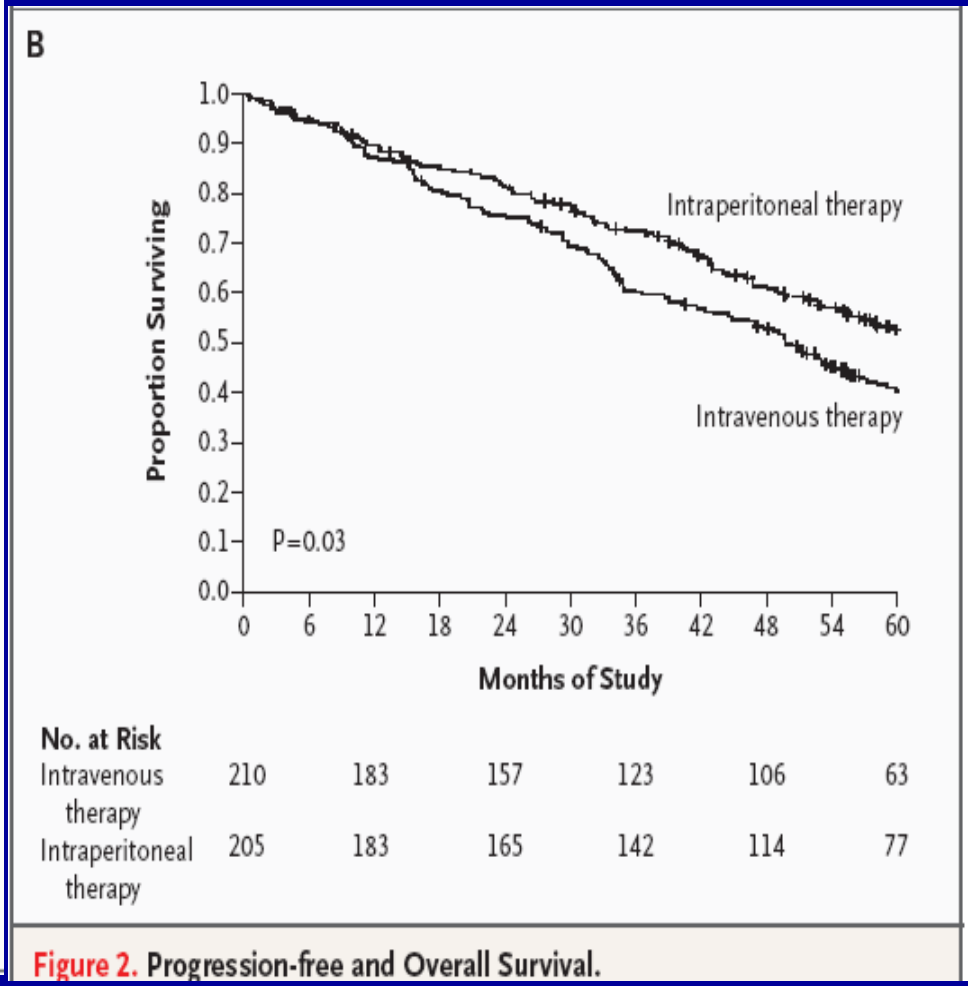
strategy	TRIAL	NUMBER OF PATIENTS	STAGE	ARMS	PRIMARY ENDPOINT	RESULTS
IP CHT	GOG 172	429	III	PS→IPCisP x 6 IVCisP x 6	PFS e OS	↑ PFS (23,8 vs 18,3 mesi) ↑OS (65,6 vs 49,7 mesi)
	GOG 114	462	III	IVC→IVP+ IPCis X 6 PS→IVCis x 6	PFS e OS	↑PFS (27.9 vs 22,2 mesi) ↑OS (63.2 vs 52.2 mesi)

IP CHT chemioterapia intraperitoneale IPCisP cisplatino intraperitoneale100 mg/mq g1 +Paclitaxel intraperitoneale 60 mg/mq g8 ogni 21 gg
IVCisP cisplatino ev 75 mg/mq g2 + paclitaxel135 mg/mq ev g1 ogni 21 gg
IVC carboplatino ev AUC 9 IVP paclitaxel ev 135 mg/mq ogni 21gg



at Risk

venous	210	142	86	57	48	33
erapy						
peritoneal	205	154	100	74	57	40
erapy						



No. at Risk

Intravenous therapy	210	183	157	123	106	63
Intraperitoneal therapy	205	183	165	142	114	77

Figure 2. Progression-free and Overall Survival.

