Associazione Italiana di Oncologia Medica

IL CARCINOMA AVANZATO DELLA CERVICE

Claudia Marchetti
Pierluigi Benedetti Panici
Dipartimento di Scienze Ginecologico-ostetriche e Scienze Urologiche, Policlinico Umberto I, "Sapienza" Università di Roma

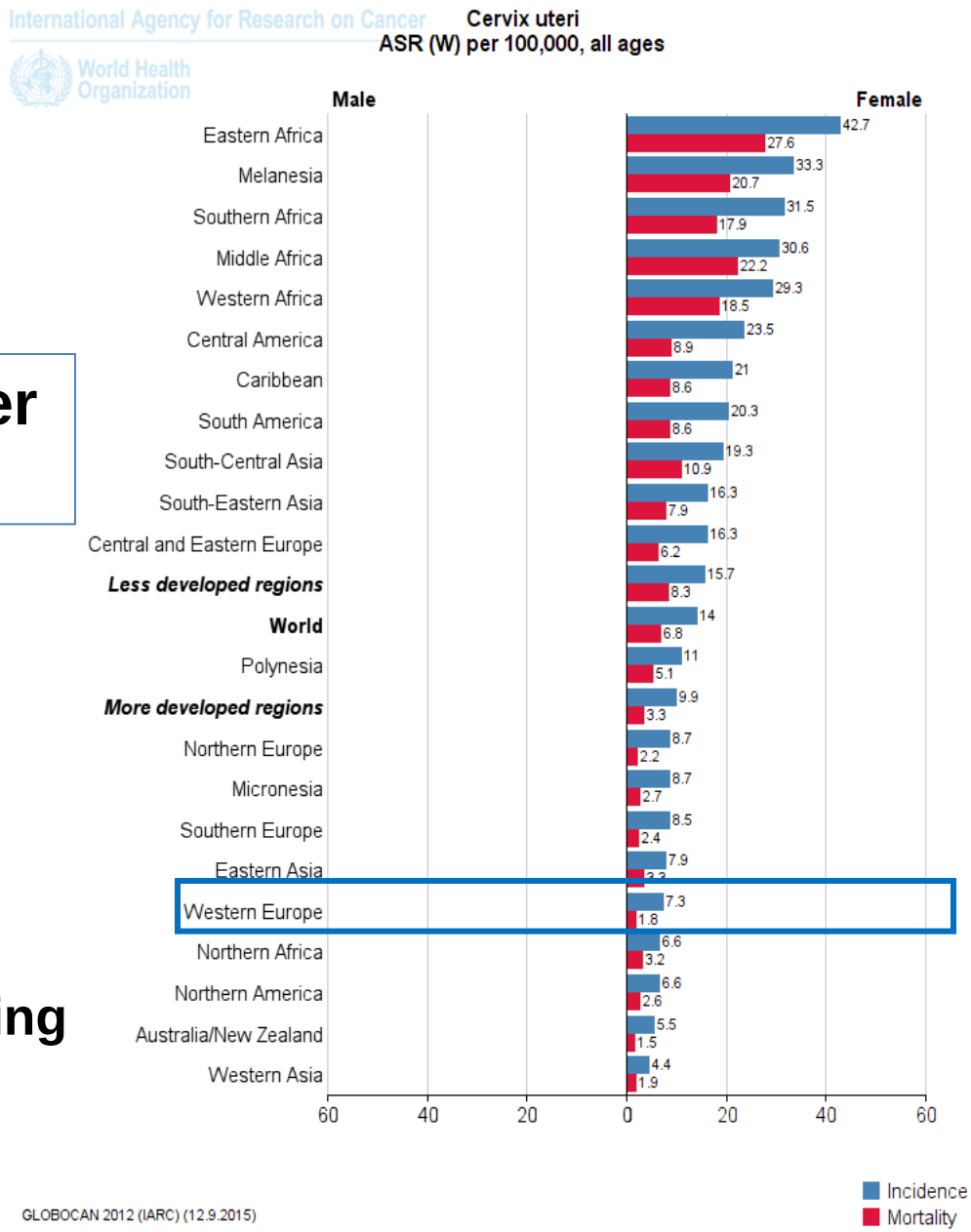
EPIDEMIOLOGY

The Global Burden of Cancer to Women Worldwide

9% of all new cancer cases

8% of total cancer deaths

85% of deaths occur in developing countries



TREATMENT

33.7% Early	62.4% Locally Advanced	2.7% Metastatic Disease
EARLY STAGES	**LOCALLY ADVANCED STAGES**	**ADVANCED/META STATIC DISEASE**
STADIO IA1-IA2-IB1	**STADIO IB2-IIA-III-IVA**	**STADIO IVB**
RS or RT	?	?

TREATMENT

33.7%
Early

EARLY STAGES

STADIO
IA1-IA2-IB1

RS or RT

62.4%
Locally Advanced

LOCALLY ADVANCED STAGES

STADIO
IB2-IIA-III-IVA

?

2.7%
Metastatic Disease

ADVANCED/META STATIC DISEASE

STADIO
IVB

?

TREATMENT

33.7%
Early

EARLY STAGES

STADIO IA1-IA2-IB1

RS or RT

62.4%
Locally Advanced

LOCALLY ADVANCED STAGES

STADIO IB2-IIA-III-IVA

?

2.7%
Metastatic Disease

ADVANCED/META STATIC DISEASE

STADIO IVB

?

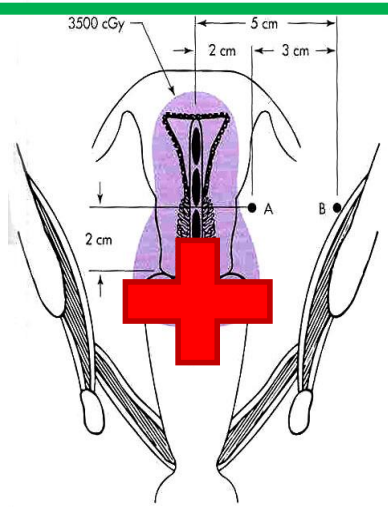
STANDARD THERAPY FOR STAGE IB2-IVA

The New England Journal of Medicine

CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

PETER G. ROSE, M.D., BRIAN N. BUNDY, PH.D., EDWIN B. WATKINS, M.D., J. TATE THIGPEN, M.D., GUNTHER DEPPE, M.D., MITCHELL A. MAIMAN, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND SAM INSALACO, M.D.

CT-RT



EXTERNAL BEAM
pelvic
radiation(40 to 60 Gy)

BRACHYTHERAPY
(8,000 to 8,500 cGy
to Point A)

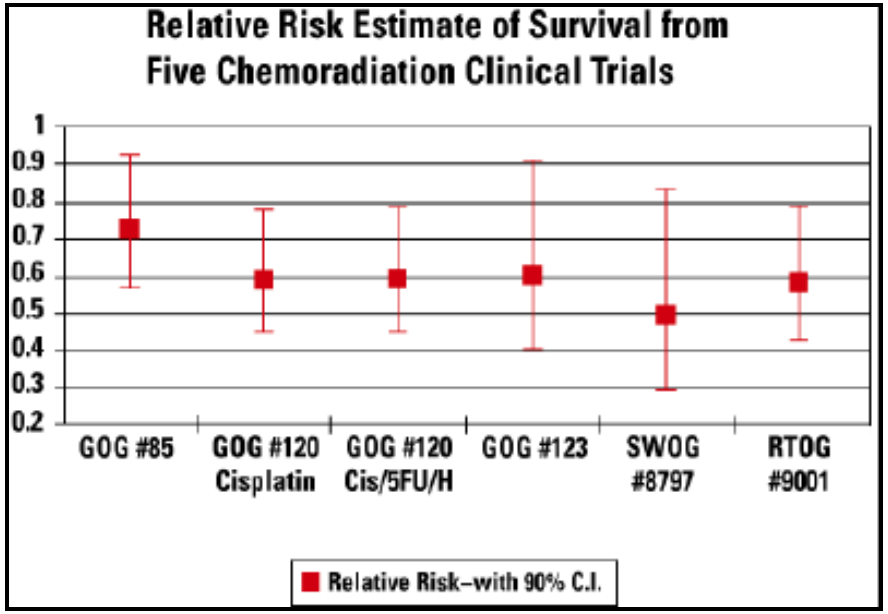
I.V. CISPLATIN CHEMOTHERAPY
Cisplatin 40mg/m2 (Max dose 70mg)
IV q wk during RT (6wks)

GOG 120 Rose PG et al. NEJM 1999 *Monk et al J Clin Oncol. 2007*

CHEMORADIATION IS CONSIDERED THE WORLD STANDARD TREATMENT FOR LACC

Feb-1999: NCI issues clinical announcement on cervical cancer

1. **reduction in the risk of death (HR 0.69, 95% CI 0.61-0.77**
2. **reduction in the risk of local recurrence OR 0.59, 95% CI 0.50-0.69)**
3. **Trend in reduction distant metastasis (OR 0.81, 95% CI 0.65-1.01).**



Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

WHAT COMBINATIONS IN CTRT

Table 2. Results of Trial Group Analyses for Survival

Variable	Main Analysis (13 trials) HR	95% CI	Interaction *P*
Planned chemotherapy type			
Platinum based	0.84	0.72 to 0.98	
Nonplatinum based	0.76	0.62 to 0.94	.48
Planned radiotherapy dose			
≥ 45 Gy + BRT	0.78	0.68 to 0.89	
< 45 Gy + BRT	0.93	0.70 to 1.24	.26
Planned radiotherapy duration, weeks			
≤ 8	0.83	0.72 to 0.96	
> 8	0.73	0.57 to 0.93	.35
Planned chemotherapy cycle length, weeks*			
≤ 1	0.74	0.60 to 0.92	
> 1	0.95	0.72 to 1.25	.16
Planned cisplatin dose-intensity, mg/m²/wk*			
≤ 25	0.93	0.70 to 1.24	
> 25	0.76	0.62 to 0.96	.25
Cisplatin regimen*			
Single agent	0.76	0.62 to 0.93	
Combination	0.93	0.70 to 1.24	.25
Chemotherapy regimen			
Single agent	0.75	0.63 to 0.88	
Combination	0.86	0.71 to 1.04	.29

NOTE. Two trials in which additional adjuvant chemotherapy was administered on the treatment arm are excluded.
*Results are based only on trials in which cisplatin-based chemoradiation was administered.

