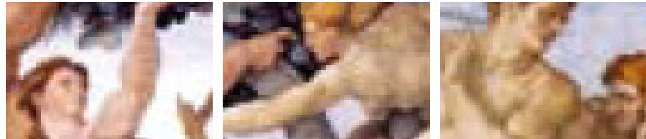


CONVEGNO

I TUMORI DEL TESTICOLO

una neoplasia guaribile

La chemioterapia ad alte dosi è utile ?

Giovanni Rosti , Treviso

Chi vince?

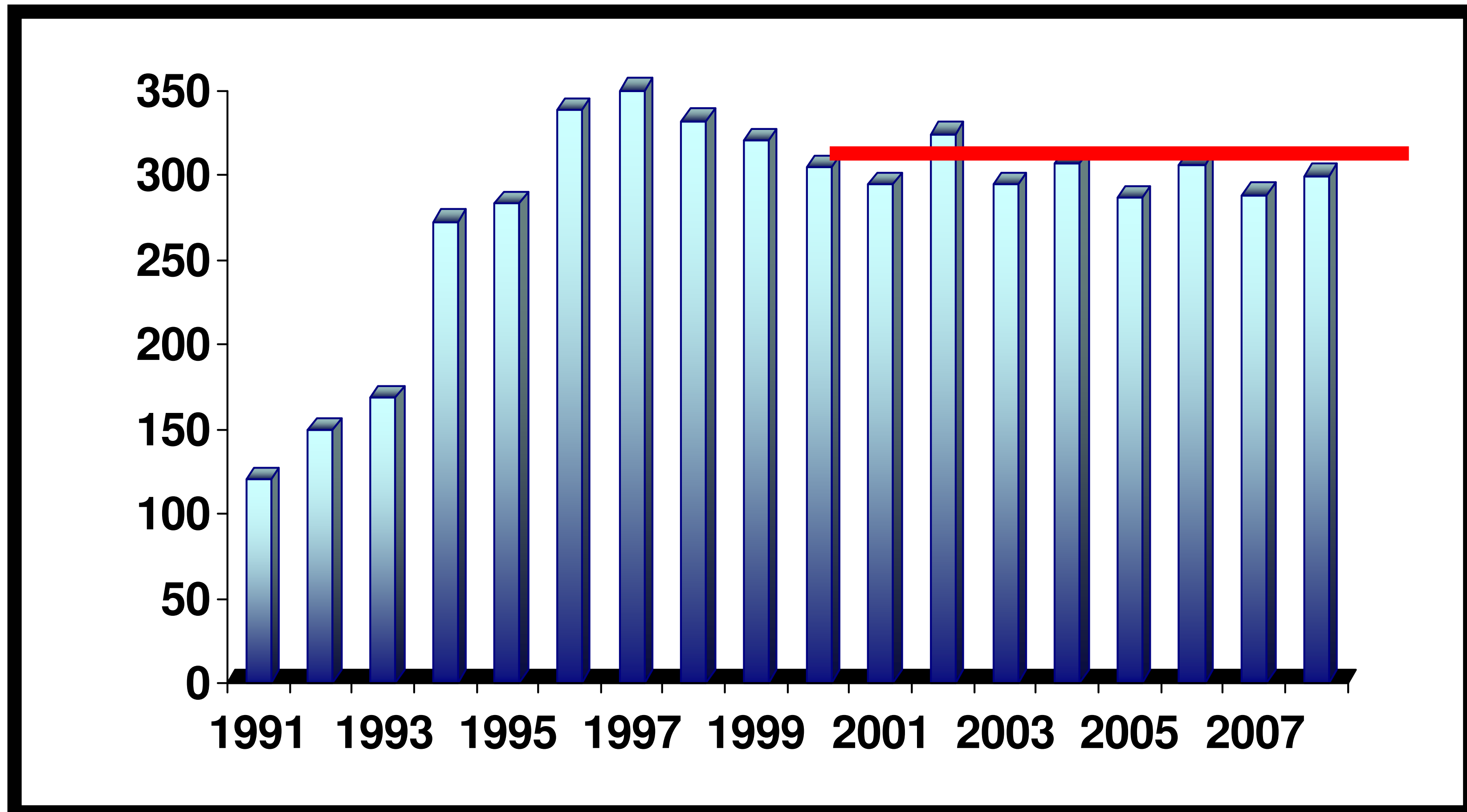
CT alte dosi e trapianto autologo nei tumori solidi

- **1980'**: studi "pilota" e fase II
  - elevate percentuali di risposta
  - apparente miglioramento della sopravvivenza
- **1990':** incremento progressivo del numero di Tx
  - riduzione della mortalità (CSE del sangue periferico)
  - al di fuori di studi clinici controllati
  - studi di fase III con arruolamento lento
- **1999:** primi studi randomizzati senza vantaggio OS
  - conclusioni affrettate sulla non efficacia del trapianto
  - riduzione del numero di trapianti
  - chiusura anticipata di studi randomizzati in corso
- **2005-2009 :** pubblicazione di studi "moderni" con vantaggio di sopravvivenza (carcinoma mammario,GCT)

A,a,a,a,a……chi ?

Fausto Leali et al. Sanremo 1968

Autotrapianti in Europa per GCT



Dr Baldomero, 2009

High-Dose Sequential Chemotherapy Versus Conventional-Dose Chemotherapy As First-Line Treatment For Advanced Poor Prognosis Germ-Cell Tumors: A MulticenterPhase III Italian Trial

M. Di Nicola, A. Necchi, N. Nicolai,

C. Bengala, S. Siena, A. Novarino, C. Carlo-Stella, L. Piva,

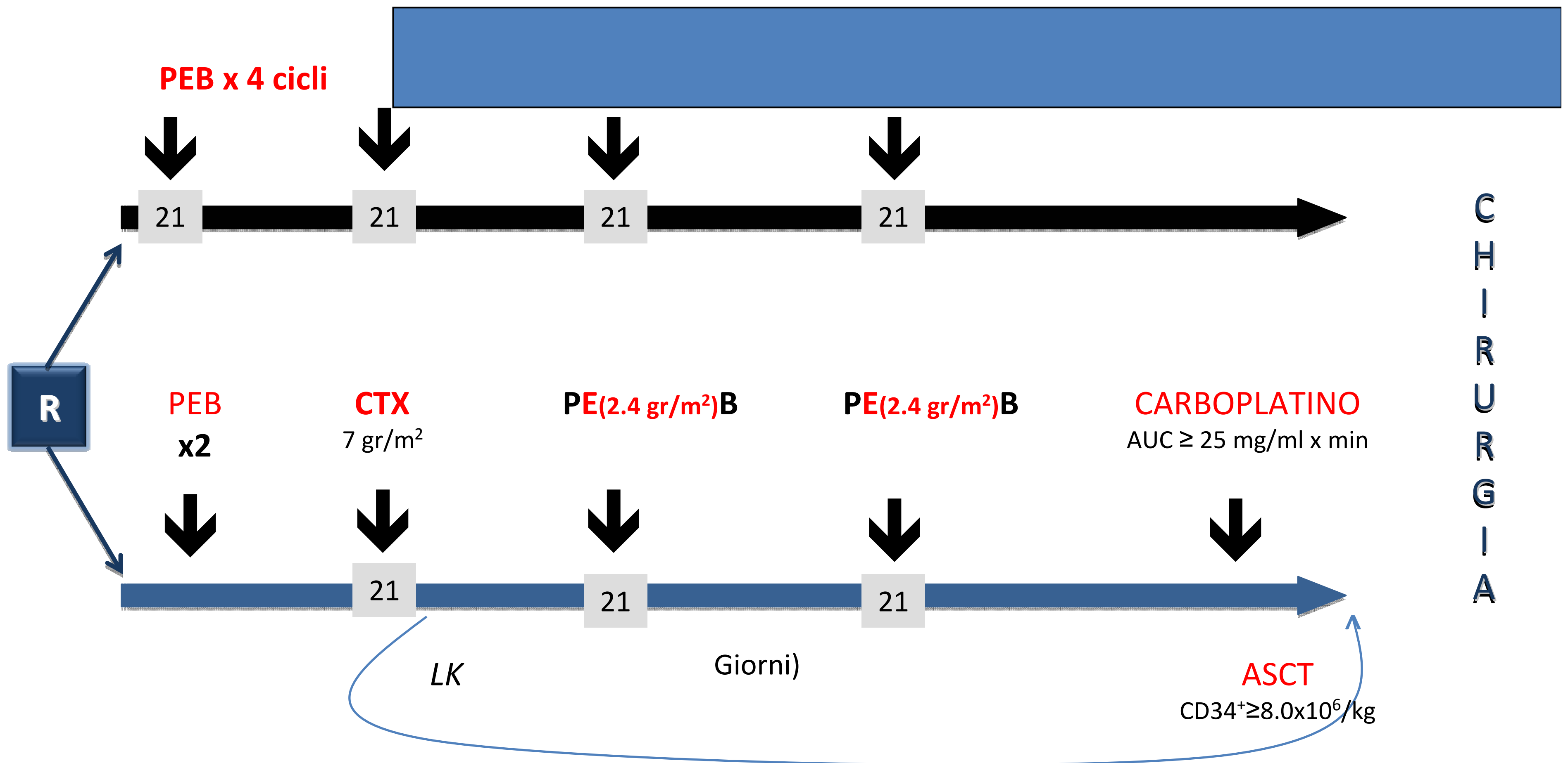
A.M. Gianni, and R. Salvioni

High-dose CT *vs* PEB

Criteri di inclusione	e di esclusione
Diagnosi di tumore germinale	Precedente chemioterapia
Uno dei seguenti: 1.T. mediastinico primario 2.Metastasi non polmonari viscerali 3.hCG>50 000 4.AFP>10 000 5.LDH>10 x ULN	Comorbidità o infezioni serie compreso HIV, HBV,HCV
	Di Nicola AIOM 2009