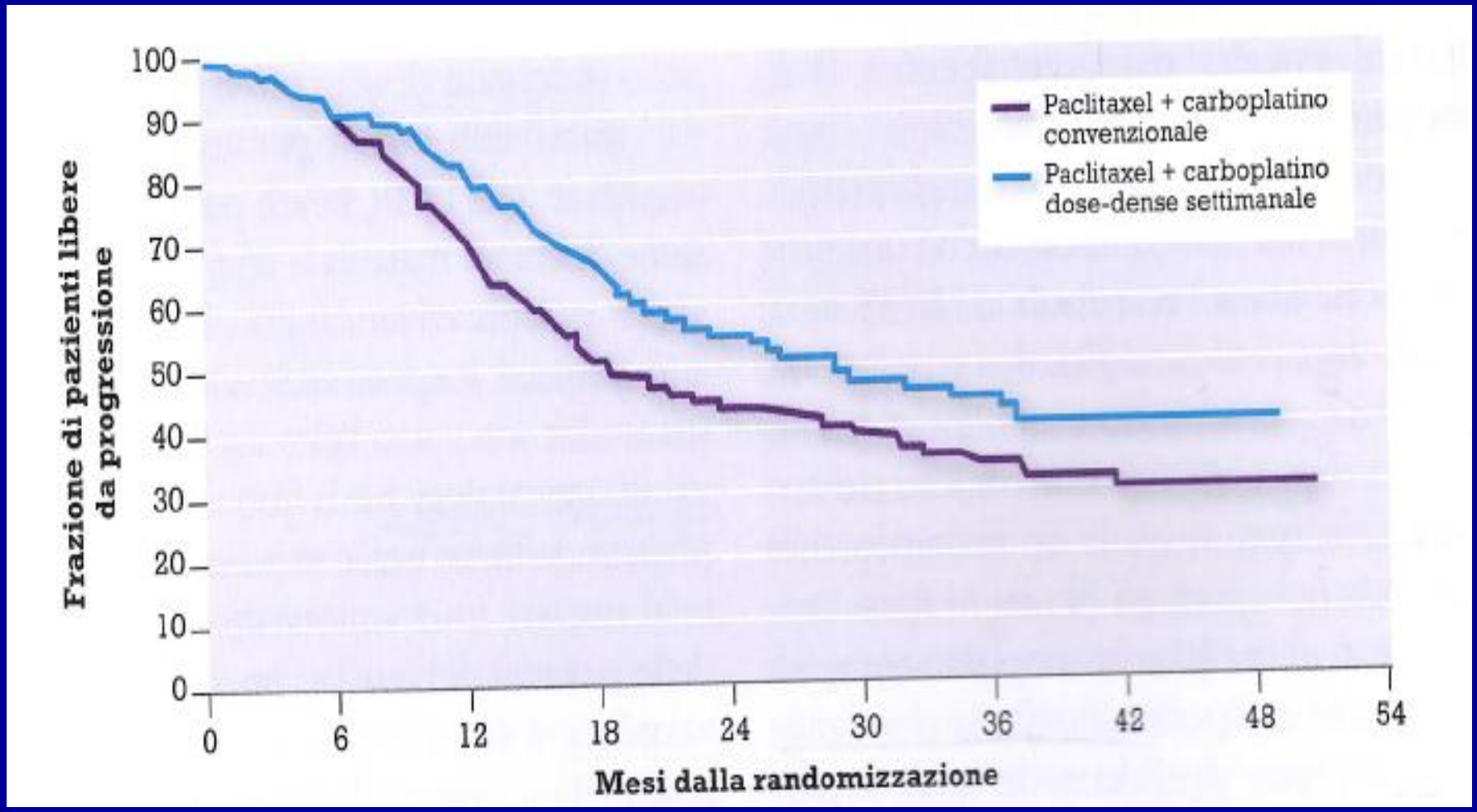
Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

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 January 5, 2006

strategy	trial	Number of patients	stage	arms	Primary endpoint	results
DD CHT	JGOG 3016	637	II - IV	3weeCP x 6 3weeC + wP x 6	PFS e OS	↑PFS (28 vs 17.2 mesi) ↑OS (100 vs 62 mesi)
	MITO-7	822	IC - IV	3weeCP x 6 wCP x 6	QoL e PFS	Miglior QoL x wCP no beneficio in PFS
	GOG 262	692	II - IV	3weeCP x 6 3weeBCP x 6→ Bm 3weeC+wP x 6 3weeC+wP→ Bm	PFS	↑PFS solo senza Beva

DD CHT dose dense chemotherapy 3weeCP :carbo + taxolo trisettimanale
3weeC : carbo trisettimanale wP:taxolo settimanale wCP carbo + taxolo settimanale
3weeBCP : carbo+taxolo+beva trisettimanale Bm : beva in mantenimento



DOSE DENSE PACLITAXEL ONCE A WEEK IN COMBINATION WITH CARBOPLATIN EVERY 3 WEEKS FOR ADVANCED OVARIAN CANCER
JGOG 3016

Carboplatino AUC 6 **Paclitaxel 175 mg/mq**	**X 8**
Carboplatino AUC 5 g1 Paclitaxel 175 mg/mq g1 Gemcitabina 800 mg/m2 gg1,8	X 8
Carboplatino AUC 5 g1 Paclitaxel 175 mg/mq Doxorubicina liposomiale 30 mg/m2 g1	X 8
Carboplatino AUC 5 g3 Topotecan 1,25 mg/mq gg1—3 x 4 ---------- Carboplatino AUC 6 g8 Gemcitabina 1g/mq gg1,8 x4 ----------	x4

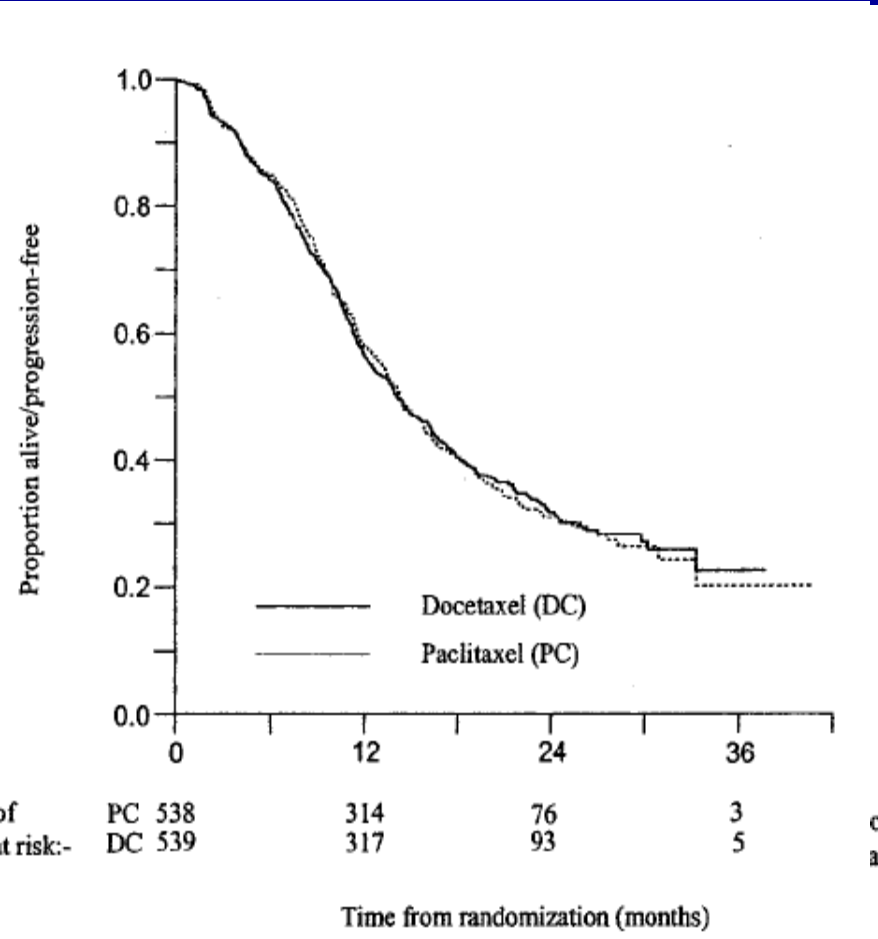
Carboplatino AUC 6
g1
Paclitaxel 175 mg/mq