To date, no chemotherapy regimen has been found to be superior to 40 mg/m2 of cisplatin weekly. However, the meta-analysis does suggest that substituting other agents that have demonstrated efficacy such as carboplatin or 5-flurouracil (5-FU) should be considered for women with a contraindication to cisplatin.

WHICH COMBINATION OF CTRT?

ASCO
American Society of Clinical Oncology

Munetaka Takekuma et al, ASCO 2015

68 PTS

Pts characteristics
• FIGO STAGE III-IVA • NO PARA-AORTIC LYNPHADENOPATHY

RT (external beam whole pelvic RT and HDR-ICBT) 62-65 Gy

+

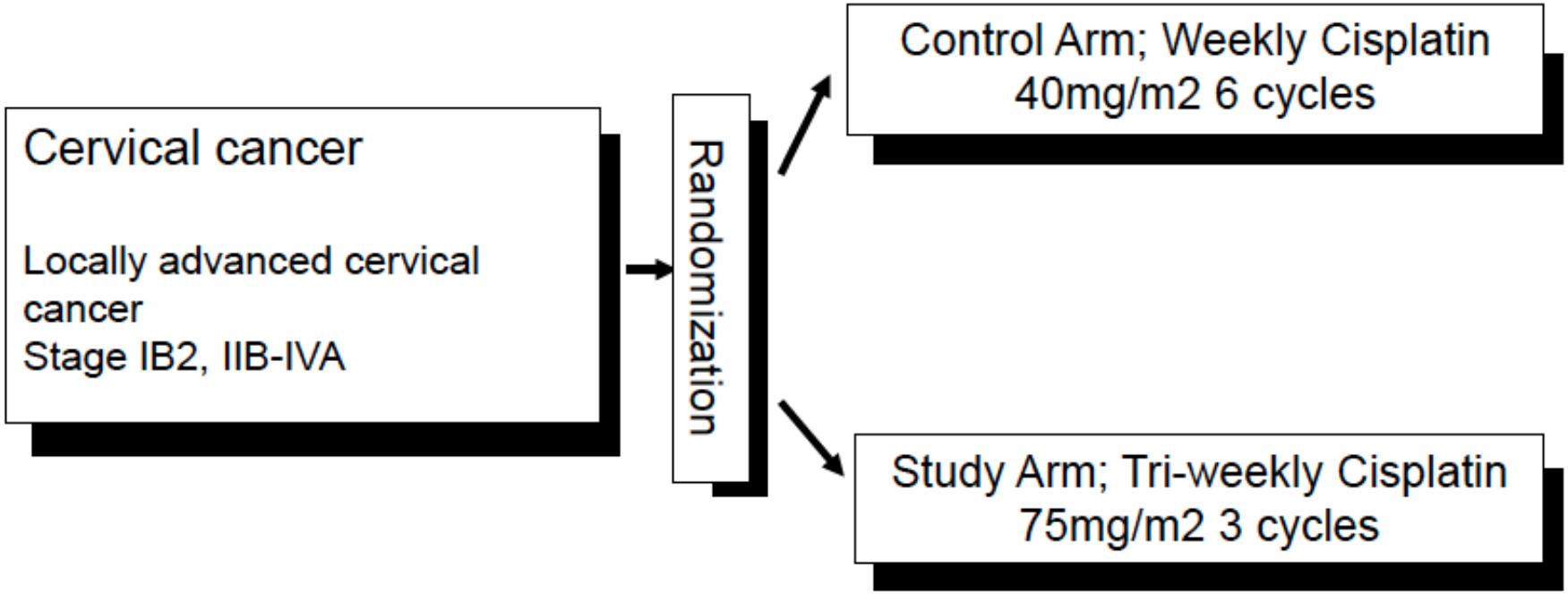
CDDP 30 mg/mq + PTX 50 mg/mq weekly for 5 courses.

CR	76.5 %
2 YRS PFS	83.8%
2 YRS OS	92.7%

CONCURRENT CHEMORADIOTHERAPY WITH WEEKLY CDDP/PTX FOR LOCALLY ADVANCED CERVICAL CANCER DEMONSTRATED FAVORABLE ANTITUMOR ACTIVITY, AND IS FEASIBLE AND

TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)



CTRT IS REALLY THE BEST OPTION?

ACUTE GRADE 3-4 AND LIFE THREATENING →

- **HAEMATOLOGICAL 19%**
- **GASTROINTESTINAL 9%**

LATE GRADE 3-4 →

- **UP TO 22% URINARY OR INTESTINAL**
- **UP TO 80% SEXUAL PROBLEMS**

RECURRENCE OF DISEASE →

- **20-30% LOCAL FAILURE**
- **18-25% DISTANT FAILURE**

…and more… →

- **DO NOT ALLOW ACCURATE STAGING OF THE DISEASE**
- **FERTILITY REDUCTION**

Green J, Lancet 2001
Tan L Clin Oncol (R Coll Radiol) 2008

OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation

Chemoradiation With Concomitant Boosts Followed by Radical Surgery in Locally Advanced Cervical Cancer: Long-term Results of the ROMA-2 Prospective Phase 2 Study

International Journal of Radiation Oncology biology • physics

Accrual: 103 pts

Eligibility

- Cervix carcinoma stage IB2-IVA
- Age<80y
- Adequate bone marrow function
- Adequate renal function
- Normal liver function

T

RT

39.6 GY(PELVIC LYMPH NODE DRAINAGE, BULKY TUMOR,PARAMETRIA) + 10.8 GY(PRIMARY TUMOR,PARAMETRIA)

+

CT

CISPLATIN 20 MG/M2 P1Q25+CAPECITABINE 1300 MG/M2 DAILY

+

RADICAL HYSYTER ECTOMY

TOXICITY

-Leukopenia	19.4% G1
	19.4% G2
-Gastrointestinal	32% G1
	9.7% G2
-Genitourinary	11.6% G1
	2.9% G2

Clinical Response

-CR 36 pt(34.9%)
-PR 63 pt(61.2%)
-SD 2 pt(1.9%)
-PD 2 pt(1.9%)

DFS 73%
OS 86.1%

3 years

RELAPSE 25 pt(24.3%)
DEATH 10 pt(9.7%)

Ferrandina et al. Int J Radiat Oncol Biol Phys 2014

SURGERY AFTER CTRT YES OR NO?

The Oncologist®

Gynecologic Oncology

Results of the GYNECO 02 Study, an FNCLCC Phase III Trial Comparing Hysterectomy with No Hysterectomy in Patients with a (Clinical and Radiological) Complete Response After Chemoradiation Therapy for Stage IB2 or II Cervical Cancer

Philippe Morice,[a,o,p] Philippe Rouanet,[d] Annie Rey,[b] Pascale Romestaing,[e] Gilles Houvenaeghel,[f] Jean Charles Boulanger,[g] Jean Leveque,[h] Didier Cowen,[i] Patrice Mathevet,[j] Jean Pierre Malhaire,[k] Guillaume Magnin,[l] Eric Fondrinier,[m] Jocelyne Berille,[n] Christine Haie-Meder[c]

[a]Department of Gynecologic Surgery, [b]Department of Biostatistics, and [c]Department of Radiation Therapy, Institut Gustave Roussy, Villejuif, France; [d]Centre Val d'Aurelle, Montpellier, France; [e]Groupe Hospitalier Lyon-Sud, Pierre-Benite, France; [f]Institut Paoli Calmette, Marseille, France; [g]Centre Hospitalo-Universitaire, Amiens, France; [h]Centre Eugene Marquis, Rennes, France; [i]Centre Hospitalier La Timone, Marseille, France; [j]Hôpital Edouard Herriot, Lyon, France; [k]Centre Hospitalier Universitaire de Brest, Brest, France; [l]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [m]Centre Paul Papin, Angers, France; [n]Fédération Nationale des Centres de Lutte Contre le Cancer, Paris France; [o]University Paris Sud, Le Kremlin-Bicêtre, France; [p]Unit INSERM 30–10, Villejuif, France

Annals of Oncology

original articles

Annals of Oncology 24: 2043–2047, 2013
doi:10.1093/annonc/mdt142
Published online 21 April 2013

Brachytherapy versus radical hysterectomy after external beam chemoradiation with gemcitabine plus cisplatin: a randomized, phase III study in IB2–IIB cervical cancer patients

L. Cetina[1], A. González-Enciso[2], D. Cantú[1], J. Coronel[1], D. Pérez-Montiel[3], J. Hinojosa[4], A. Serrano[1], L. Rivera[4], A. Poitevin[4], A. Mota[4], E. Trejo[4], G. Montalvo[2], D. Muñoz[2], J. Robles-Flores[2], J. de la Garza[1], J. Chanona[3], R. Jiménez-Lima[1], T. Wegman[1] & A. Dueñas-González[5*]

[1]*Division of Clinical Research; Departments of* [2]*Gynecology;* [3]*Pathology;* [4]*Radiotherapy, National Cancer Institute, Mexico;* [5]*Unit of Biomedical Research on Cancer, Institute of Biomedical Research, National Autonomous University of Mexico/National Cancer Institute, Mexico City, Mexico*