Diagramma dello studio

89 paz entrati dal Dic 1996 ad Apr 2007



Tossicità non ematologica (grado ≥3)

Tossicità	PEB	HD CT
Renale	1 (2%)	1 (2%)
Neurologica	1 (2%)	0
Epatica	0	1 (2%)
Gastro-intestinale	5 (10%)	25 (58%)
FUO/infezione documentata	3*(6%)	38 (88%)

* 1 grado 5

I pazienti inclusi nello studio

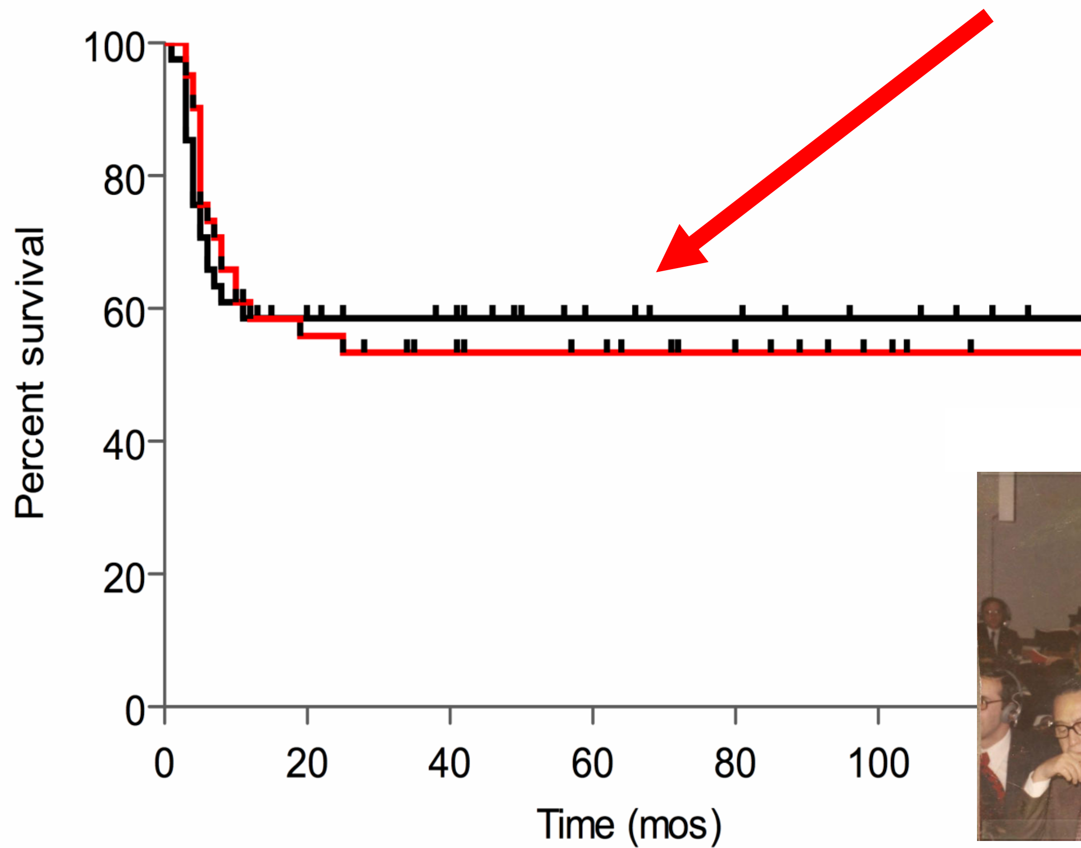
	PEB		HD-CT	
	N	%	N	%
•Età •Mediana •Range	 27.5 19-51		 30 17-61	
•Primitivo				
•Testis	34	74	29	67
•Retroperitoneo	3	6	4	9
•Mediastino	9	19	10	23

Risultati
- Intent To Treat Analysis-

	PEB	Alte dosi	
			p
OS @ 2 anni PFS @ 2 anni	66.8 **%** 58.5 **%**	60.5 **%** 55.8 **%**	p=0.42 p=0.94
Ricaduti/PD*	39% (18)	44% (19)	
Mesi alla PD	4 (1-8)	5.5 (3-25)	
Paz recuperati con salvataggio	17% (3)	11% (2)	

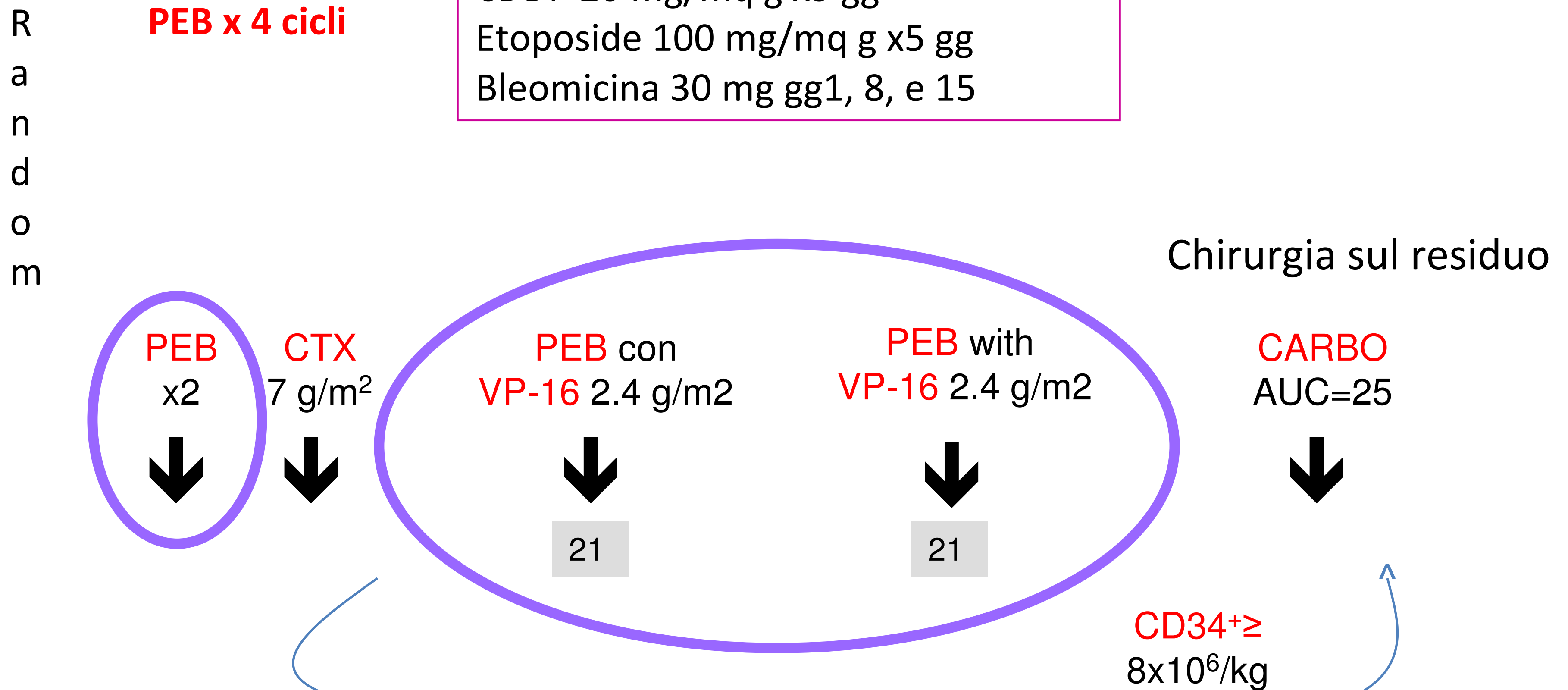
*Nessun paziente HDCT come salvataggio

Ottima performance del PEB in questo studio



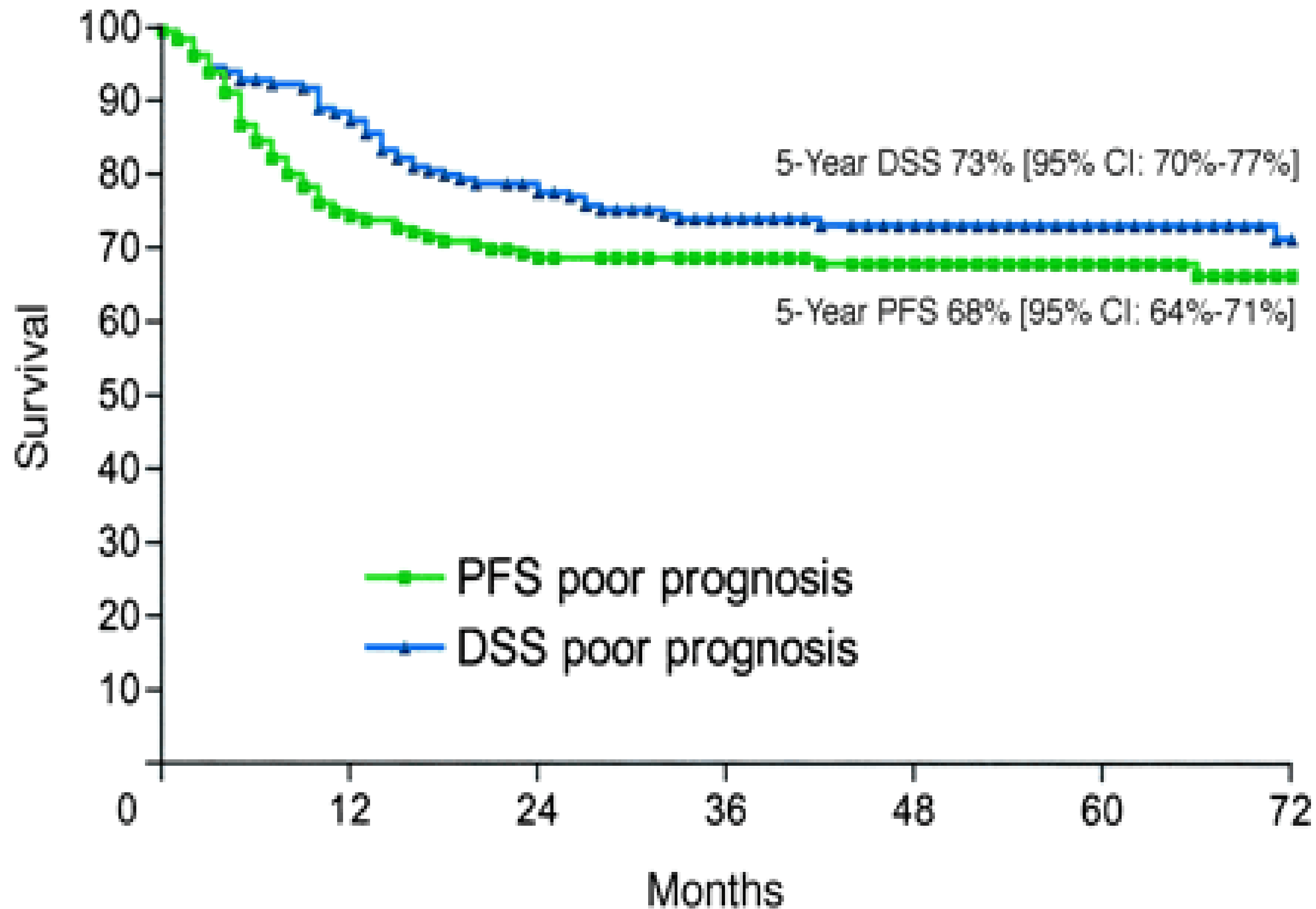
Importanza della qualità del centro dove si tratta il paziente