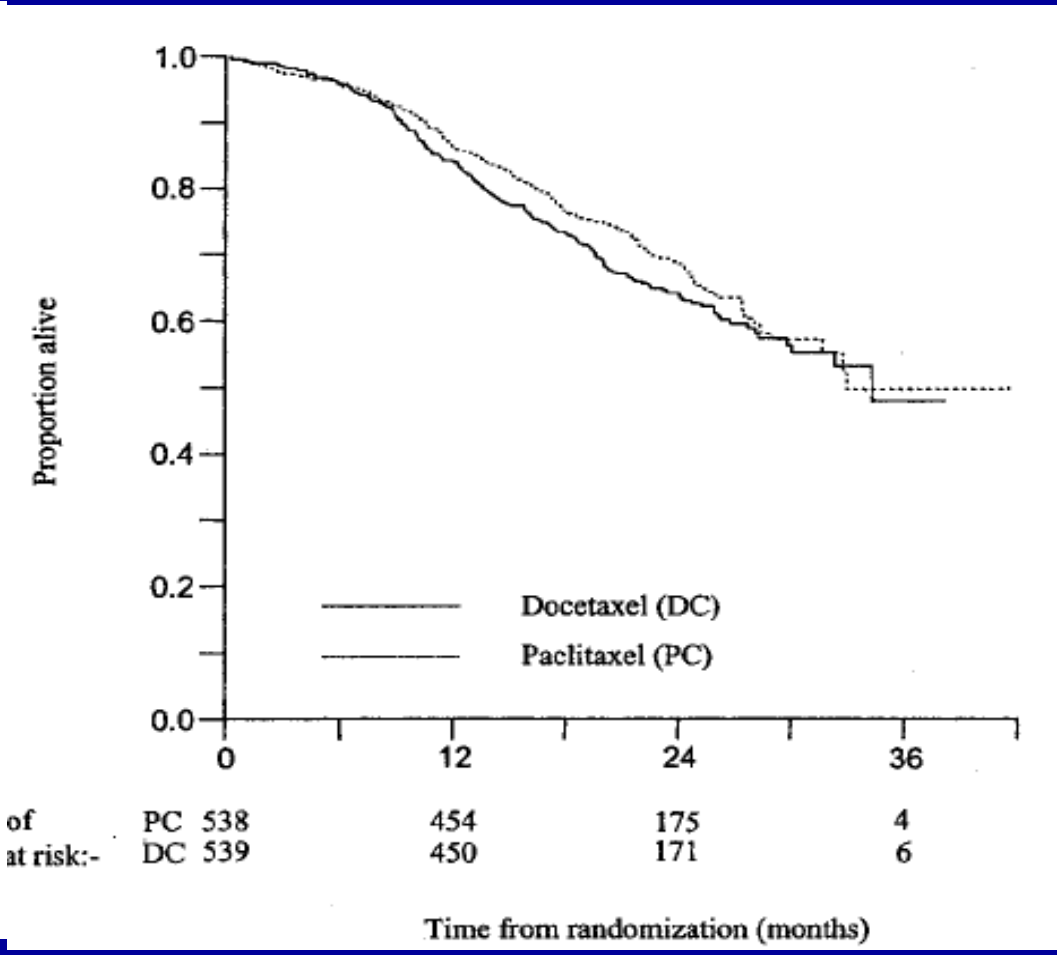
ICON 5

strategy	trial	Number of patients	stage	arms	results	
CHT	SCOTROC	1077	IC - IV	TC vs DC	PFS 15 vs 14,8 mesi OS(2y) 64,2vs 68,9% RR 58,7 vs 59,5%	
	MITO2	820	IC - IV	C-LPD vs TC	PFS 19 vs 16,8 mesi OS 61.6 vs 53,2 mesi RR 57 vs 59%	

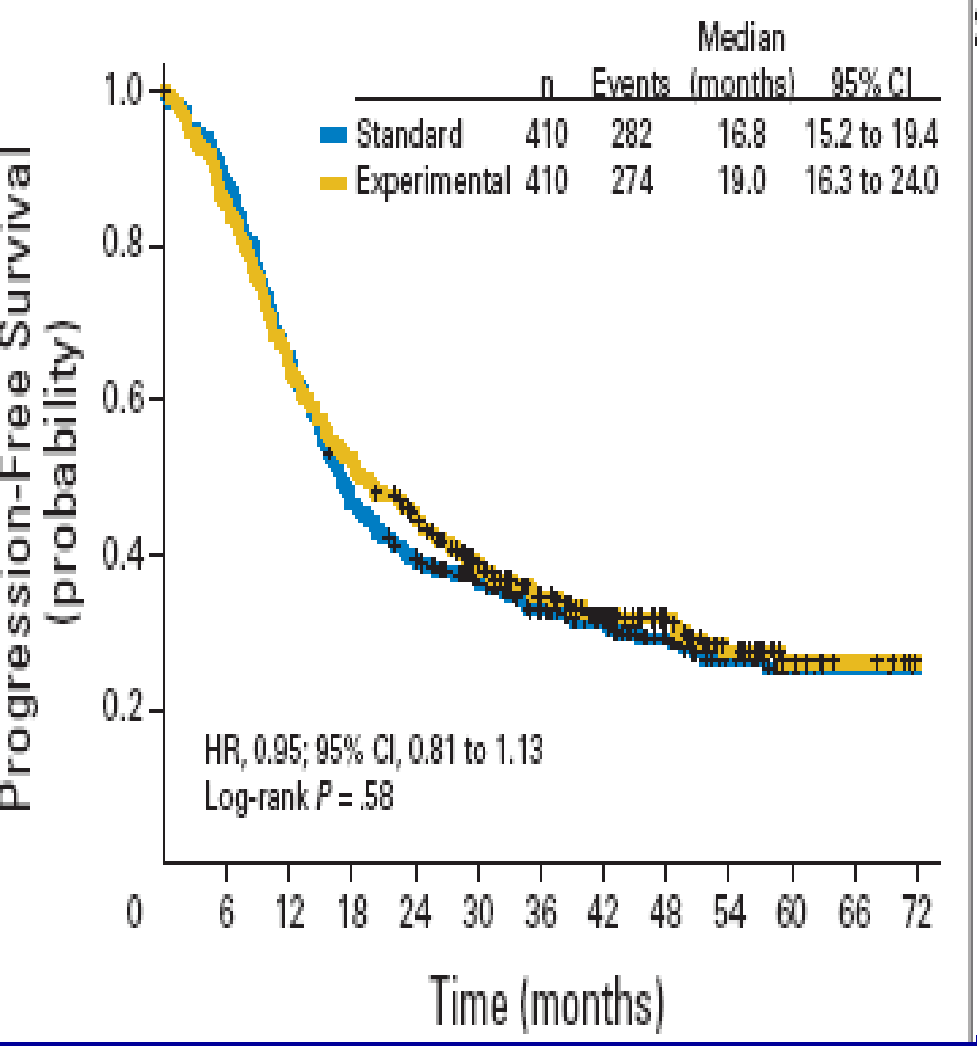
TC : Taxolo 175 mg/mq + Carboplatino AUC5
DC : Docetaxel 75 mg/mq + Carboplatino AUC 5