- **Trial closed for poor accrual**
- **No difference OS between surgery vs no surgery after CTRT**

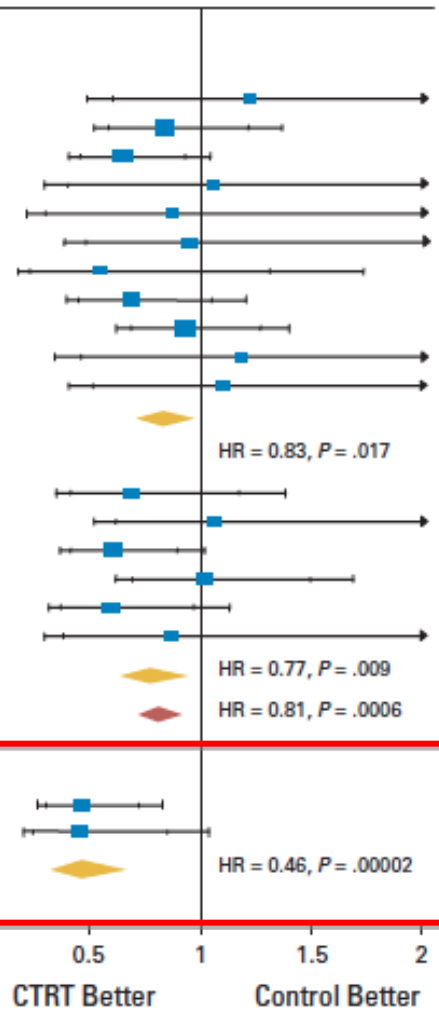
- **This study failed to demonstrate that RH after EBRT-CT is superior to standard BCT**

OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation

HOW CAN WE REDUCE DISTANT FAILURES?

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[6,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10



- Improved survival in the 2 trials that gave 2 cycles of additional CT
- Might treat micrometastasis and improve OS
- Absolute 5 yrs OS benefit of 19%

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008

JOURNAL OF CLINICAL ONCOLOGY

Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

Accrual: 515 pts

Eligibility

Cervix carcinoma stage IIB-IVA

Para-aortic lymph nodes neg

T

I linea

Cis 40 mg/mq+
Gem 125mg/mq+
RT 50.4 Gy+BCT

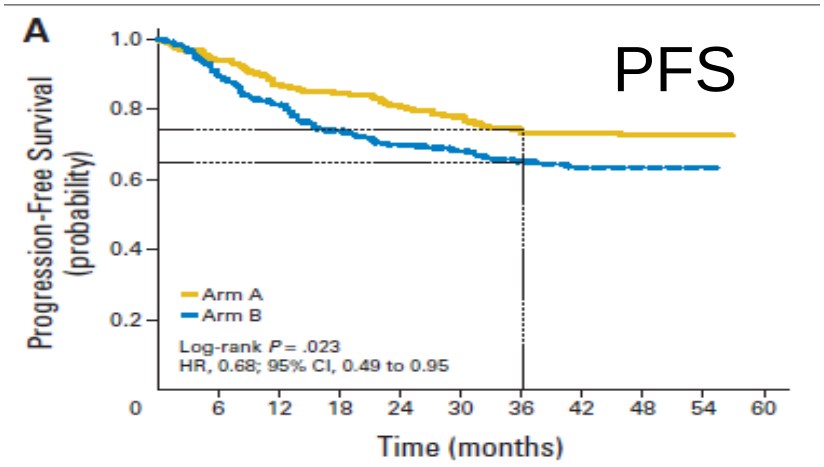
+

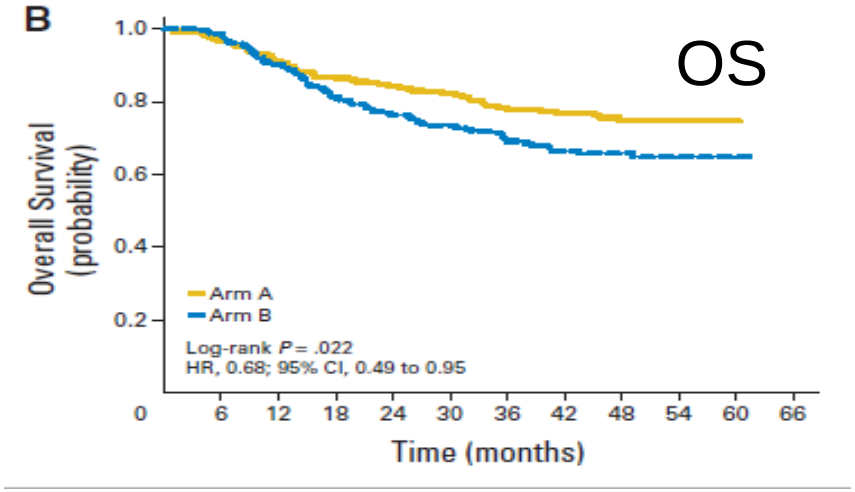
Tp adiuvante

Cis 50 mg/mq p1q21+
Gem 1000 mg/mq
p1,8q21

Cis 40 mg/mq+
RT 50.4 Gy+BCT

	Cis	Cis+Gem
3 y PFS	65%	74.4%





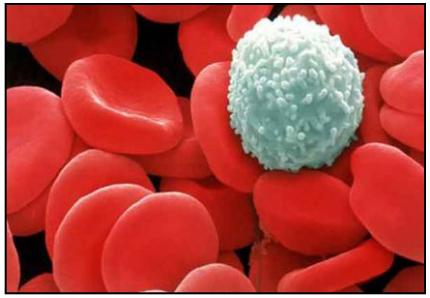
P:0.029

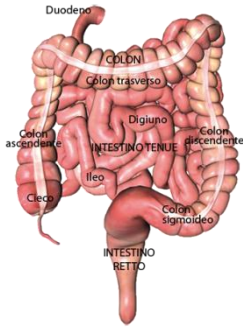
Dueñas-Gonzalez A, et al. J Clin Oncol.2011

TOXICITY

A. More grade 3-4 **adverse events**:

- More hematological toxicity,mainly neutropenia (51% vs 5.9%)
- More vomiting (7.7% vs 2.8%) and diarrhea (17% vs 4.7%)
- Late Grade 4 GI toxicity (2.4% vs 0%)





B. **3 deaths** in the first 30 days, 2 related with CT-RT in Arm A

C. More **discontinuations** in arm A than in arm B(p 0.001)

- 14% of pts did not receive 1° adj
- 24% of pts did not receive 2° adj

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP

OUTBACK trial: randomized phase III study

Patients with stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer who have given informed consent

↓

Eligible patients

↓

RANDOMISE

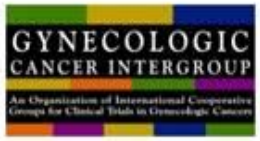
↓ Max 6 weeks ↓

Arm A – Control Arm
Concurrent chemoradiation

Arm B – Intervention Arm
Concurrent chemoradiation followed by 4 cycles of Carboplatin/Paclitaxel

↓ ↓

Follow up for a minimum of 3 years



OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation

NACT: AIMS

- ✓ DEBULKING EFFECT AND TUMOR SIZE REDUCTION
- ✓ IMPROVING SURGICAL OUTCOMES
- ✓ BETTER ACTIVITY AGAINST MICROMETASTASIS
- ✓ PERMIT CONSERVATIVE SURGERY
- ✓ LESS TOXICITY
- ✓ EASIER MANAGEMENT OF SALVAGE THERAPY

OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation

NACT & RS vs RT

Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration*,[1]

- 5 randomized trials
- 872 pts (97% of total)
- Stage:
  - IB 35%
  - II 38%
  - III 26%

Analysis 2.1. Comparison 2 Treatment comparison 2, Outcome 1 Survival.

Review: Neoadjuvant chemotherapy for locally advanced cervix cancer

Comparison: 2 Treatment comparison 2

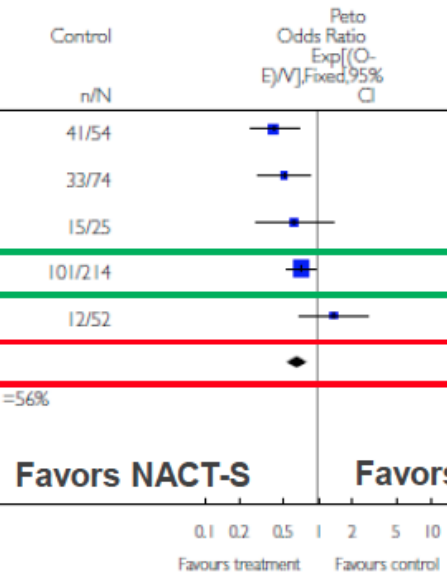
Outcome: 1 Survival

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Sardi 1996	25/53	41/54		17.4 %	0.41 [0.25, 0.68]
Sardi 1998	22/80	33/74		14.8 %	0.50 [0.29, 0.85]
Kigawa 1996	10/25	15/25		6.9 %	0.62 [0.28, 1.35]
Benedetti 2002	88/227	101/214		51.8 %	0.71 [0.54, 0.95]
Chang 2000	21/68	12/52		9.0 %	1.38 [0.69, 2.74]
Total (95% CI)				**100.0 %**	**0.65 [0.53, 0.80]**

Heterogeneity: $Chi^2 = 9.18$, df = 4 (P = 0.06); $I^2 = 56\%$

Test for overall effect: Z = 4.13 (P = 0.000036)

Test for subgroup differences: Not applicable



Tierney et al. Eur J Cancer 2003

NACT & RS vs RS

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer (Review)

- **Better OS and PFS for NACT/RS vs RS**
- **Fewer local recurrences**
- **Fewer distant recurrences**
- **More radical resections**
- **Less N+**
- **Less parametrial involvement**