Schema dello studio



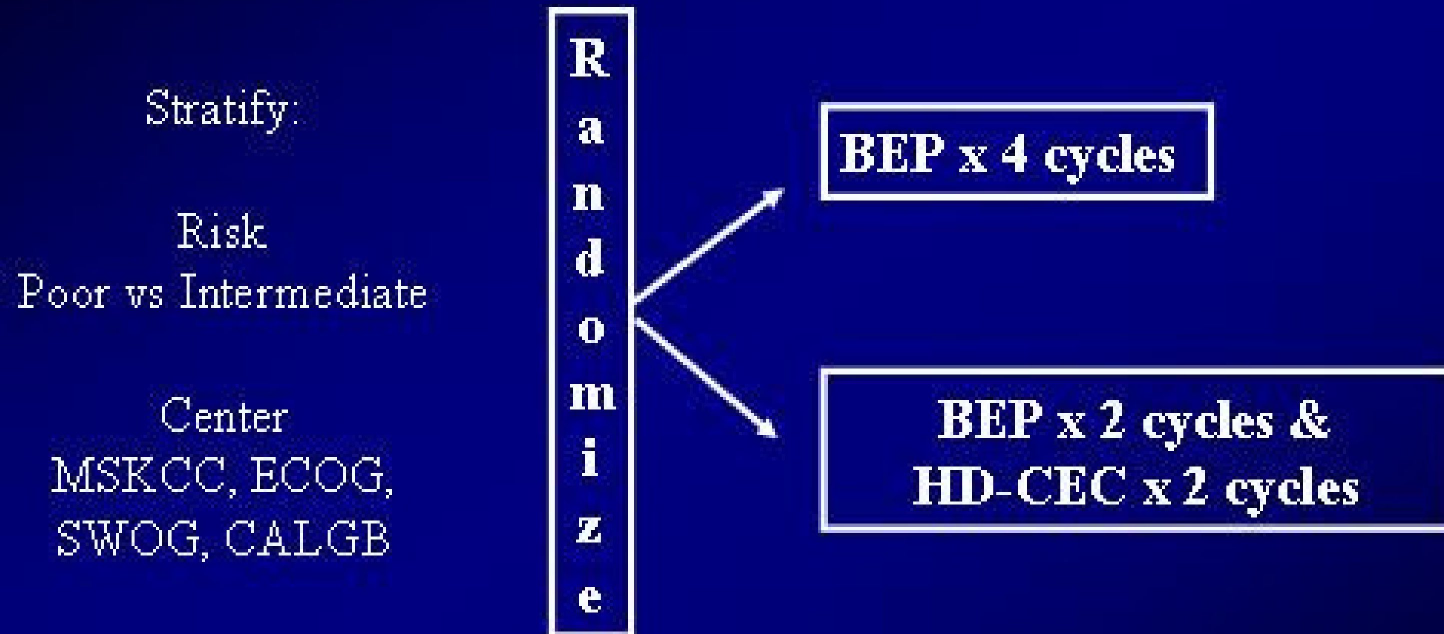
Take home message: non serve aggiungere altra chemioterapia ai 4 PEB