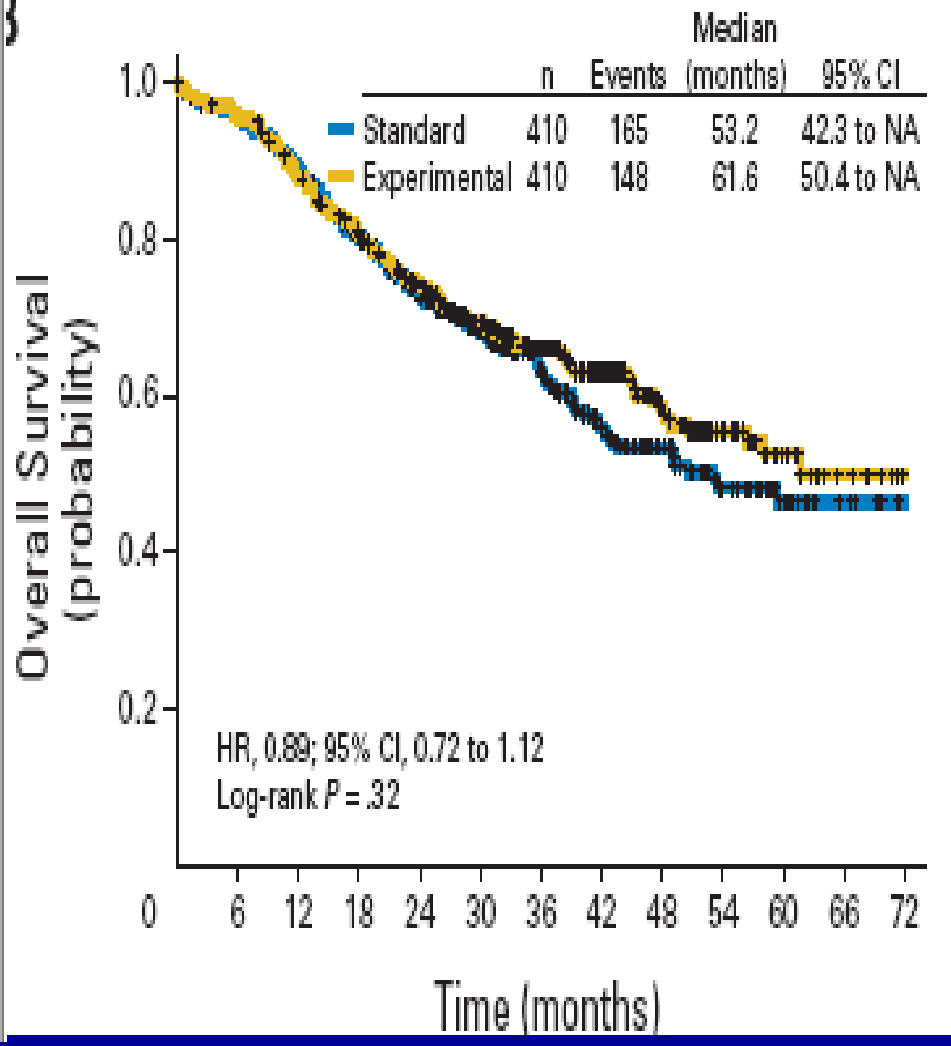
C-LPD : Carboplatino AUC 5 + Doxorubicina liposomiale 30 mg/mq


Proportion alive/progression-free
1.0
0.8
0.6
0.4
0.2
0.0
Docetaxel (DC)
Paclitaxel (PC)
0
12
24
36
of
t risk:-
PC 538
DC 539
314
317
76
93
3
5
Time from randomization (months)


Proportion alive
1.0
0.8
0.6
0.4
0.2
0.0
Docetaxel (DC)
Paclitaxel (PC)
0
12
24
36
of
at risk:-
PC 538
DC 539
454
450
175
171
4
6
Time from randomization (months)

SCOTROC 1


Median
n Events (months) 95% CI
Standard 410 282 16.8 15.2 to 19.4
Experimental 410 274 19.0 16.3 to 24.0
HR, 0.95; 95% CI, 0.81 to 1.13
Log-rank P = .58
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
6 12 18 24 30 36 42 48 54 60 66 72
Time (months)