THE COCHRANE COLLABORATION®

Analysis 1.1. Comparison 1 Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 1 Overall survival (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: 1 Neoadjuvant chemotherapy plus surgery versus surgery alone

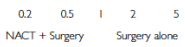
Outcome: 1 Overall survival (fixed-effect analysis)

Study or subgroup	NACT + Surgery N	Surgery alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Sardi 1997	104	106	-0.63 (0.28)		15.8 %	0.53 [0.31, 0.92]
Napolitano 2003	106	86	-0.17 (0.26)		18.3 %	0.84 [0.51, 1.40]
Cai 2006 (1)	52	54	-0.44 (0.32)		12.1 %	0.64 [0.34, 1.21]
Katsumata 2006	67	67	0.11 (0.35)		10.1 %	1.12 [0.56, 2.22]
Eddy 2007	145	143	0.01 (0.2)		30.9 %	1.01 [0.68, 1.49]
Chen 2008	71	70	-0.67 (0.31)		12.9 %	0.51 [0.28, 0.94]
Total (95% CI)	**545**	**526**			**100.0 %**	**0.77 [0.62, 0.96]**

Heterogeneity: $Chi^2 = 6.87$, df = 5 (P = 0.23); $I^2 = 27\%$

Test for overall effect: Z = 2.30 (P = 0.022)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 3 Progression-free survival (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: 1 Neoadjuvant chemotherapy plus surgery versus surgery alone

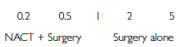
Outcome: 3 Progression-free survival (fixed-effect analysis)

Study or subgroup	NACT + Surgery N	Surgery alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Sardi 1997	104	106	-0.63 (0.28)		14.8 %	0.53 [0.31, 0.92]
Napolitano 2003	86	70	-0.63 (0.29)		13.8 %	0.53 [0.30, 0.94]
Cai 2006 (1)	52	54	-0.47 (0.34)		10.0 %	0.63 [0.32, 1.22]
Katsumata 2006	67	67	0.06 (0.29)		13.8 %	1.06 [0.60, 1.87]
Eddy 2007	145	143	-0.002 (0.18)		35.7 %	1.00 [0.70, 1.42]
Chen 2008	68	65	-0.56 (0.31)		12.0 %	0.57 [0.31, 1.05]
Total (95% CI)	**522**	**505**			**100.0 %**	**0.75 [0.61, 0.93]**

Heterogeneity: $Chi^2 = 7.90$, df = 5 (P = 0.16); $I^2 = 37\%$

Test for overall effect: Z = 2.66 (P = 0.0077)

Test for subgroup differences: Not applicable



Rydzewska L et al. Cochrane Database Syst Rev 2012

EORTC 55994

INCLUSION CRITERIA
- FIGO IB2, IIA, IIB
- PS 0-2
- Age 18-75
- Squamous
- Adenocarcinoma
- Adenosquamous

STRATIFICATION
- FIGO
- Institution
- Age 18-50 vs 50-75
- Histology:
  - Squamous vs
  - Adenocarcinoma vs
  - Adenosquamous

ENDPOINTS
- Primary: OS
- Secondary:
  - PFS
  - Toxicity
  - QoL

RANDOM

Cisplatin based chemotherapy:
- ✓Min. total dose of 225 mg/mq
- ✓25 mg/mq per week
- ✓Final dose no later than 8° week

→ Radical hysterectomy

Chemo-radiotherapy
- CDDP 40 mg/mq (6 week) + EBRT 45-50 Gy

Randomized Trial of Neoadjuvant Chemotherapy Comparing Paclitaxel, Ifosfamide, and Cisplatin With Ifosfamide and Cisplatin Followed by Radical Surgery in Patients With Locally Advanced Squamous Cell Cervical Carcinoma: The SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study

Alessandro Buda, Roldano Fossati, Nicoletta Colombo, Francesca Fei, Irene Floriani, Desiderio Gueli Alletti, Dionyssios Katsaros, Fabio Landoni, Andrea Lissoni, Carmine Malzoni, Enrico Sartori, Paolo Scollo, Valter Torri, Paolo Zola, and Costantino Mangioni

A phase II, randomized trial of neo-adjuvant chemotherapy comparing a three-drug combination of paclitaxel, ifosfamide, and cisplatin (TIP) versus paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the Snap-02 Italian Collaborative Study

A. A. Lissoni[1], N. Colombo[2], A. Pellegrino[1], G. Parma[2], P. Zola[3], D. Katsaros[4], S. Chiari[1], A. Buda[1], F. Landoni[2], M. Peiretti[2], T. Dell'Anna[1], R. Fruscio[1], M. Signorelli[1], R. Grassi[5], I. Floriani[6], R. Fossati[6*], V. Torri[6] & E. Rulli[6]

FIGO IB2-IVA

R

IP
IFO 5 g/mq
CDDP 75 mg/m

TIP
IFO 5 g/mq

TIP more active but more toxic

FIGO IB2-IVA

R

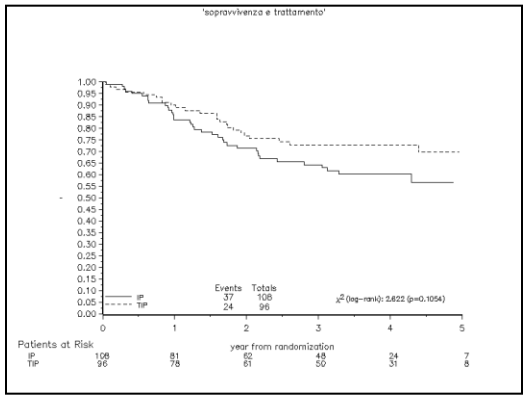
TP
Paclitaxe 175 mg/mq

TIP
IFO 5 g/mq
DP 75 mg/mq
axe 175 mg/mq

TIP seems to be the best combination but it is more toxic

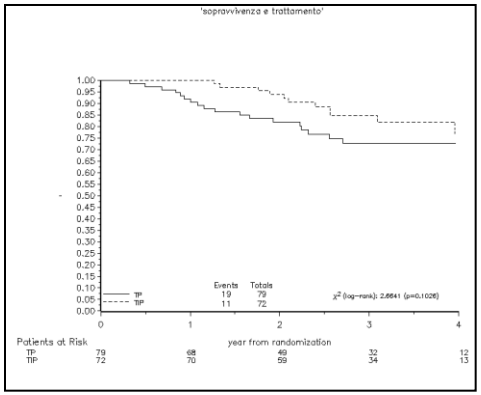
SNAP 01: IP vs TIP
Optimal response:
23% vs 48%

SNAP 02: TP vs TIP
Optimal response:
27% vs 42%



5yrsOS: 78%

Buda A et al 2005
Lissoni AA et al 2009



WHICH TYPE OF NACT?
Our experience

Op rate 81-100%
CR= 10%, PR= 67% SD 19% PD 4%
RR cumulativo circa 77%

	PTS N°	PTS FIGO STAGE	NACT SCHEDULE
Ob Gyn 1988	33	IB-IIIB	CIS+BLEO+MTX
Cancer 1991	75	IB-IIIB	CIS+BLEO+MTX
Gynecol Oncol 1996	42	Ib2-IIIb (adenok)	CBM, CB, CE
Eur J Cancer 1998	130	Ib2-III	CDDP/BLEO/MTX
JCO 2002	210	IB2-IIIB	CDDP-BASED
Ann surg oncol 2007	18	IVa	CDDP/Pacl
Gynecol Oncol 2011	46	IB2-IIIB	TOPO+CIS
Oncology 2015	22	IB2-IIIB	CDDP +TXL DD

OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation

A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer

46 pts

Pts characteristics
Locally advanced cervical cancer (stage IB2-IVA)
Squamous, adeno- or adenosquamous carcinoma
Age >18y
ECOG 0-1
Adequate bone marrow function
Adequate renal function
Normal liver function

NACT
CARBOPLATIN (AUC2) +PACLITAXEL 80 MG/M2 WEEKLY FPR 6 CYCLES

+

CRT
40Mg/Mq OF WEEKLY CISPLATIN + 50.4 GY IN 28 FRACTIONS PLUS BRACHYTHERAPY

Clinical Response
(12 weeks after NACT)

-CR 2 pt(4%)
-PR 30 pt(65%)
-SD 10 pt(22%)
-PD 2 pt(4%)
- No data 2 pt (4%)

Response
After 12 weeks post all treatments)

-CR 29 pt(63%)
-PR 10 pt(22%)
-SD 2 pt(4%)
-PD 2 pt(4%)
- No data 3 pt (7%)

Al tempo dell'analisi 14 erano morti e 4 avevano progredito

5 YRS PFS 68%
5 YRS OS 67%

RR: 39%

McCormack et al. Br J Cancer 2013

INTERLACE - Phase 3 trial

Randomize

Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6

Standard CRT

Weeks 7 – 13 Standard CRT

Standard CRT : 40—50.4Gy in 20-28 fractions plus Intracavity brachytherapy to give min total EQD2 dose of 74-80Gy to point A/volume.
Weekly cisplatin 40mg/m² x 6 weeks

Follow-up
3 monthly for 2 years; 6 monthly for 3 years

TREATMENTS IN LACC

- **Chemo/radiation**
- **Chemo/radiation followed by surgery**
- **Chemo/radiation-chemotherapy**
- **Neoadjuvant chemotherapy followed by chemo/radiation**
- **Neoadjuvant chemotherapy followed by surgery**

TREATMENTS IN LACC

- **Chemo/radiation**
- **Chemo/radiation followed by surgery**
- **Chemo/radiation-chemotherapy**
- **Neoadjuvant chemotherapy followed by chemo/radiation**
- **Neoadjuvant chemotherapy followed by surgery**

CHEMOTHERAPY IS MANDATORY!