German Group Study in GCT poor prognosis



Schmoll, JCO, Nov 2003

BEP vs BEP + High-dose Chemotherapy



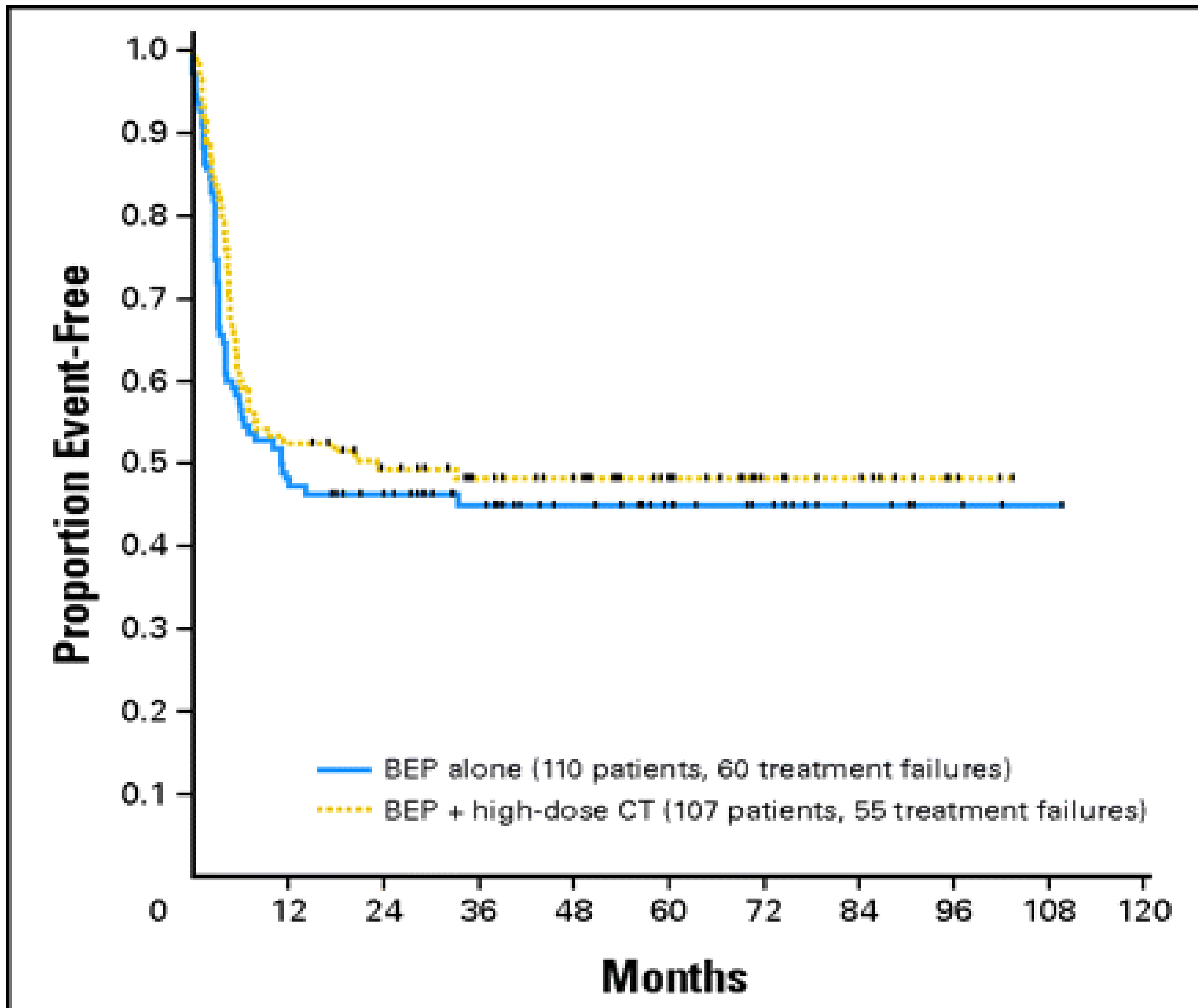
Trial Considerations

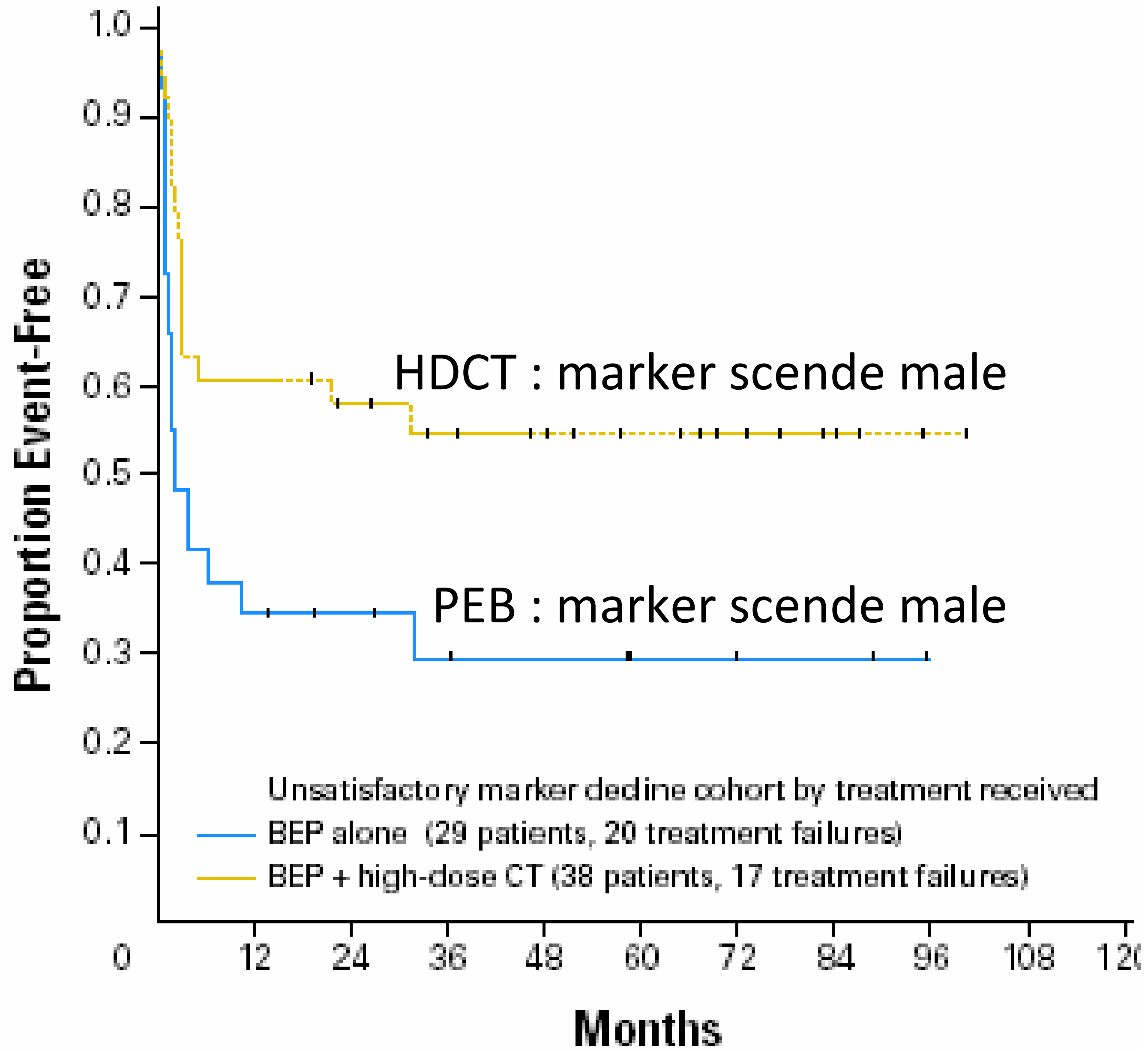
Use International Risk Criteria for eligibility; BEP as standard arm

Randomize all patients; insufficient patients to randomize by marker decline status.

Target accrual was 218 pts to detect an improvement of 20% in CR at 1 year (alpha=0.05 and 80% power).

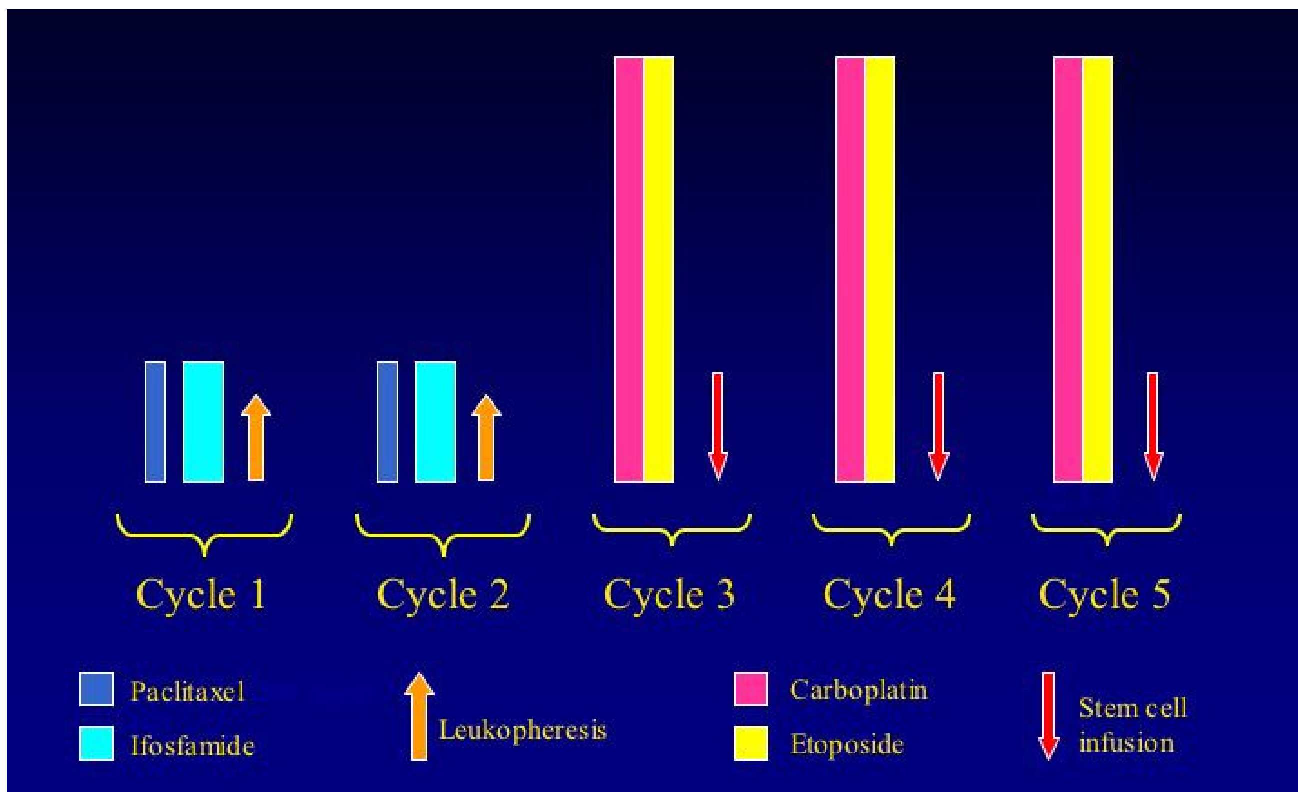
E' uno studio « negativo »?





Motzer, JCO, 2007

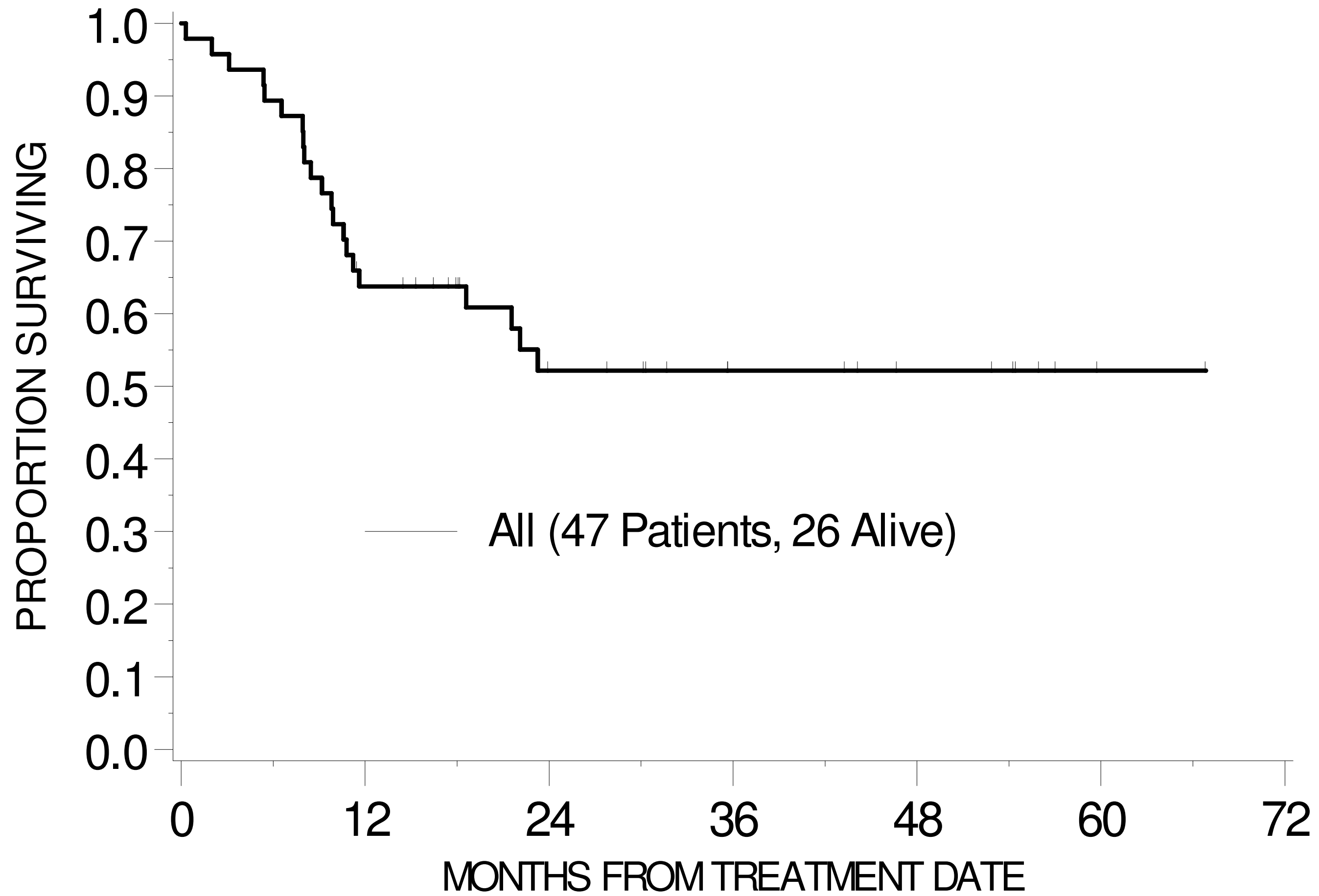
Cycle #	Lenght	
1–2	14 dd	Paclitaxel 200 mg/m^2/24hr Ifosfamide 2 g/m^2 + mesna
3,4,5	21 dd	Carboplatin AUC 21 Etoposide 1200 mg/m^2