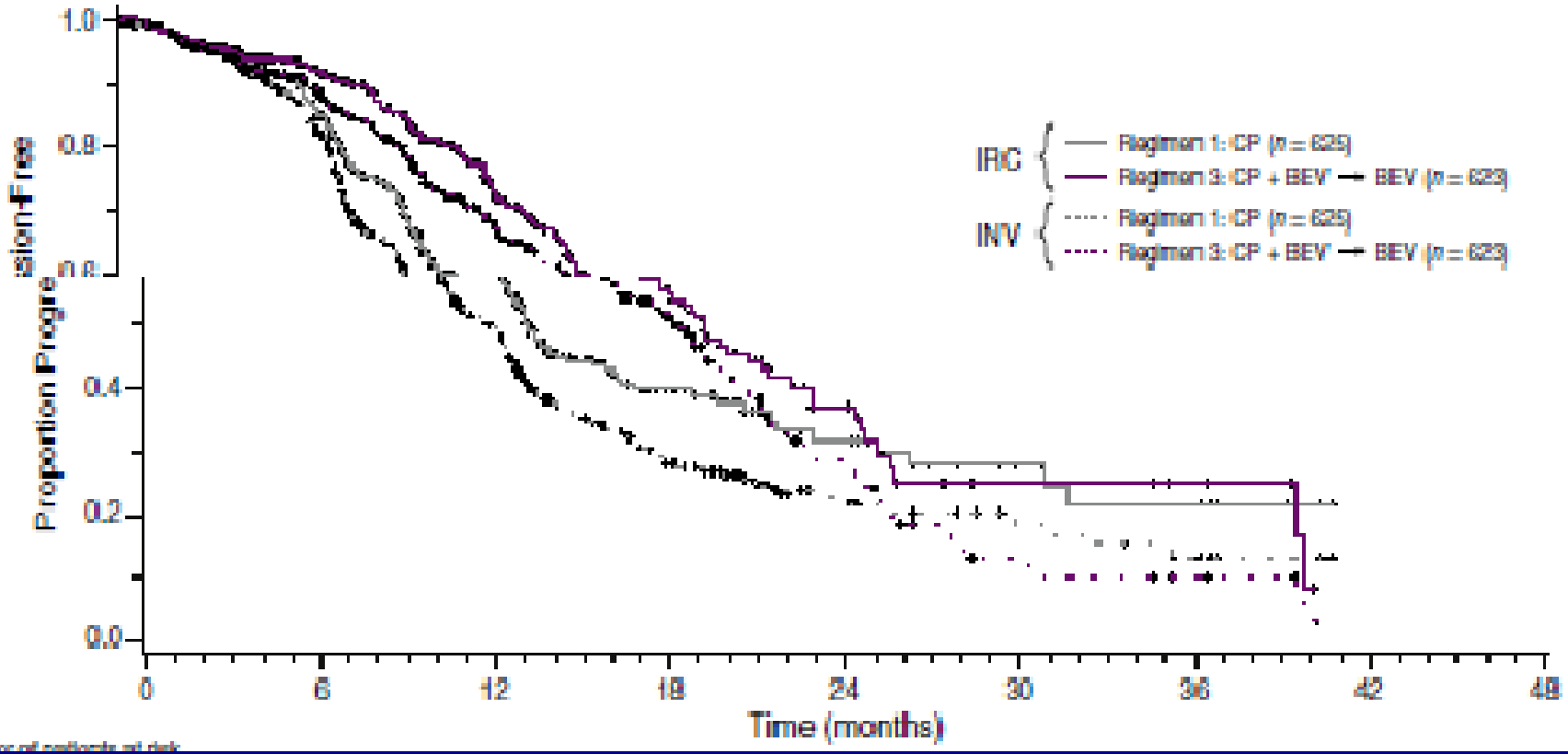

Median
n Events (months) 95% CI
Standard 410 165 53.2 42.3 to NA
Experimental 410 148 61.6 50.4 to NA
HR, 0.89; 95% CI, 0.72 to 1.12
Log-rank P = .32
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
6 12 18 24 30 36 42 48 54 60 66 72
Time (months)

MITO 2

THERAPY	AGENT	TRIAL	Number of patients	ARMS	Primary endpoint	results
Combination with chemotherapy	bevacizumab	GOG218	1873	CP x 6 +PI→PI CP x 6 + B CP x 6 +B→Bm	PFS	↑PFS (Bm vs PI 18 vs 12 mesi
“	“	ICON 7	1528	CP x 6 CPB x 6→Bm	PFS	↑PFS 17,3 vs 19 mesi

CP : carboplatinAUC 5 +paclitaxel 175 mg/mq PI :placebo B :bevacizumab
Bm bevacizumab mantenimento

BURGER RA N ENGL J MED 2011



Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

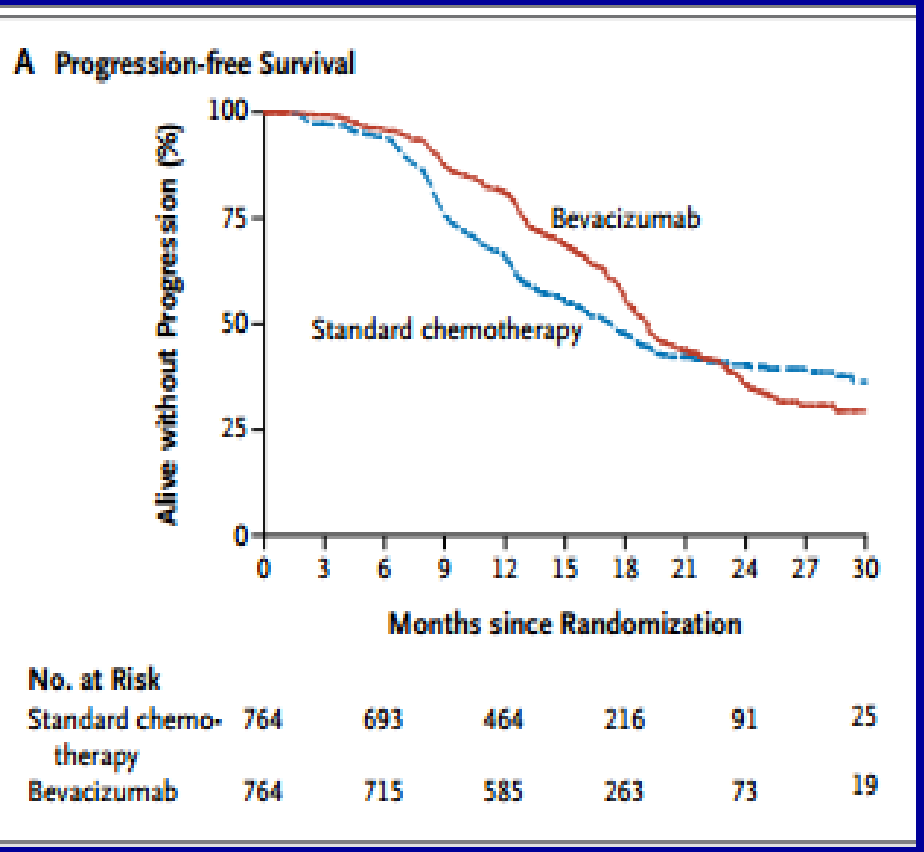
Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D. for the Gynecologic Oncology Group