TREATMENT

33.7%
Early

EARLY STAGES

STADIO
IA1-IA2-IB1

RS or RT

62.4%
Locally Advanced

LOCALLY ADVANCED STAGES

STADIO
IB2-IIA-III-IVA

?

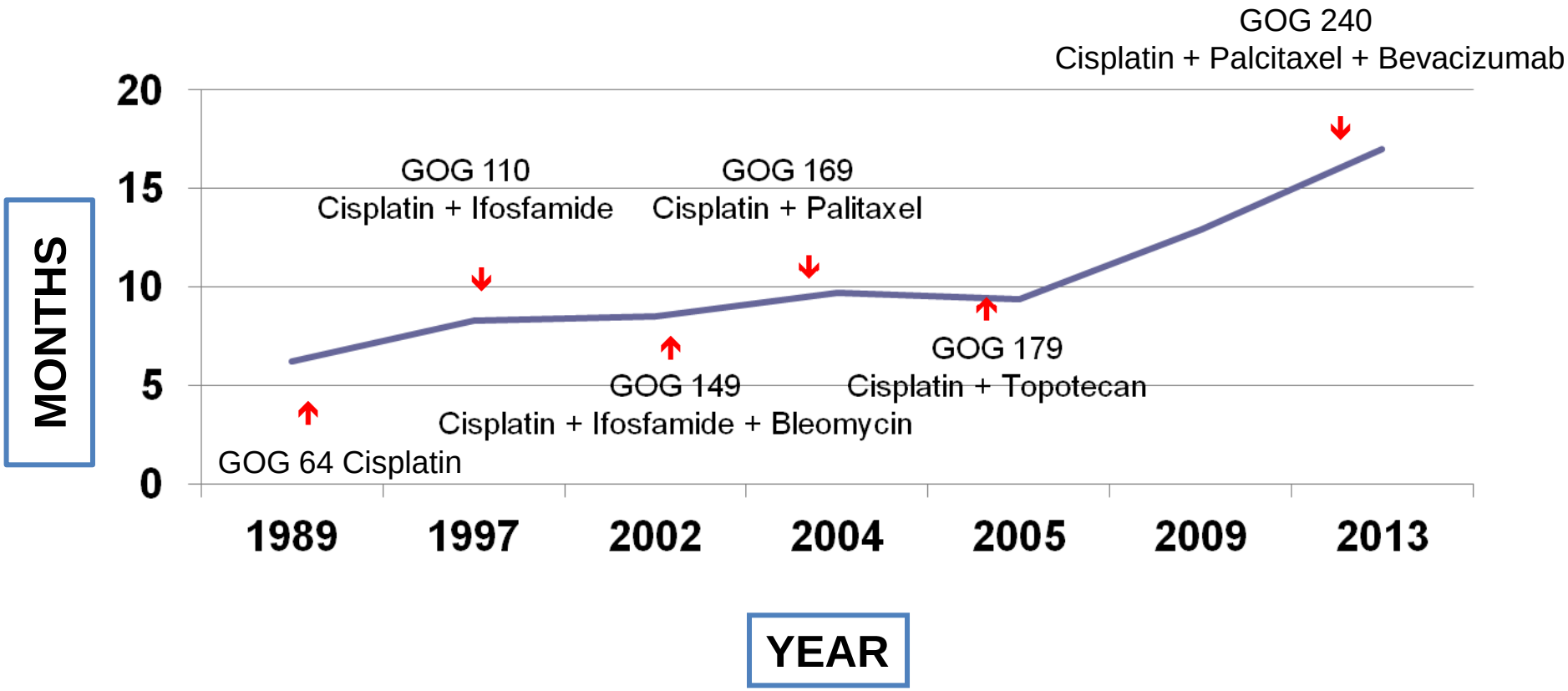
2.7%
Metastatic Disease

ADVANCED/META STATIC DISEASE

STADIO
IVB

?

PROGRESS IN SURVIVAL IN ADVANCED AND RECURRENT CERVICAL CANCER



KEY QUESTIONS

WHICH Platinum doublet?

Carboplatin or cisplatin?

Nonplatinum doublet?

Which role for TARGET THERAPY in CC?

KEY QUESTIONS

WHICH Platinum doublet?

WHICH PLATINUM DOUBLET?

GOG 204

Primary Stage IVB or recurrent/persistent carcinoma of the cervix

- measurable disease
- GOG performance status 0-1
- ANC ≥ 1500/µl
- platelets ≥100,000/µl
- serum creatinine ≤ 1.5 mg/dl
- no CNS disease
- no past or concomitant invasive cancer
- no prior chemotherapy (unless concurrent with radiation)

RANDOMIZE

Regimen 1
Paclitaxel 135 mg/m2 + CDDP 50 mg/m2 p1q 21

Regimen 2
Vinorelbina 30 mg/m2 + CDDP 50 mg/m2 p1q 21

Regimen 3
Gemcitabine 1000 mg/m2 p1,8q 21+
CDDP 50 mg/m2 p1q 21

Regimen 4
Topotecan 0.75 mg/m2 p1,2,3q 21+
CDDP 50 mg/m2 p1q 21

ALL REGIMENS

Quality of life Assessment:
Baseline
Before cycle 2
Before cycle 5
9 mo. after study entry at follow-up visit

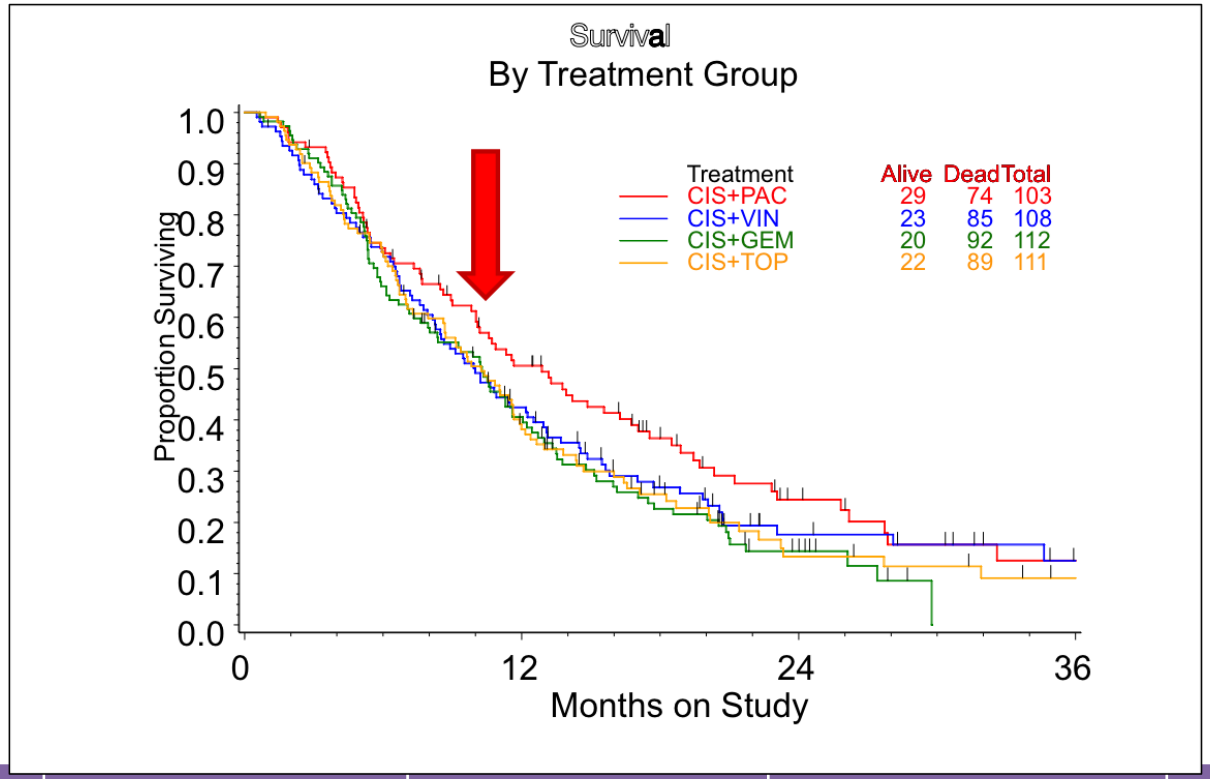
BJ Monk et al 2009

GOG 204

Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study

Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda, and David Cella

From the University of California, Irvine.



JCO, 2009

	Cis+tax		Cis+Vin		Cis+Gem		Cis+Top	
	n	%	n	%	n	%	n	%
Responders	30	29.1	28	25.9	25	22.3	26	23.4
CR	3	2.9	8	7.4	1	0.9	2	1.8
PR	27	26.2	20	18.5	24	21.4	24	21.6
Non responder	73	70.9	80	74.1	87	77.7	85	76.6
Total	103		108		112		111	

KEY QUESTIONS

WHICH Platinum doublet?

Carboplatin or cisplatin?

CARBOPLATIN OR CISPLATIN?