TRM=0

Kondagunta, JCO 2007

Overall survival



Kondagunta, JCO 2007

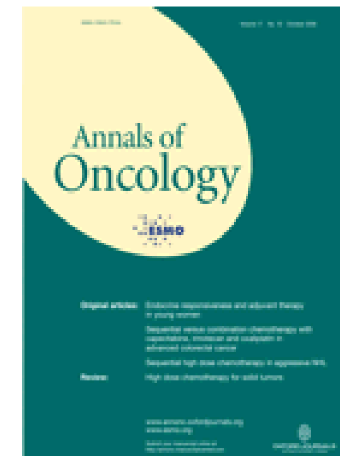
Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours

J.-L. Pico[1], G. Rosti[2], A. Kramar[3]*, H. Wandt[4], V. Koza[5], R. Salvioni[6], C. Theodore[1], G. Lelli[7], W. Siegert[8], A. Horwich[9], M. Marangolo[2], W. Linkesch[10], G. Pizzocaro[6], H.-J. Schmoll[11], J. Bouzy[1], J.-P. Droz[12] & P. Biron[12], for the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG-FNCLCC), France and the European Group for Blood and Marrow Transplantation (EBMT)

280 pts
Incomplete remission or relapse from first-line CT
15% improvement in EFS

July, 2005



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Study design

Registration and randomization of eligible pts

2 courses PEI or VeIP

If refractory after 2 courses, OFF

If not

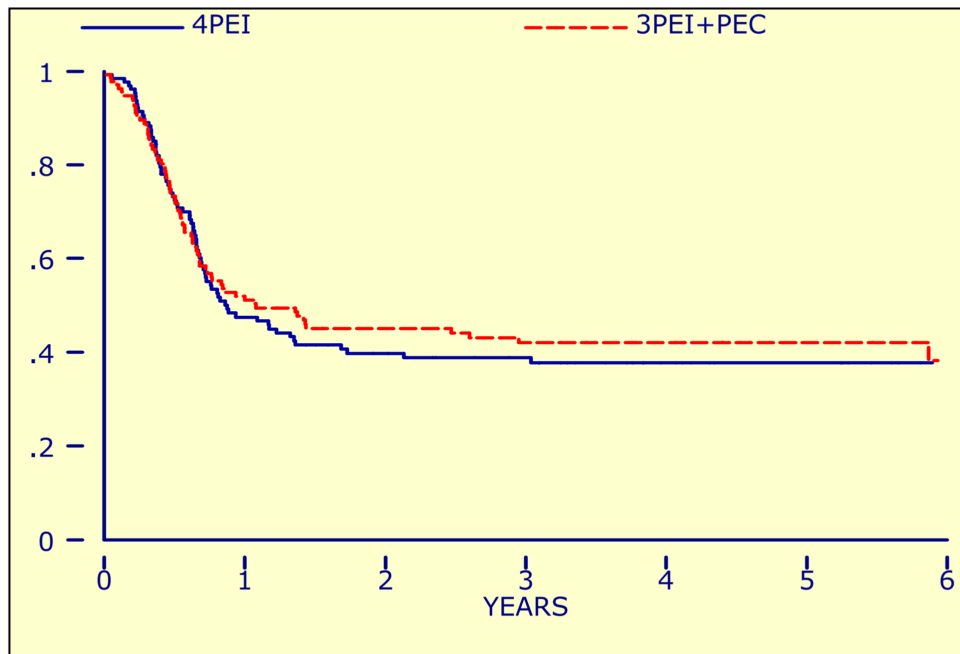
Arm A	**Arm B**
1 cycle PEI (or VeIP) + 1 cycle PEI (or VeIP)	1 cycle PEI (or VeIP) + CarboPEC + ABMT/ PBPCT

Surgery on residual disease if indicated

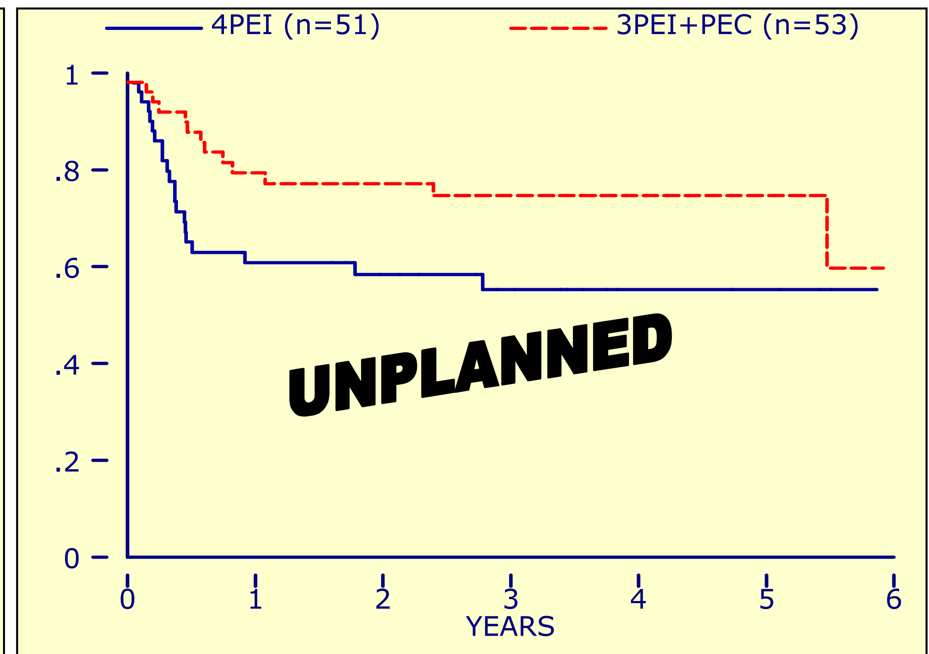
EVENT-FREE SURVIVAL Studio IT-94

Fase III: PEIx4 vs PEIx3 + carboPEC

All patients



Pts achieving CR

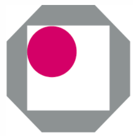


p=NS

p=0,04

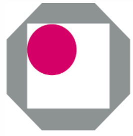
Pico, Rosti et al. Ann Oncol 2005

Sopravvivenza globale e DFS



	n°	events	2-year	[95% CI]	5-year	[95% CI]
OS	100	65	39 %	[29.5% - 48.4%]	35 %	[25.4% - 44.0%]
DFS	100	68	35 %	[25.8% - 44.3%]	31 %	[22.3% - 40.6%]

Non per tutti !



istituto
oncologico
romagnolo

	n°	events	2-year	[95% CI]	5-year	[95% CI]
2nd line	61	30	56 %	[42.4% - 67.1%]	50 %	[37.2% - 62.2%]
3rd line	20	17	20 %	[6.24% - 39.3%]	13 %	[26.5% - 32.7%]
4th-5th line	19	18	5 %	[0.36% - 21.4%]	5 %	[0.36% - 21.4%]

Log-Rank=24.5 (2), p<0.001

Overall Survival

0.0 0.2 0.4 0.6 0.8 1.0

0 6 12 18 24 30 36 42

Months

2nd line
3rd line
4th-5th line

Sopravvivenza secondo lo score di Beyer*

Intermediate risk: median OS 7 months
Poor risk: median OS 5 months

Overall survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Months after HDCT

Good risk (G)
Intermediate risk (I)
Poor risk (H)

p =
G vs **I** = 0.0004
G vs **H** = 0.0000
I vs **H** = 0.003

Rosti, Ann Onc 2005

* J Beyer, JCO 1996

Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

EBMT
European Group for Blood and Marrow Transplantation

UNIVERSITÉ PARIS-SUD 11

Does the kinetics of a tumor marker decline predict outcome in patients with relapsed disseminated germ-cell tumors treated with high-dose or conventional chemotherapy?