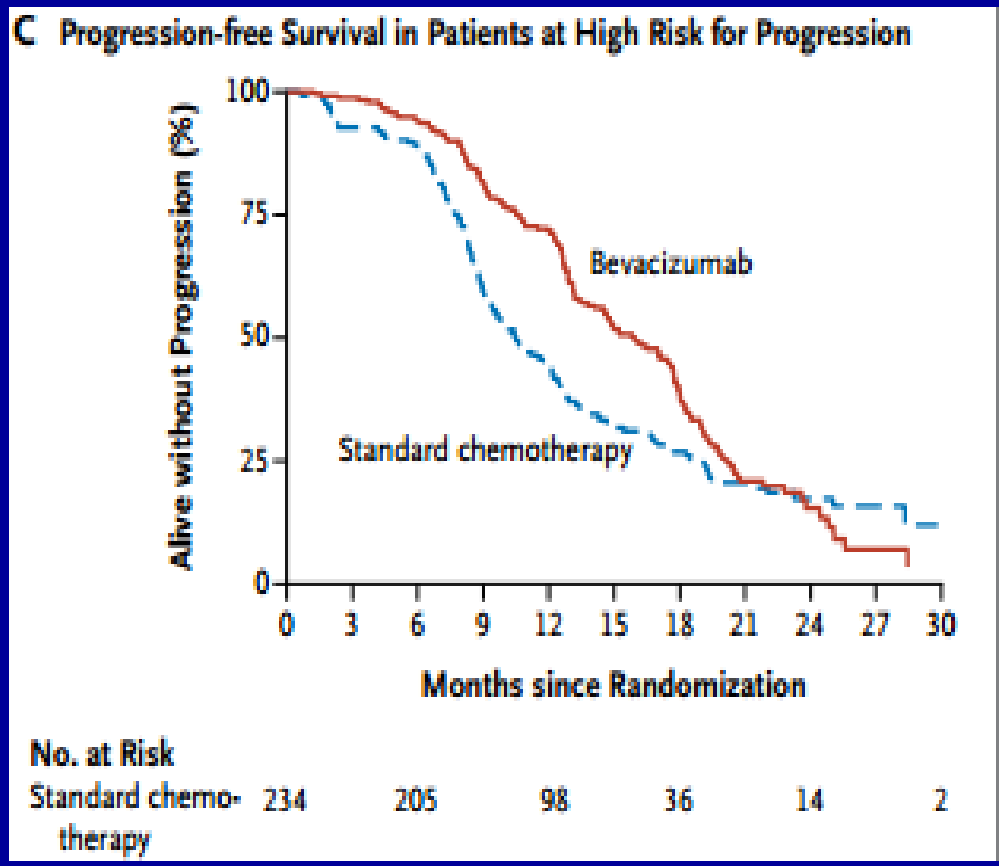
N Engl J Med 2011; 365:2473-2483December 29, 2011

N Engl J Med. 2011 Dec 29;365(26):2484-96.

A phase 3 trial of bevacizumab in ovarian cancer.

Perren TJ[1], Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A,Sehouli J, Kimmig R, Stähle A, Collinson F, Essapen S, Gourley C, Lortholary A, Selle F, Mirza MR, Leminen A, Plante M, Stark D, Qian W, Parmar MK, Oza AM; **ICON7** Investigators.





PFS 19 vs 17.3 mesi

OS 36.6 vs 28.8 mesi

Eur J Cancer. 2013 Dec;49(18):3831-8.

Efficacy and safety results from OCTAVIA, a single-arm phase II study evaluating front-line bevacizumab, carboplatin and weekly paclitaxel for ovarian cancer.

Gonzalez-Martin A[1], Gladieff L, Tholander B, Stroyakovsky D, Gore M, Scambia G, Kovalenko N, Oaknin A, Ronco JP, Freudensprung U, Pignata S; OCTAVIA Investigators.

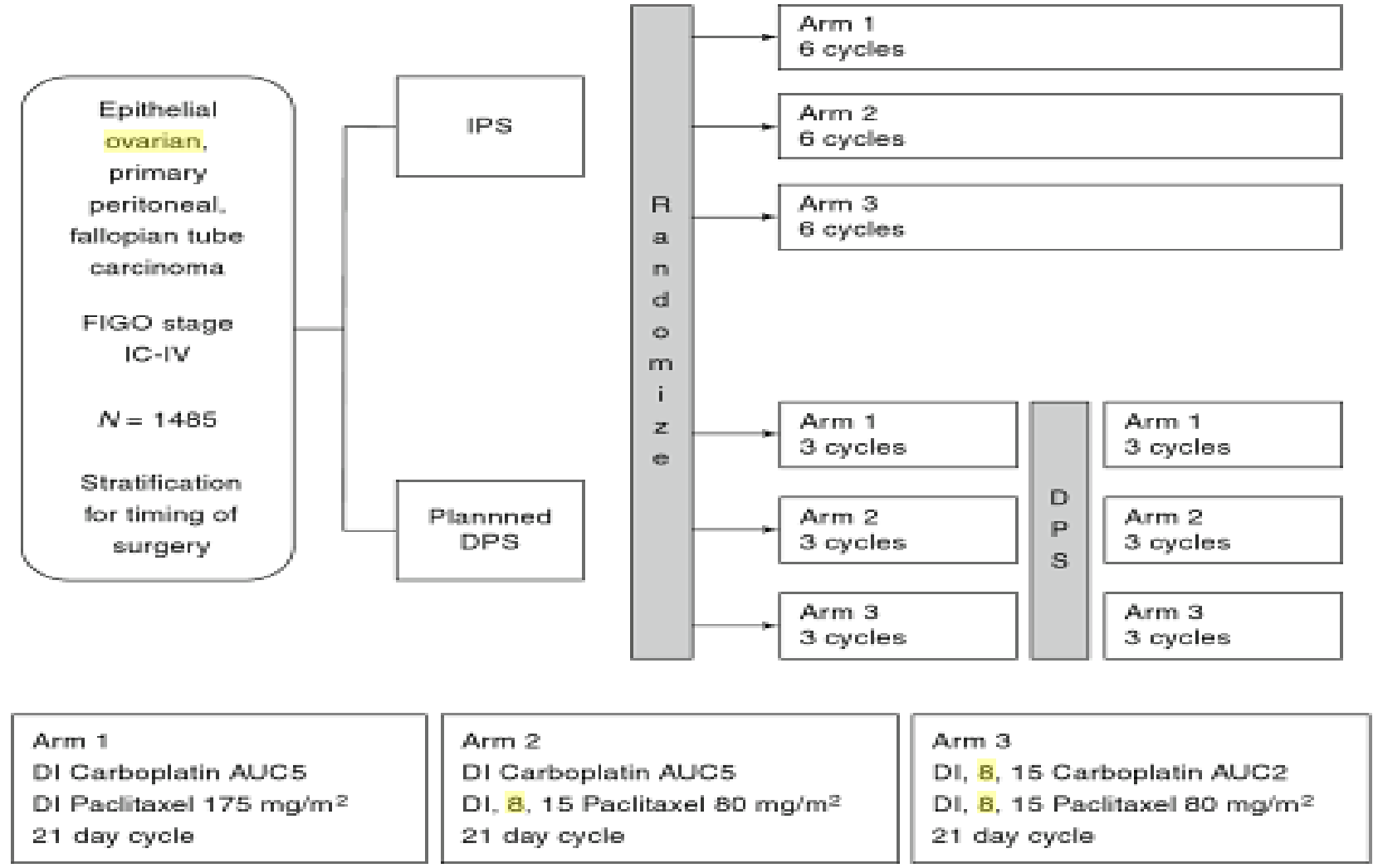
strategy	trial	Number of patients	stage	arms	objective	resultsCHT
CHT	OCTAVIA	189	IIB _ IV	TC + B	PFS>18 mesi	PFS 23,7 mesi