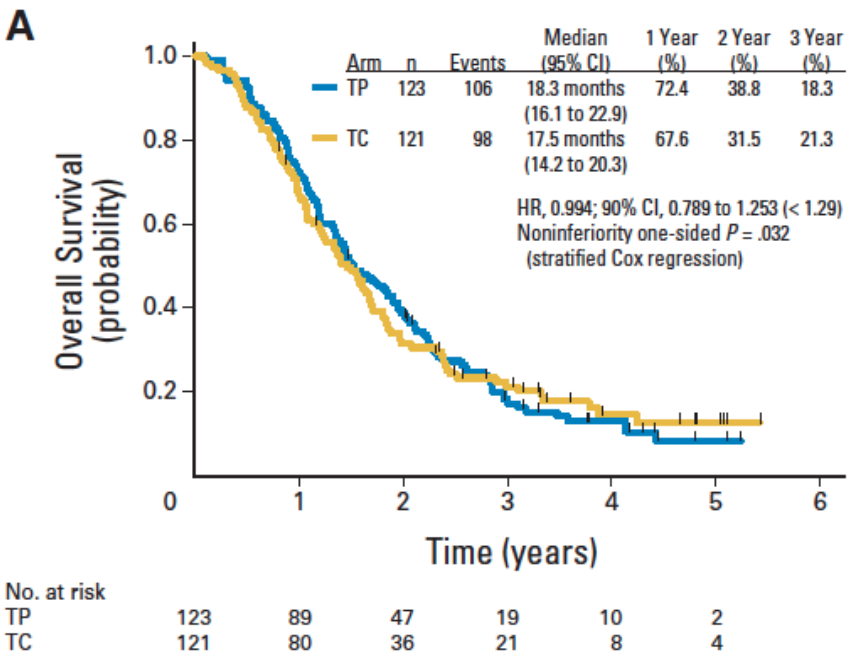
Accrual: 253 pts

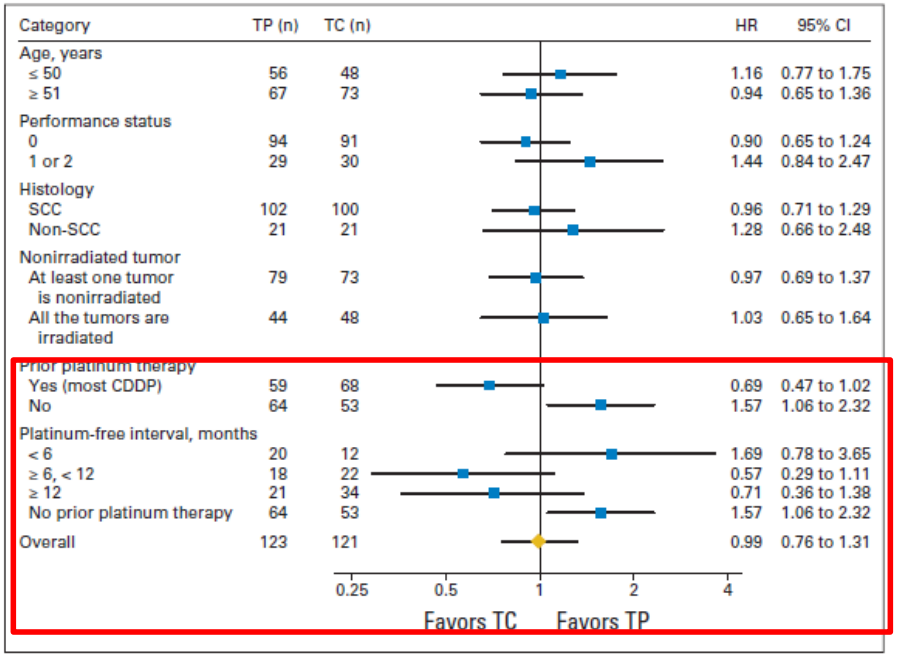
R

TP
Tax135 mg/m2
p1q21+Cis 50 mg/m2
p2q21

TC
Tax175 mg/m2+AUC5
p1q21

TOXICITY	Cis(%)	Car(%)
Neutropenia	85.5	76.2
Febril neutropenia	16	7.1
Anemia	31.2	44.4
Other GI	6.4	3.2
Fatigue	4	7.9
Neuropathy	0	4.8





Kitagawa R et al. J Clin Onc 2015

KEY QUESTIONS

WHICH Platinum doublet?

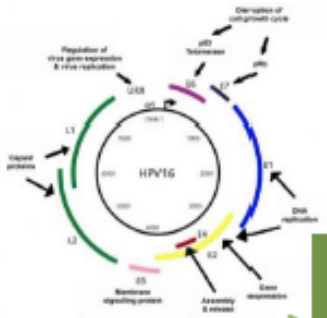
Carboplatin or cisplatin?

Nonplatinum doublet?

Which role for TARGET THERAPY in CC?

Mechanistics

Tumor Hypoxia and Viral Oncogenes Drive Angiogenesis



HPV E6 → p53 degradation → ↑ TSP-1 → ↑ VEGF → ↑ angiogenesis

Anti-VEGF therapy

HPV E7 → Displacement of HDAC1, HDAC4, HDAC7 → ↑ HIF1α

HPV E7 → pRb inactivation → p21-Rb pathway dysregulation

Bevacizumab activity in cervical cancer was demonstrated in a phase II single-agent study (GOG 227C)

GOG-240

GOG Gynecologic Oncology Group

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

Accrual: 452 pts

Eligibility

Metastatic, persistent o recurrent CC

No candidate for curative therapy

R

- Cisplatin 50 mg/m2+Paclitaxel 135/175mg/m2 p1q21
- Cisplatin 50 mg/m2+Paclitaxel 135/175mg/m2 +BEVA 15 mg/Kgp1q21
- Topotecan 0.7 mg/m2 p1,2,3q21+Paclitaxel 175mg/m2 p1q21
- Topotecan 0.7 mg/m2 p1,2,3q21+Paclitaxel 175mg/m2 p1q21+ BEVA 15 mg/kg p1q21

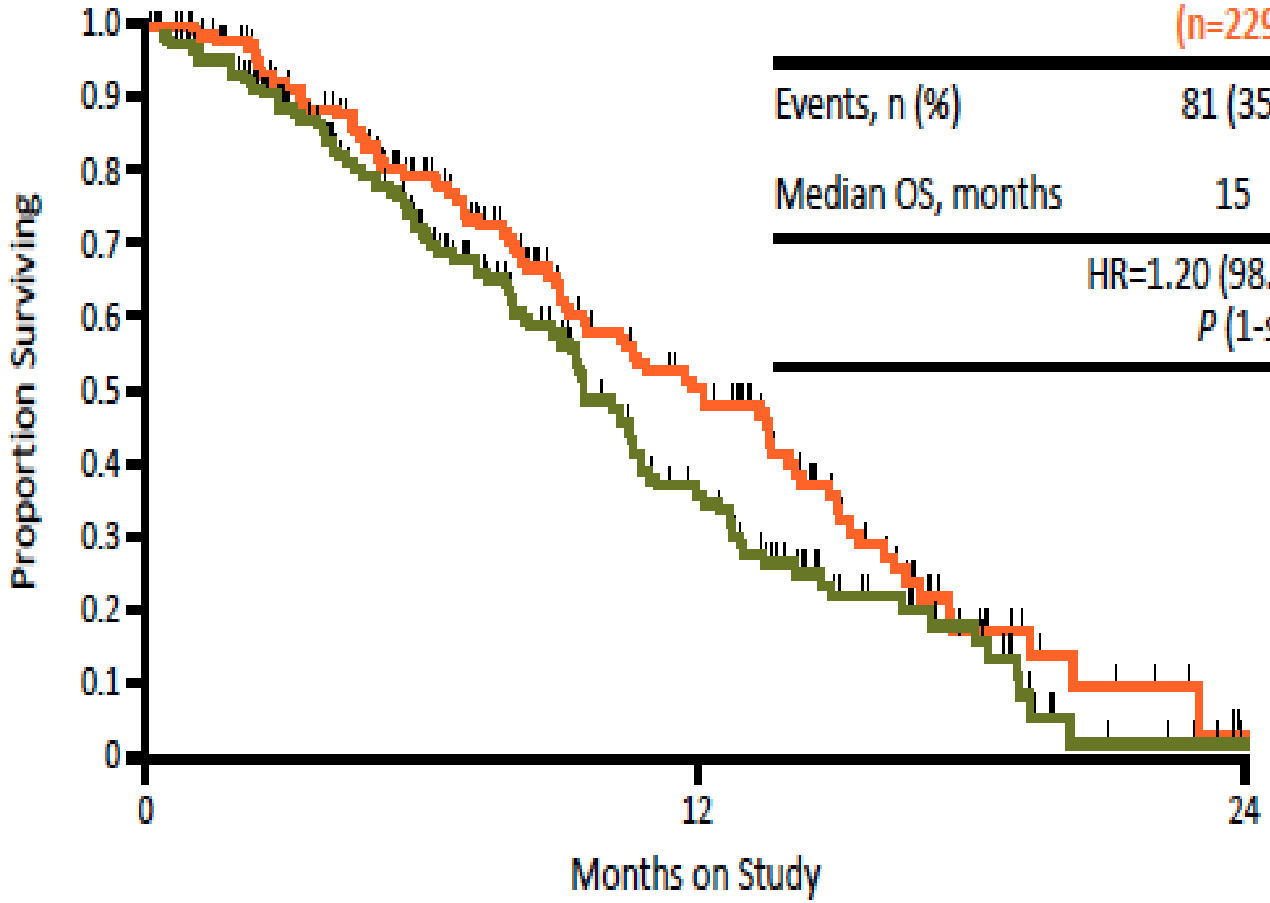
OBJECTIVEs

1. **Cisplatin+paclitaxel VS Paclitaxel + Topotecan**
2. **Chemo + Bevacizumab VS Chemo alone**

Krishnansu S Tewari et al 2014

GOG-240
TOPOCIS vs CISTAXOL

- Topotecan + paclitaxel shown to not be superior or inferior to cisplatin + paclitaxel