An analysis of the EBMT IT94 randomized trial

Massard C, Kramar A, Pico JL, Rosti G, Wandt H, Koza V, Salvioni R, Droz JP, Biron P, Fizazi K

Institut Gustave Roussy, Villejuif, France

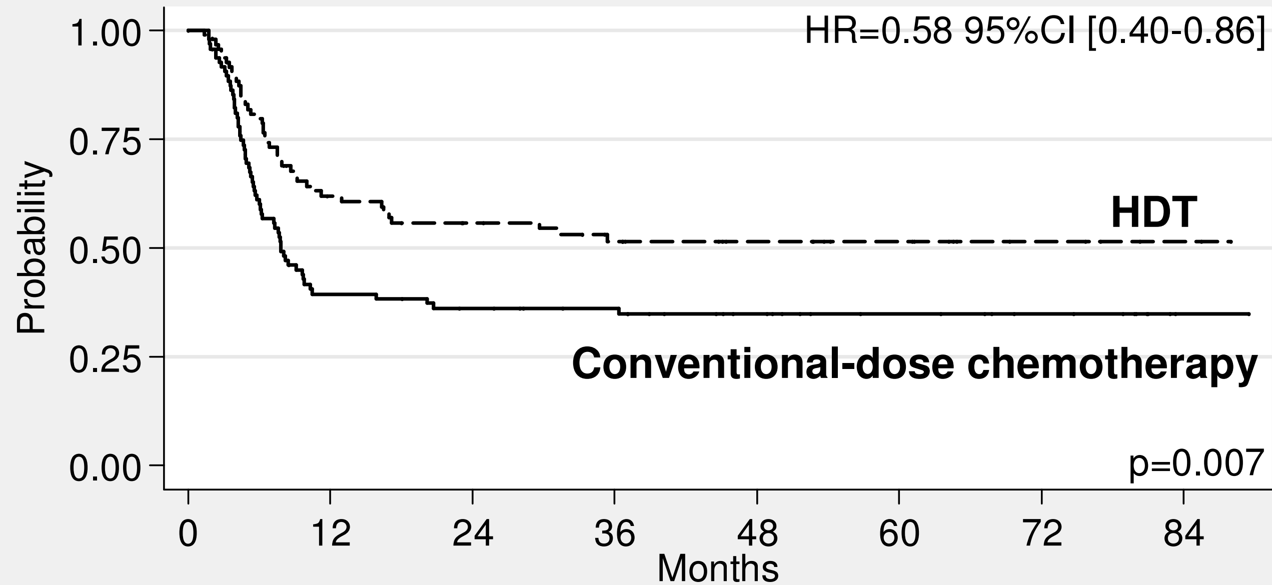
The European Group for Blood and Marrow Transplantation

Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

RFS in patients with favorable AFP decline according to treatment arm

Massard, Rosti et al, ASCO GU 2008

Relapse-Free Survival
Favorable AFP Half-life



Number at risk	0	12	24	36	48	60	72	84
4PEI	96	36	31	27	19	13	9	1
4PEI+PEC	95	53	42	34	26	16	8	4

Treatment Carbo
——— 4PEI - - - - - 3PEI+PEC

2-year RFS: 56% vs 36%; HR=0.58; p=0.007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

Lawrence H. Einhorn, M.D., Stephen D. Williams, M.D., Amy Chamness, B.A., Mary J. Brames, R.N., Susan M. Perkins, Ph.D., and Rafat Abonour, M.D.

July, 2007

Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score

Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.*

Prognostic Variable	Hazard Ratio (95% CI)	P Value	β Regression Coefficient	Prognostic Score†
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	0.78	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	0.55	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	0.51	2

* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.
† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.

Einhorn L et al. N Engl J Med 2007;357:340-348

Timing of HDCT IGCCCG CDDP sensitivity

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Characteristics of 184 Patients at the Beginning of High-Dose Chemotherapy.*

Characteristic	No. of Patients (%)
No. of previous chemotherapy regimens	
1	135 (73.4)
2	45 (24.4)
≥3	4 (2.2)
Histologic type	
Seminoma	35 (19.0)
Nonseminomatous germ-cell tumor	149 (81.0)
Response to initial chemotherapy	
Complete remission (with or without resection of tumor)	75 (40.8)
Partial remission (normal hCG and alpha-fetoprotein levels)	9 (4.9)
Other (less than complete remission or partial remission with normal hCG and alpha-fetoprotein levels)	100 (54.3)
Initial IGCCCG stage	
Low risk	71 (38.6)
Intermediate risk	38 (20.7)
High risk	75 (40.8)
Platinum sensitivity	
Sensitive	144 (78.3)
Refractory	40 (21.7)
Serum hCG level	
≥1000 IU/liter	22 (12.0)
<1000 IU/liter	162 (88.0)
Serum alpha-fetoprotein level	
≥1000 μg/liter	8 (4.3)
<1000 μg/liter	176 (95.7)
Beyer score†	
0	136 (73.9)
1	24 (13.0)
2	9 (4.9)
3–4	15 (8.2)

Characteristics of 184 Patients at the beginning of High-Dose Chemotherapy

Mobilization:

G-

HD

Carboplatin: 2100 mg/m^2

Etoposide: 2250 mg/m^2

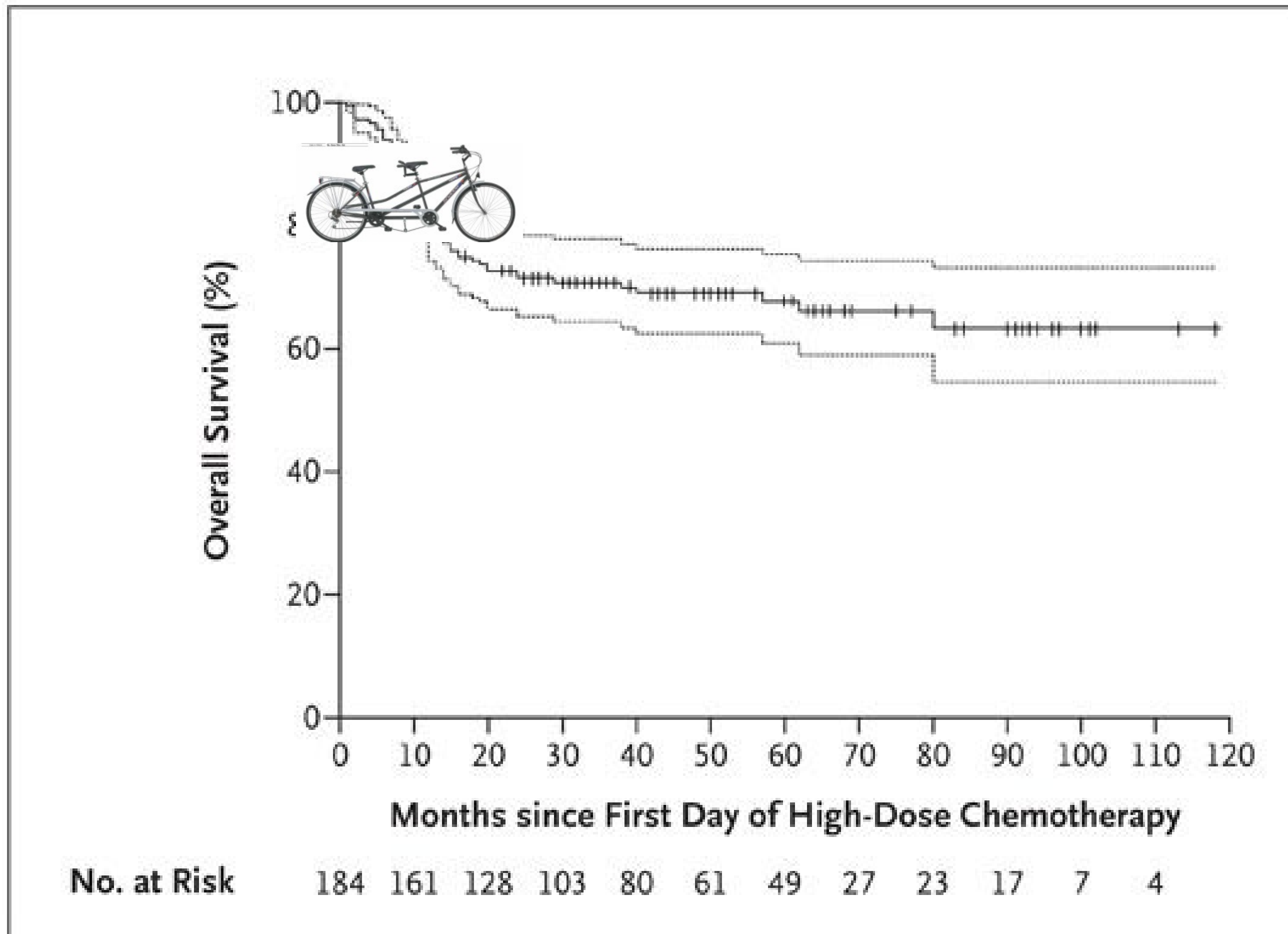
(Tandem)

Stem cell support:

> 1x10^6 selected CD34+ cells/Kg

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan-Meier Estimates of Overall Survival



Einhorn L et al. N Engl J Med 2007;357:340-348

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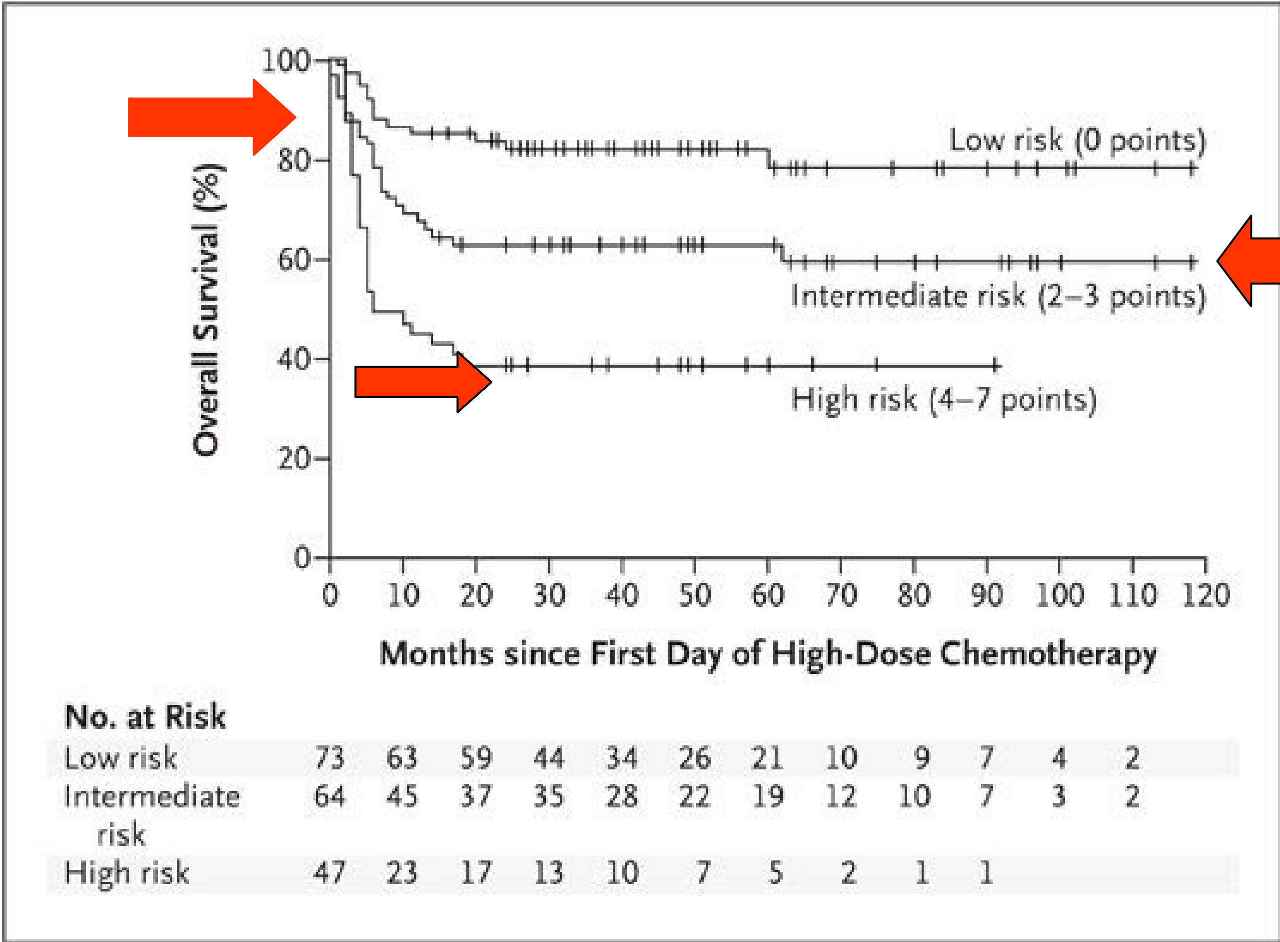
Disease-free Survival according by the scoring algorythm based on three-variable model