TC+B : paclitaxel 80 mg/mq gg1-8-15 + Carboplatino AUC 6 g1 + Bevacizumab 7,5 mg/kg g1

Eur J Cancer. 2014 Mar;50(4):862-3.

Updated results from OCTAVIA (front-line bevacizumab, carboplatin and weekly paclitaxel therapy for ovarian cancer).

Gonzalez-Martin A[1], Gladieff L[2], Tholander B[3], Stroyakovsky D[4], Gore M[5], Scambia G[6], Oaknin A[7], Sneller V[8], Freudensprung U[8], Pignata S[9];OCTAVIA Investigators.



IPS : immediate primary surgery
DPS :delayed primary surgery

ICON 8

PRINCIPLES OF CHEMOTHERAPY
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER)
(3 of 3)

PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY REGIMENS FOR STAGE II-IV[1,2]

- Intraperitoneal (IP)/Intravenous (IV) Regimen
  - Paclitaxel 135 mg/m² IV continuous infusion over 3 or 24 h[3] Day 1; cisplatin 75-100 mg/m² IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)

- Intravenous (IV) Regimens
  - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[4] AUC 5-7.5 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 and carboplatin[4] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Docetaxel 60-75 mg/m² IV over 1 hour followed by carboplatin[4] AUC 5-6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Bevacizumab-containing regimens per ICON-7 and GOG-218:
    Paclitaxel 175 mg/m² IV over 3 hours, carboplatin[4] AUC 5-6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30-90 minutes Day 1. Repeat every 3 weeks x 5-6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 3)
    or
    Paclitaxel 175 mg/m² IV over 3 hours and carboplatin[4] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30-90 minutes every 3 weeks for up to 22 cycles. (category 3)

NEOPLASIE EPITELIALI DELL'OVAIO

RECIDIVA

NCCN Guidelines Version 3.2014
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Ovarian Cancer TOC
Discussion

ACCEPTABLE RECURRENCE THERAPIES (1 OF 2)[a]

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Single Agents or Combinations	**Platinum-Sensitive Disease**[b,c] Carboplatin[1] Carboplatin/docetaxel[2,3] Carboplatin/gemcitabine[1] Carboplatin/gemcitabine/bevacizumab[d,e] (category 2B)[4] Carboplatin/liposomal doxorubicin[5] Carboplatin/paclitaxel (category 1)[6] Carboplatin/paclitaxel (weekly)[7] Cisplatin[6] Cisplatin/gemcitabine[8] **Platinum-Resistant Disease** Docetaxel[9] Etoposide, oral[10] Gemcitabine[11,12] Liposomal doxorubicin[11,12] Liposomal doxorubicin/bevacizumab[d,e,13] Paclitaxel (weekly)[14] Paclitaxel (weekly)/bevacizumab[d,e,13] Topotecan[15,16] Topotecan/bevacizumab[d,e,13]		Bevacizumab[d,e,17,18]	
Other Potentially Active Agents	**Single Agents**[19] Altretamine Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Anastrozole Letrozole Leuprolide acetate Megestrol acetate Tamoxifen		Palliative localized radiation therapy

Ann Oncol. 2012 May;23(5):1185-9.

Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitiveovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial.

Gladieff L[1], Ferrero A, De Rauglaudre G, Brown C, Vasey P, Reinthaller A, Pujade-Lauraine E, Reed N, Lorusso D, Siena S, Helland H, Elit L, Mahner S.

Aut

344 partially platinum-sensitive patients

C-PLD : Carboplatin AUC 5 + Doxorubicina liposomiale 30 mg/mq

TC : Paclitaxel 175 mg/mq + Carboplatin AUC 5

Median PFS times were 9.4 months (C-PLD) and 8.8 months (TC)

Carboplatin-PLD has a more favorable risk-benefit profile than TC in patients with partially platinum-sensitive ROC and should be considered an effective treatment option for these patients.

Eur J Cancer. 2015 Feb;51(3):352-8.

Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO phase III trial.

Mahner S[1], Meier W[2], du Bois A[3], Brown C[4], Lorusso D[5], Dell'Anna T[6], Cretin J[7], Havsteen H[8], Bessette P[9], Zeimet AG[10], Vergote I[11], Vasey P[12], Pujade-Lauraine E[13], Gladieff L[14], Ferrero A[15]

259 very platinum-sensitive patients C-PDL vs TC
C-PDL : carboplatin AUC 5+ PDL 30 mg/mq
TC : Carboplatin AUC 5 + paclitaxel 175 mg/mq

patients with a TFI>24months (treatment-free interval)were analysed separately for progression free survival (PFS), the primary endpoint of CALYPSO, overall survival (OS) and safety.