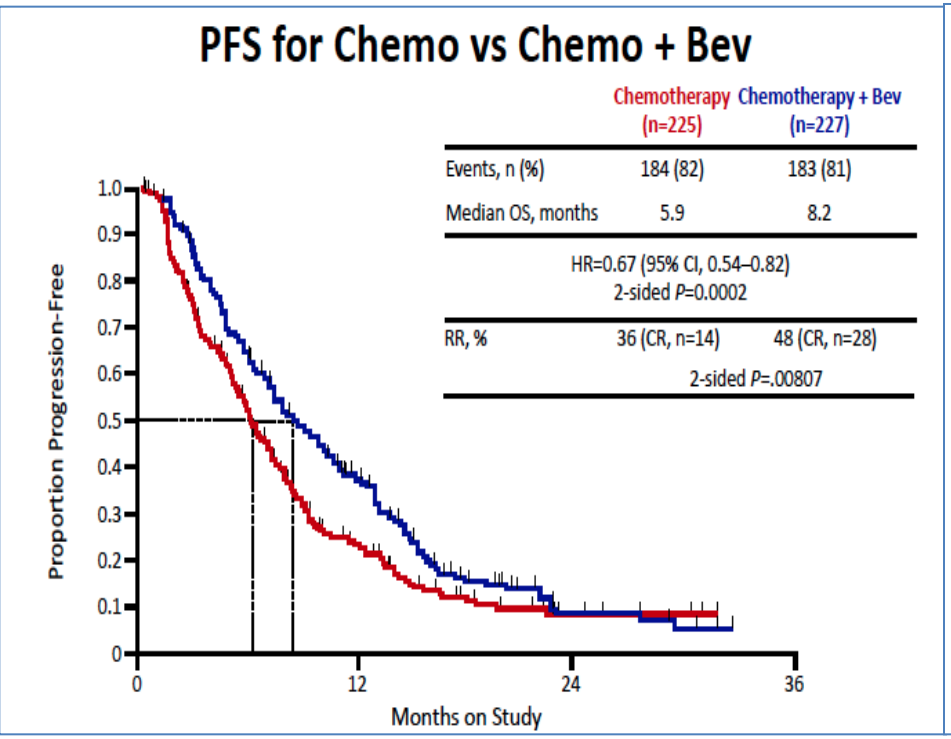


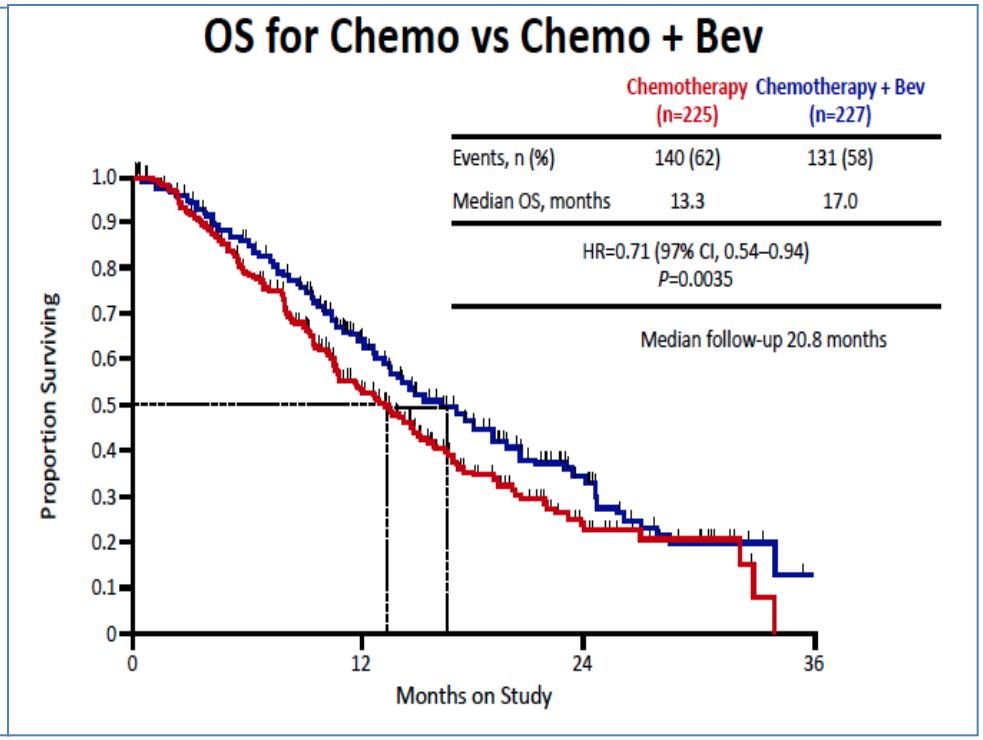
	Cis + Pac (n=229)	Topo+Pac (n=223)
Events, n (%)	81 (35)	93 (42)
Median OS, months	15	12.5
	HR=1.20 (98.74% CI, 0.82–1.76) *P* (1-sided)=.880	

Regardless of prior cisplatin

Tewari KS, et al. N EngIJ Med 2014

GOG-240
CHEMO vs CHEMO+VEBACIZUMAB





WITHOUT significant deterioration in health-related quality of life.

Tewari KS, et al. N EnglJ Med 2014
Penson, Lancet Oncology, 2015

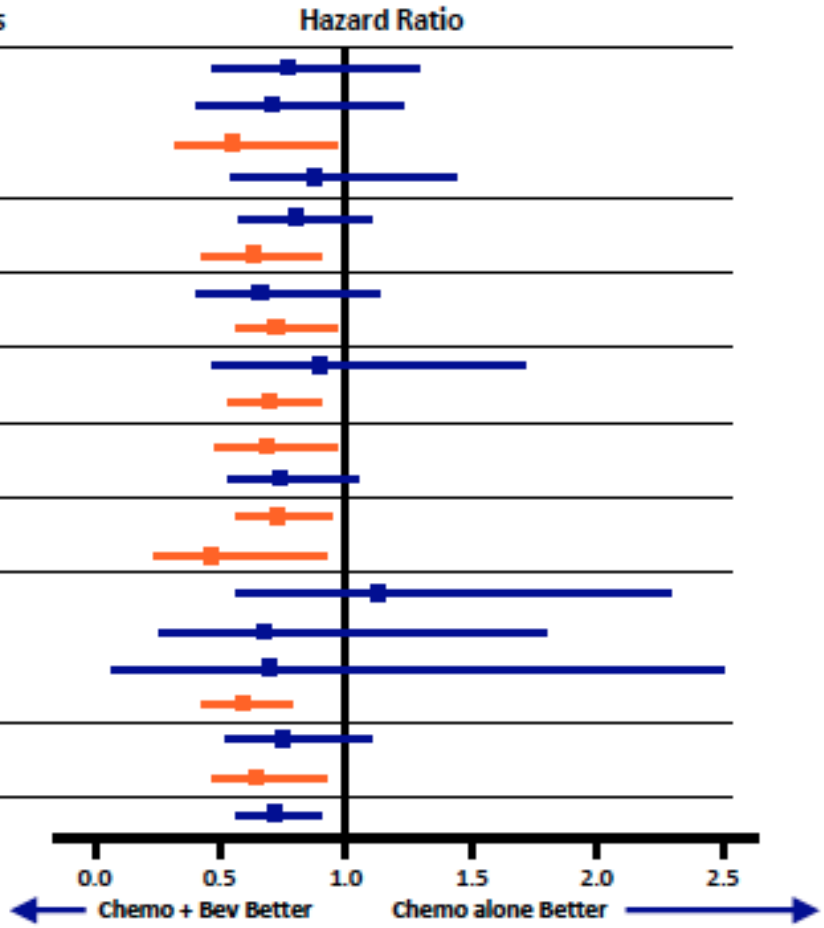
GOG-240 TOXICITY

Adverse Event, n (%)	Chemo Alone (n=220)	Chemo + Bev (n=220)
Treatment cycles, median (range)	6 (1-50)	7 (1-40)
Grade 5 AE(s)	3 (1.3)	7 (3.2)
GI events, non-fistula (grade ≥2)	97 (44)	115 (53)
GI fistula (grade ≥2)	1(0.5)	11 (5)
GI perforation (grade ≥2)	0 (0)	5 (2.3)
GU fistula (grade ≥2)	1 (0.5)	8 (3.6)
Hypertension (grade ≥2)	4 (1.8)	55 (25)
Proteinuria (grade ≥3)	0 (0)	5 (2.3)
Pain (grade ≥2)	63 (29)	72 (33)
Neutropenia (grade ≥4)	58 (26)	80 (36)
Febrile neutropenia (grade ≥3)	12 (5.5)	12 (5.5)
Thromboembolism (grade ≥3)	4 (1.8)	18 (8.2)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0.5)	4 (1.8)
GU (grade ≥3)	1 (0.5)	6 (2.7)

Tewari KS, et al. N EnglJ Med 2014

GOG-240
OS and Prognostic Factors

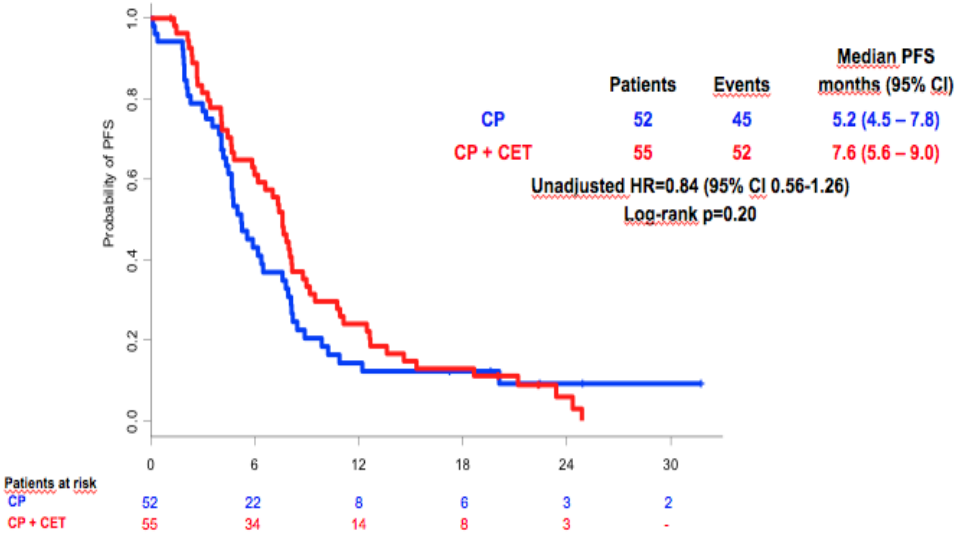
Subgroup		No. of Patients
Age	Age ≤ 40 years	112
	40 < Age ≤ 48 years	111
	48 < Age ≤ 56 years	108
	56 years < Age	121
Performance Status	0	263
	1	189
Prior Platinum RT	No	115
	Yes	337
Disease Status	Advanced	76
	Recurrent/Persistent	376
Topotecan Treatment	No	229
	Yes	223
Race	Not Black	392
	Black	60
Histology	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic Disease	No	210
	Yes	242
Overall		452



Even patients with target lesions contained within a previously irradiated field experienced sustained clinical benefit from bevacizumab which was a unique finding and a departure from previous studies that had suggested that these lesions are chemoresistant.