Einhorn L et al. N Engl J Med 2007;357:340-348

The NEW ENGLAND JOURNAL of MEDICINE

PICADORES
E la tossicità?

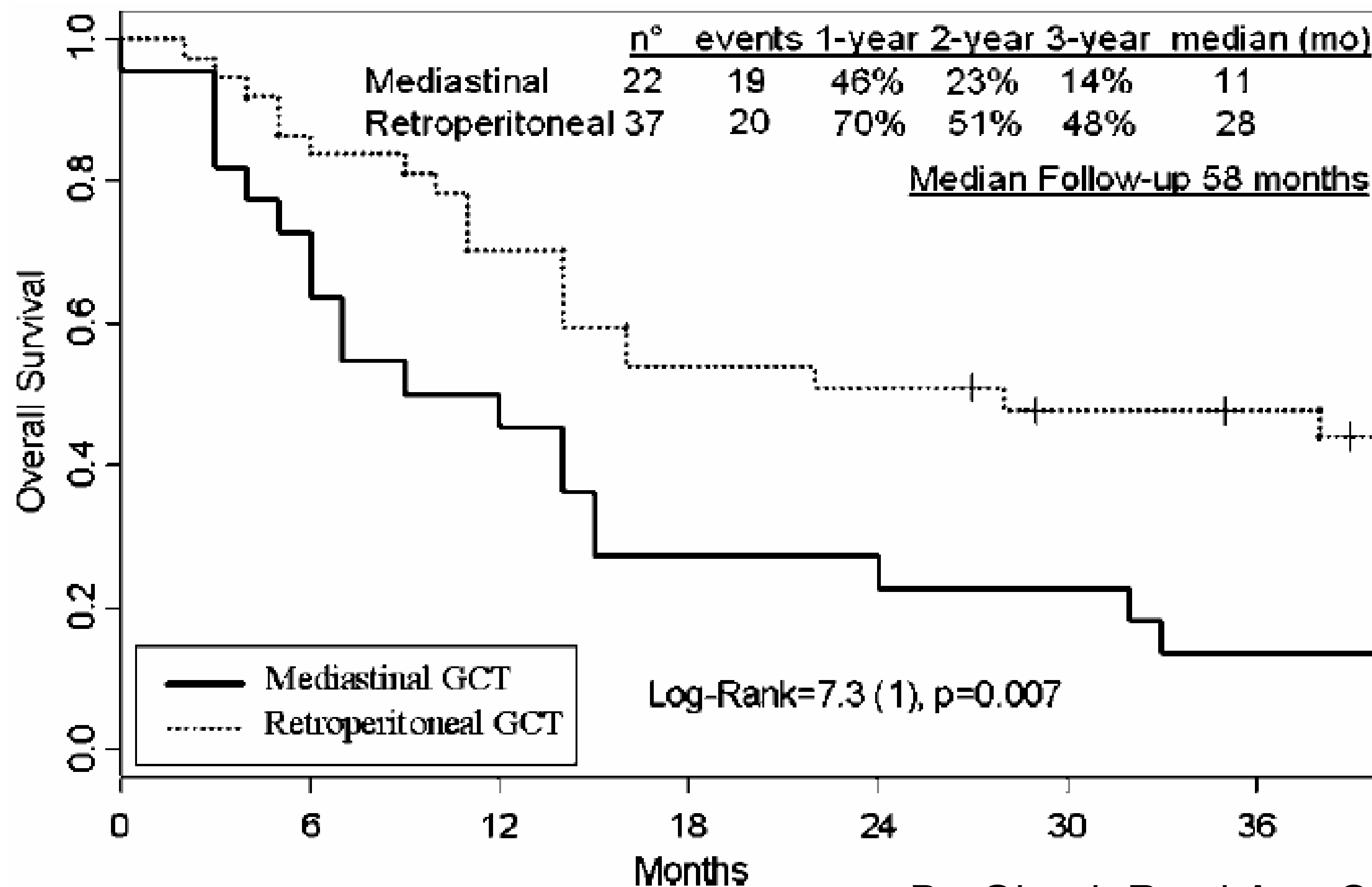
Toxicity of HDCT

Toxic Effect	No. of Patients	No. of Deaths
Hematologic (leukemia)	3	2
Renal (serum creatinine, 3–6× ULN)	4	0
Gastrointestinal	30	0
Hepatic	6	2
Neurologic	9	0
Pulmonary	3	1

TRM=1,7%

Overall mortality: 2,7%

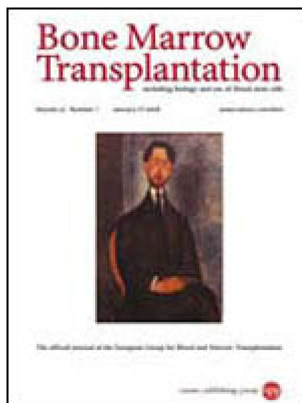
HDCT at relapse in EGGCT

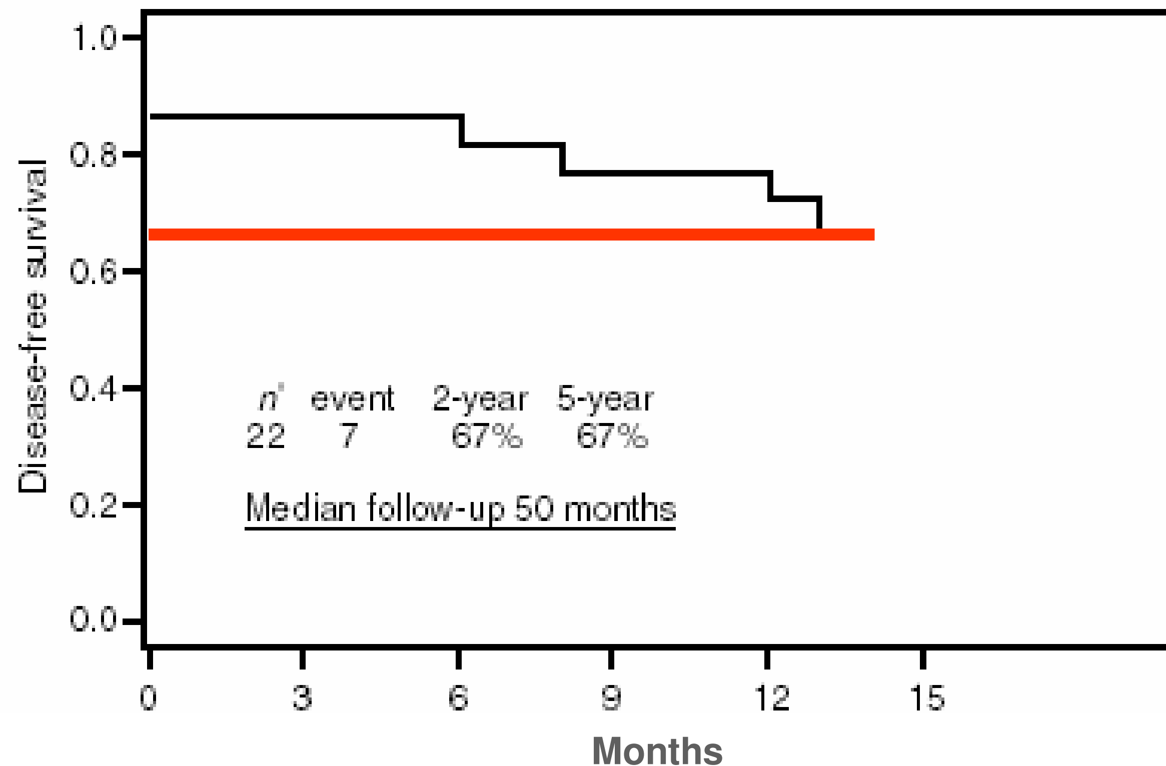


De Giorgi, Rosti Ann Oncol 2006

First-line high-dose chemotherapy for patients with poor prognosis extragonadal germ cell tumors: the experience of the European Bone Marrow Transplantation (EBMT) Solid Tumors Working Party