Median PFS was 12.0months for the CD arm and 12.3months for CP
median OS was 40.2months for CD and 43.9 for CP [HR=1.18 (95%

TC and C-Pld were equally effective treatment regimens for patients with very platinum-sensitive ROC. The favourable risk-benefit profile suggests carboplatin-PLD as treatment of choice for these patients.

J Clin Oncol. 2006 Oct 10;24(29):4699-707.

Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG.

Pfisterer J[1], Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, Wagner U, Stähle A, Stuart G, Kimmig R, Olbricht S, Le T, Emerich J, Kuhn W, Bentley J, Jackisch C, Lück HJ, Rochon J, Zimmermann AH, Eisenhauer E; AGO-OVAR; NCIC CTG; EORTC GCG.

356 pazienti PFS 8.6 mesi nel braccio Gemcitabina + carboplatino
5.8 mesi nel braccio con Carboplatino

Gemcitabine plus carboplatin significantly improves PFS and response rate without worsening quality of life for patients with platinum-sensitive recurrent ovarian cancer.

J Clin Oncol. 2012 Jun 10;30(17):2039-45.

OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tubecancer.

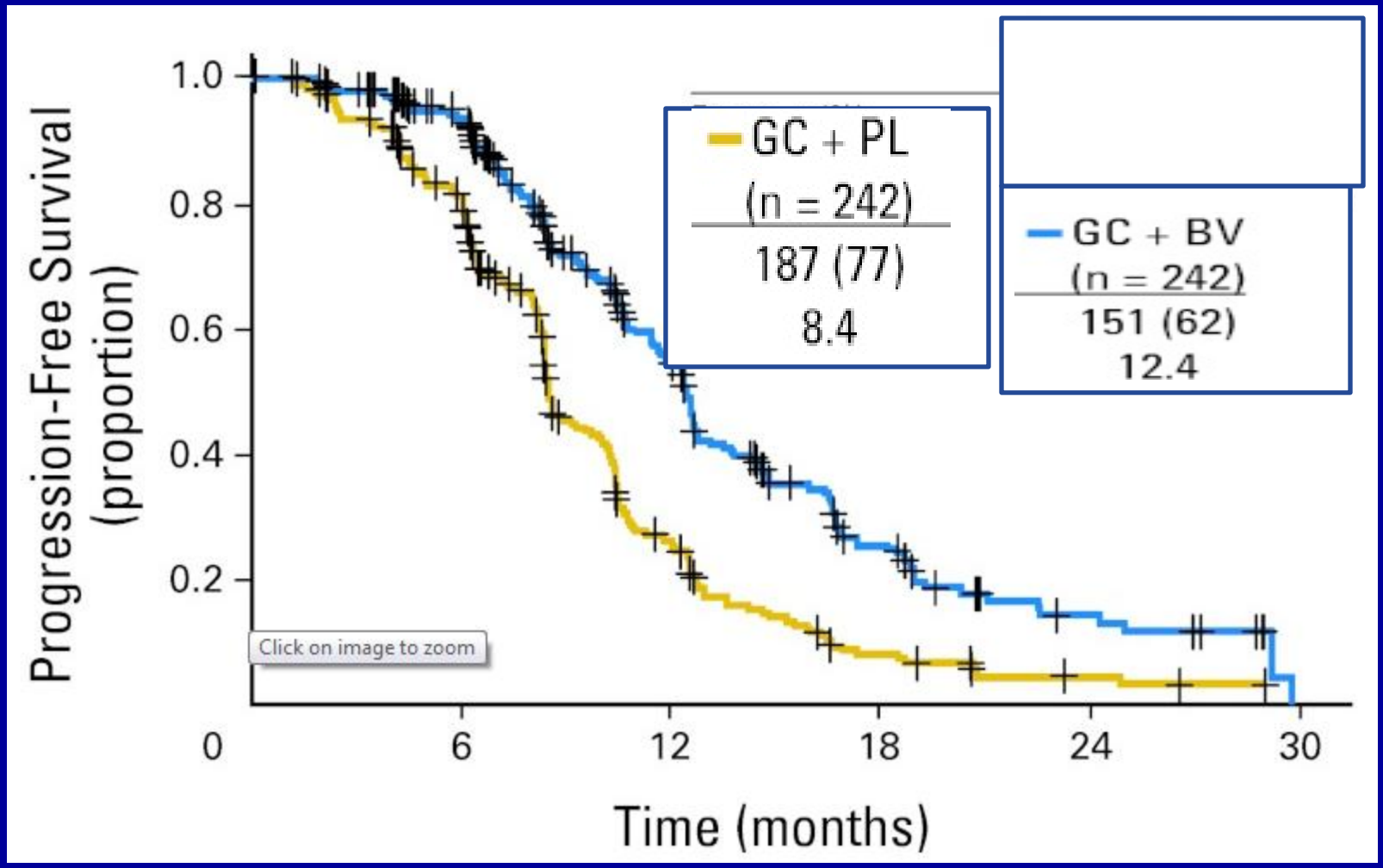
Aghajanian C[1], Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR.

484 patients disease recurrence 6 months

GC (gemcitabine 1000 mg/mq gg1-8 + Carboplatin AUC 4 g1) plus either BV (bevacizumab 15 mg/kg) or placebo (PL) for six to 10 cycles.

median PFS was 12.4 v 8.4 months, respectively.

GC plus BV followed by BV until progression resulted in a statistically significant improvement in PFS compared with GC plus PL in platinum-sensitive ROC.


Progression-Free Survival (proportion)
1.0
0.8
0.6
0.4
0.2
0
6
12
18
24
30
Time (months)
GC + PL
(n = 242)
187 (77)
8.4
GC + BV
(n = 242)
151 (62)
12.4
Click on image to zoom

Oceans

J Clin Oncol. 2014 May 1;32(13):1302-8.

Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial.

Pujade-Lauraine E[1], Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I.

After investigators selected chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone.

The primary end point was progression-free survival (PFS) by RECIST. Secondary end points included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes.

Median PFS was 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy.

ORR was 11.8% versus 27.3%