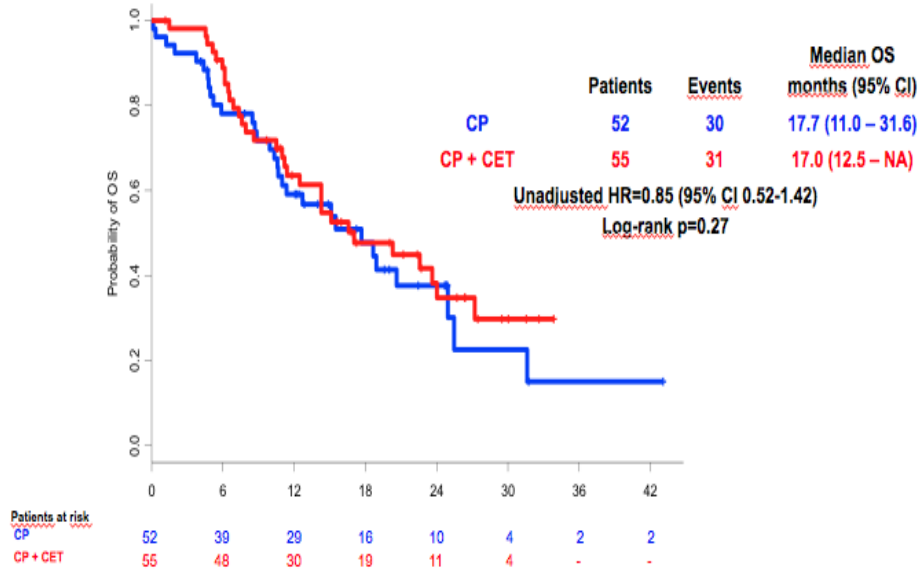
Tewari KS, et al. N EnglJ Med 2014

MITO (MULTICENTRE ITALIAN TRIALS IN OVARIAN CANCER) - CERV2 TRIAL: A RANDOMIZED PHASE II STUDY OF CARBOPLATIN AND PACLITAXEL +/- CETUXIMAB, IN ADVANCED AND/OR RECURRENT CERVICAL CANCER



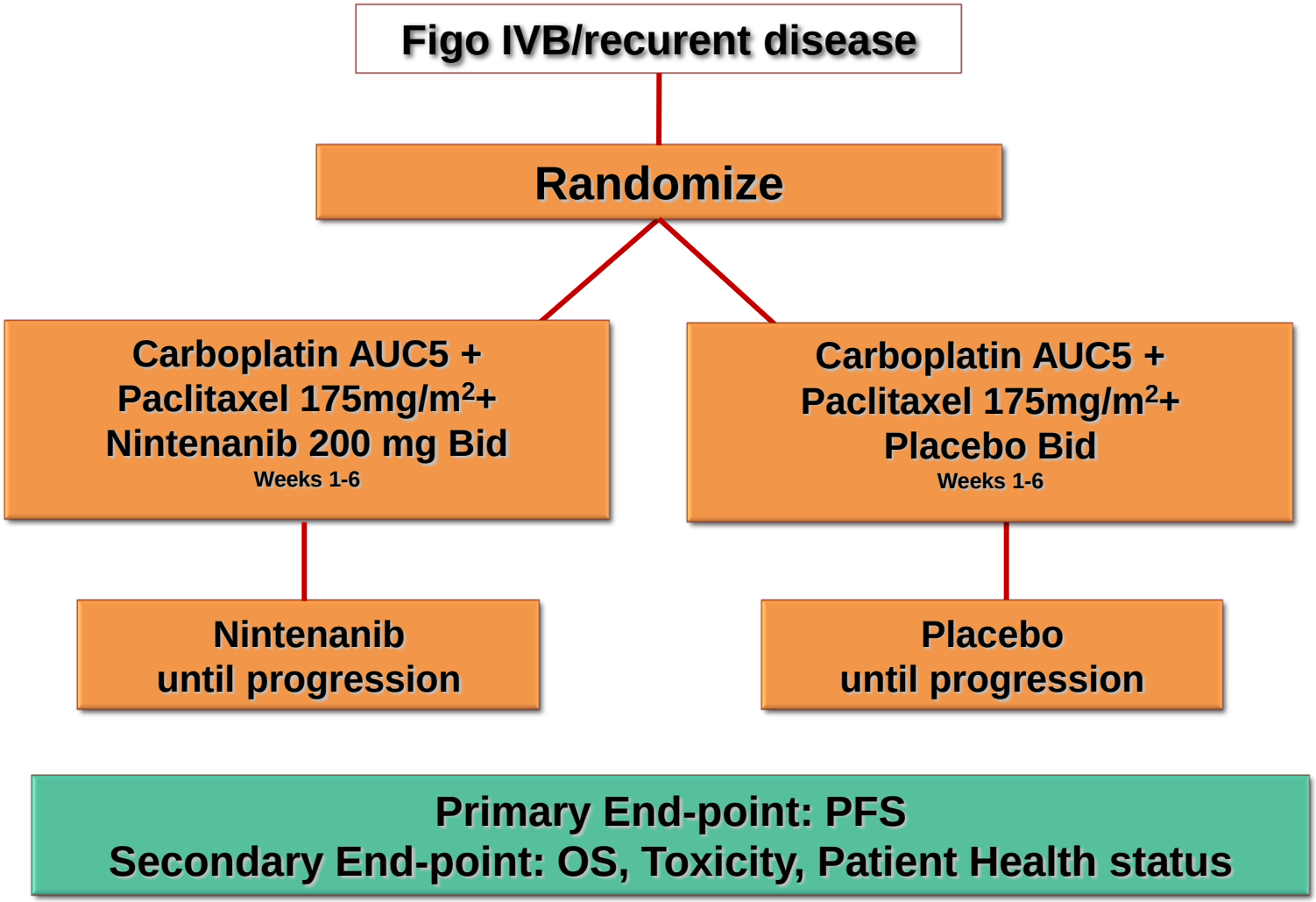
PFS

OS



NINTENANIB

<u>Ongoing Trial</u>: Phase II, randomized, double bind and placebo controlled trial



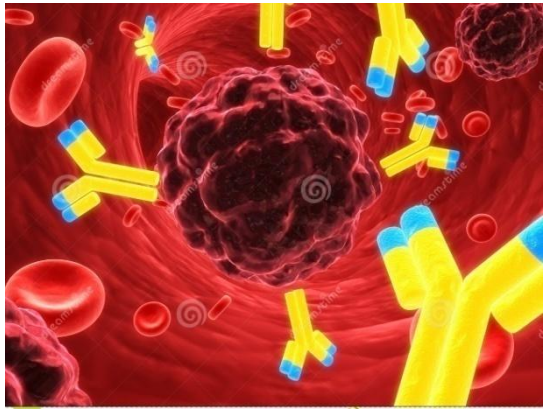
IMMUNOTHERAPY

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

A phase 1/2 study of ipilimumab in women with metastatic or recurrent HPV-related cervical carcinoma
A study of the Princess Margaret and Chicago N01 Consortia.

Lheureux S[1], Butler MO[1], Clarke B[1], Cristea MC[2], Martin LP[3], Tonkin K[4], Fleming GF[5], Tinker AV[6], Hirte HW[7], Tsoref D[1], Mackay H[1], Dhani NC[1], Ghatage P[8], Pham NA[1], Motta V[1], Wang L[1], Karakasis K[1], Udagani S[1], Streicher HZ[9], Oza AM[1]

[1]Princess Margaret Cancer Centre, Toronto; [2]City of Hope, Duarte, CA; [3]Fox Chase Cancer Center, Philadelphia; [4]Cross Cancer Institute Edmonton Alberta; [5]University of Chicago Medical Center, Chicago; [6]BC Cancer Agency, Vancouver; [7]Juravinski Cancer Centre, Hamilton; [8]Tom Baker Cancer Centre, Calgary, AB; [9]National Cancer Institute Bethesda.



OBJECTIVES:

-Primary: to assess the **safety and antitumor activity** by objective response rates(ORR) at the end of cycle 4 of ipilimumab in recurrent CC

-Secondary: to assess the **antitumor activity** of ipilimumab by disease stabilization and PFS

CONCLUSIONS

- **In locally advanced cervical cancer radio-chemotherapyis the standard**
- **NACT role will be defined by the EORTC trial of NACT/surgery vs chemo-RT**
- **CTRT followed by should be further investigate**
- **In metastatic disease cisplatin/paclitaxel plus bevacizumab is the new standard**
- **Platinum doublets are better than nonplatinum doublets**
- **Carboplatin may replace cisplatin in patients pretreated with the drug**

Grazie per l’attenzione