G Rosti[1], U De Giorgi[1], H Wandt[2], B Lioure[3], S Leyvraz[4], K Kolbe[5], G Papiani[1], M Ballardini[6], A Kulekci[7] and T Demirer[7], on behalf of the EBMT Solid Tumours Working Party





Prognostic factors in relapsed or refractory germ-cell tumors: results from an international database

A. Lorch [1], J. Beyer [2],
C. Mollevi [3], M. Guerra [3], A. Kramar [3]
for the International Group on Prognostic Factors in Relapsed or Refractory Germ-Cell Tumors

ASCO Annual '09 Meeting

FORMATION OF PROGNOSTIC GROUPS

To each variable a score was assigned relative to it's hazard ratio in multivariate analysis

Variable / Points	0	1	2	3
Primary site	Gonadal	Retroperitoneal		Mediastinal
Response	CR/PRm-	PRm+/SD	PD	
PFI	> 3 months	≤ 3 months		
AFP salvage	Normal	<1000	≥1000	
HCG salvage	<1000	≥1000		
LBB	No	Yes		

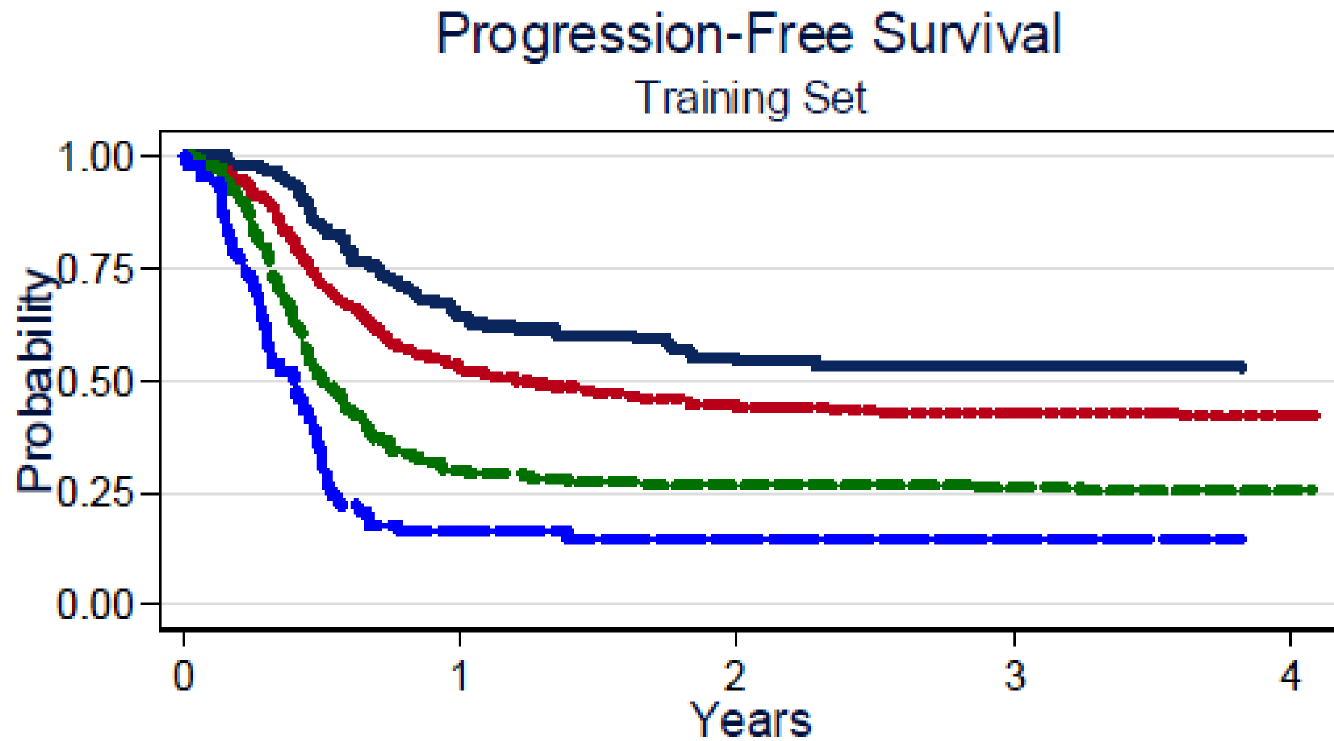
A scoring system resulted with scores ranging from 0 to 10

IGCCCG-2 risk group classification

Four significant prognostic groups were identified with significantly different risks of relapse

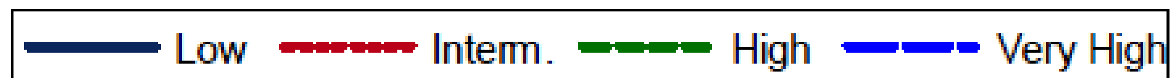
- Score = 0 ⇒ Low risk
- Score = 1 and 2 ⇒ Intermediate risk
- Score = 3 and 4 ⇒ High risk
- Score $\geq$ 5 ⇒ Very high risk

IGCCCG-2 risk group classification



Number at risk

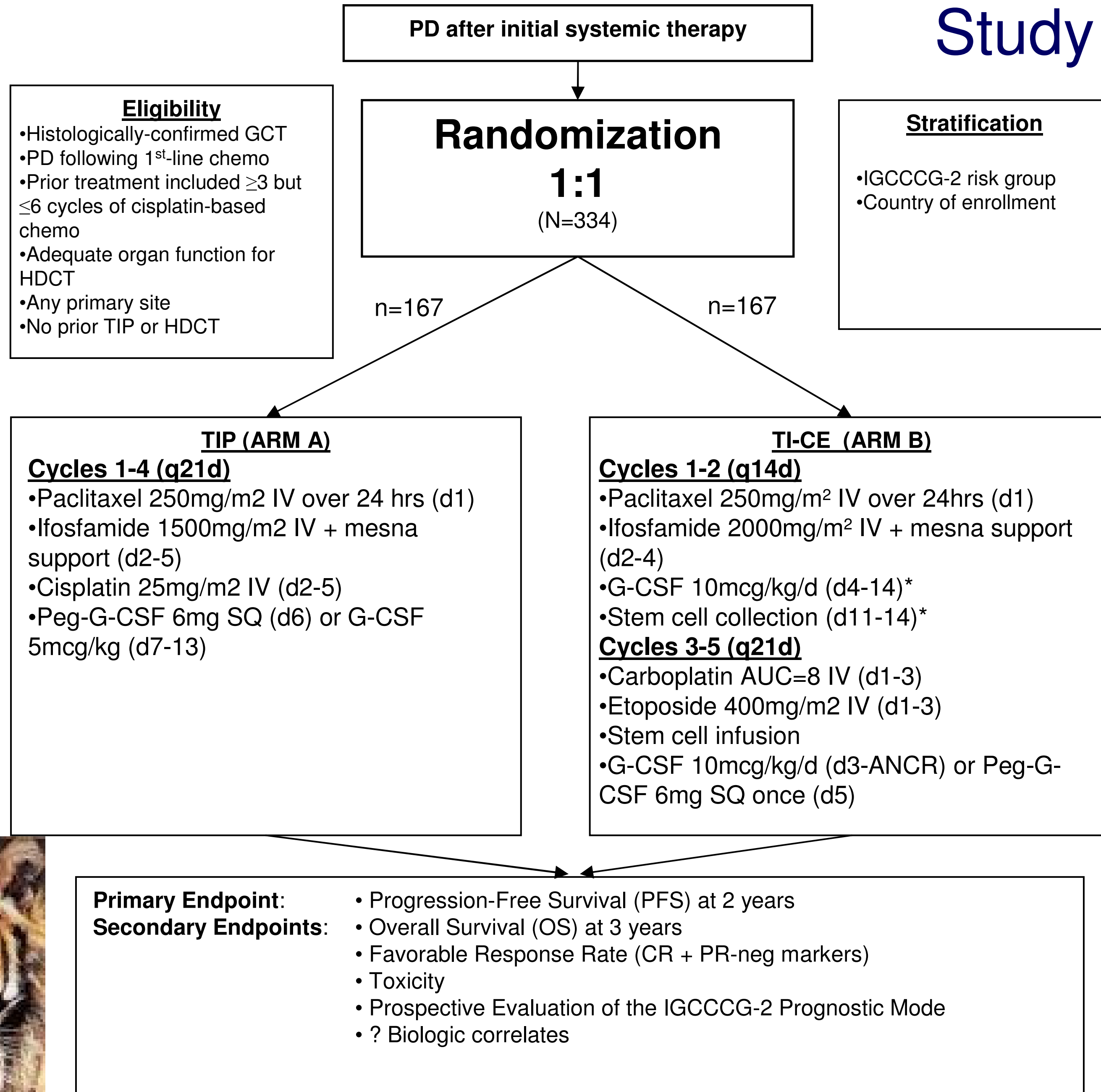
	0	1	2	3	4
Low	125	75	62	51	0
Intermediate	427	211	165	135	110
High	229	61	53	41	32
Very High	69	11	8	6	0



TIGER STUDY

A RANDOMIZED PHASE III TRIAL COMPARING CONVENTIONAL-DOSE CHEMOTHERAPY USING PACLITAXEL, IFOSFAMIDE, AND CISPLATIN (TIP) WITH HIGH-DOSE CHEMOTHERAPY USING MOBILIZING PACLITAXEL PLUS IFOSFAMIDE FOLLOWED BY HIGH-DOSE CARBOPLATIN AND ETOPOSIDE (TI-CE) AS FIRST SALVAGE TREATMENT IN RELAPSED OR REFRACTORY GERM CELL TUMORS

Study design



Selezione dei pazienti

- Terza linea o successive
- Seconda linea
  → Platinum refractory
  → Prognostic factors?

Raccolta CSE

Trapianto tandem
(Einhorn NEJM 2007)

Pedrazzoli, 2010