Approccio multidisciplinare nel carcinoma della vescica

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Disclosures

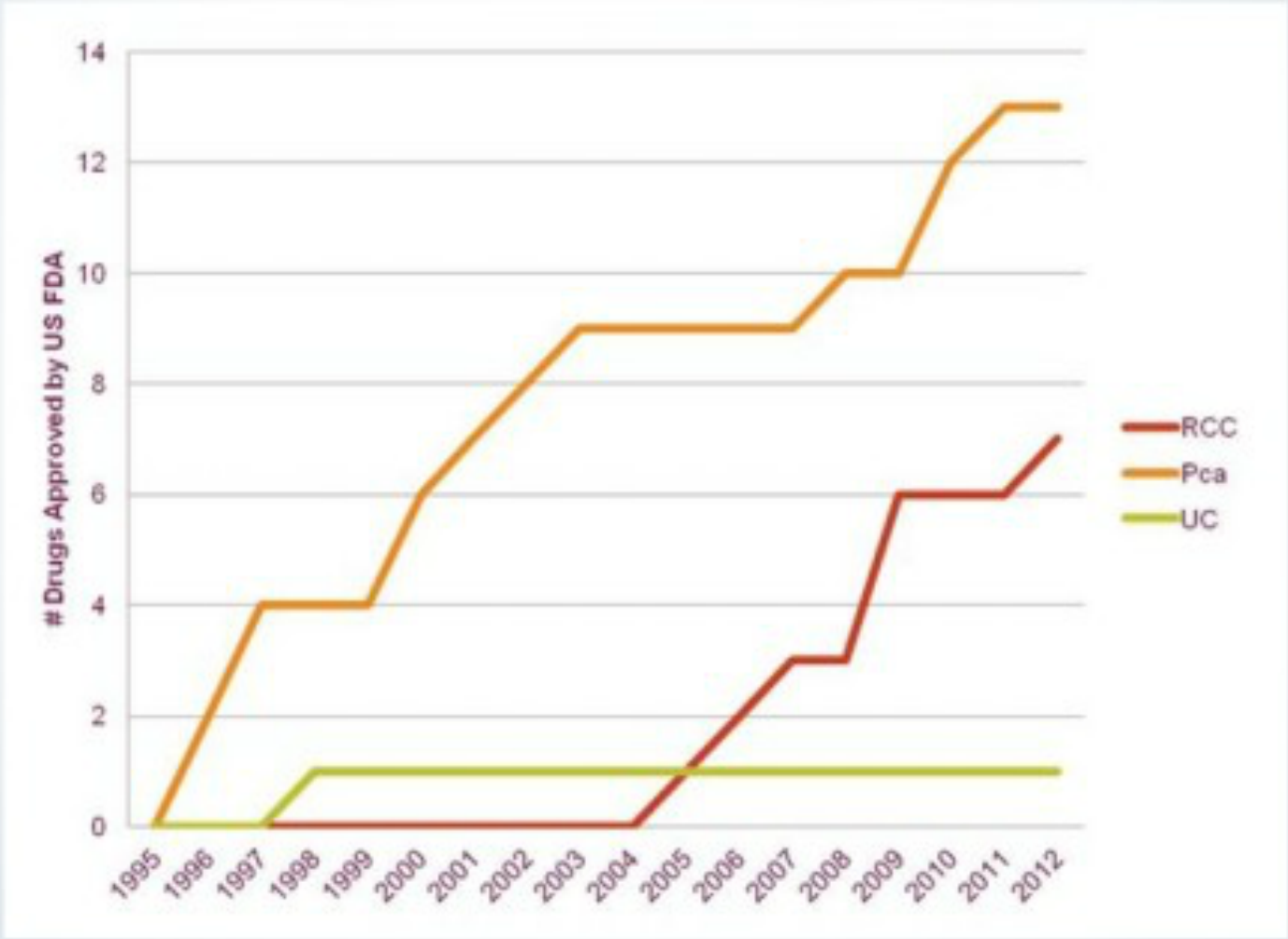
Advisory Role, Honoraria:

- ✓ **Roche**
- ✓ **Italfarmaco**

Outline

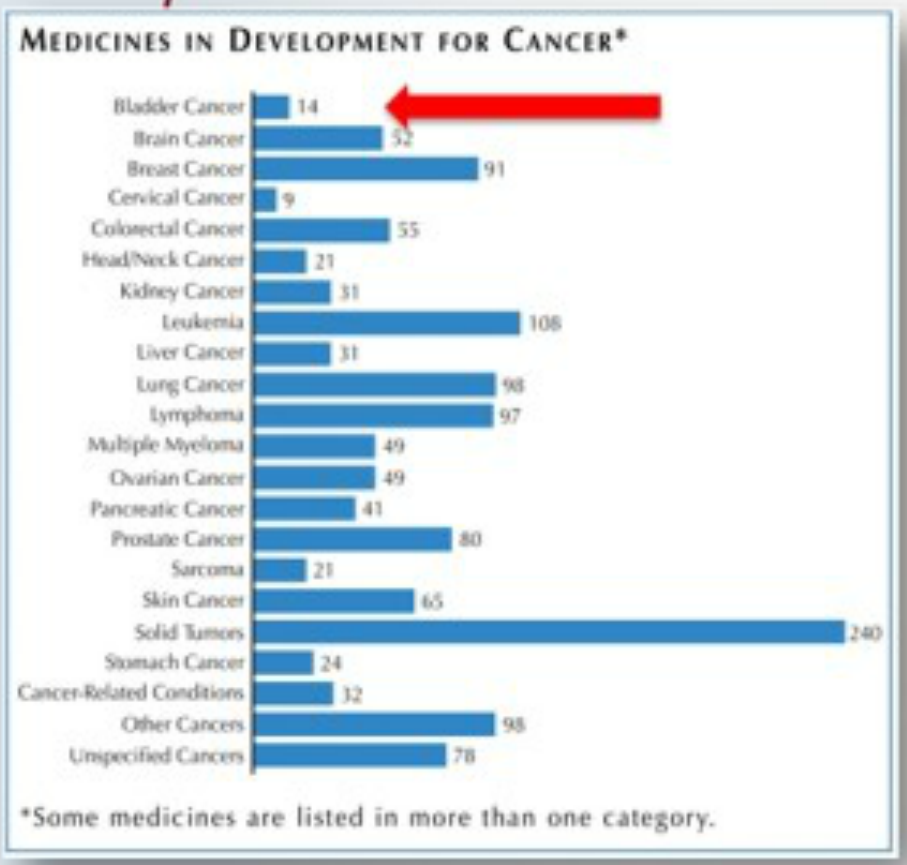
- Introduction
- Where we currently are
  - Neoadjuvant chemotherapy
  - Adjuvant chemotherapy
  - First line
  - Targeted agents
- Clinical and molecular biomarkers
- Conclusions

Drug Approvals in GU Cancers



Courtesy Matt Galsky, New York, NY

Are we making progress? How can we do better?



- Understand barriers
- Improve risk prediction and communication
- Design trials/treatments for "real world" patients
- Improve therapies/patient selection

PhRMA Report 2011, Medicines in development for cancer

Urothelial Carcinoma of the Bladder

Natural History

Vaidja A, J _Urol 2001

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Neoadjuvant chemotherapy

The Oncologist®

Editorial

Invasive Bladder Cancer: Ignoring the Data

DEREK RAGHAVAN

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Disclosures of potential conflicts of interest may be found at the end of this article.

The Oncologist 2013;18:895–896 www.TheOncologist.com

- Despite the sobering facts on surgery alone and robust results from multiple randomized trials testing neoadjuvant chemotherapy, data from 2003 to 2008 demonstrated that ***only 12%*** of patients treated at leading academic institutions across the United States were treated with neoadjuvant cisplatin-based chemotherapy.
- National data show ***even less*** use.

Dean F. Bajorin and Harry W. Herr, JCO 2011

Adjuvant chemotherapy

Tabella 2. Studi di chemioterapia adiuvante dopo cistectomia

Investigatore	Anno	Regime	Chemio	No Chemio	Risultati
Logothetis (1)	1988	CISCA	62	71	Beneficio Non randomizzato
Skinner (2)	1991	CAP	47	44	Beneficio Pochi pazienti
Stockle (3;4)	1992	M-VAC/M-VEC	23	26	Beneficio No terapia a ripresa
Studer (5)	1994	DDP	40	37	Non beneficio
Bono (6)	1995	CM	48	35	Non beneficio per N0
Freiha (7)	1996	CMV	25	25	Beneficio in relapse free survival
Otto (8)	2001	M-VEC	55	53	Non beneficio
Cognetti (9)	2008	GC	97	86	Non beneficio per N0 o N+
Paz Ares (10)	2010	PGC	78	64	Beneficio in OS e PFS

CISCA=cisplatino, ciclofosfamide e doxorubicina; CAP= cisplatino, ciclofosfamide e doxorubicina; M-VAC= methotrexate, vinblastina, doxorubicina e cisplatino; M-VEC= methotrexate, vinblastina, epirubicina e cisplatino; DDP or C= cisplatino; CMV= cisplatino, methotrexate e vinblastina, GC= gemcitabina e cisplatino

PCG=paclitaxel, ciplatino, gemcitabina

European Urology

European Urology 48 (2005) 189–201

Review—Bladder Cancer

Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

Accepted 6 April 2005

Available online 25 April 2005

	(no. events/no. entered) Adj CT	Control	O-E	Variance
Single agent cisplatin				
Studer	23/46	22/45	0.23	11.03
Sub-total	23/46	22/45	0.23	11.03
Cisplatin-based combinations				
Skinner	34/50	40/52	-5.24	18.39
Bono	14/43	23/47	-3.91	9.04
Freiha	13/26	17/25	-2.18	7.39
Stockle	20/26	20/23	-5.48	9.07
Otto	28/55	29/53	-2.86	14.11
Sub-total	109/200	129/200	-19.66	58.00
Total	132/246	151/245	-19.43	69.03

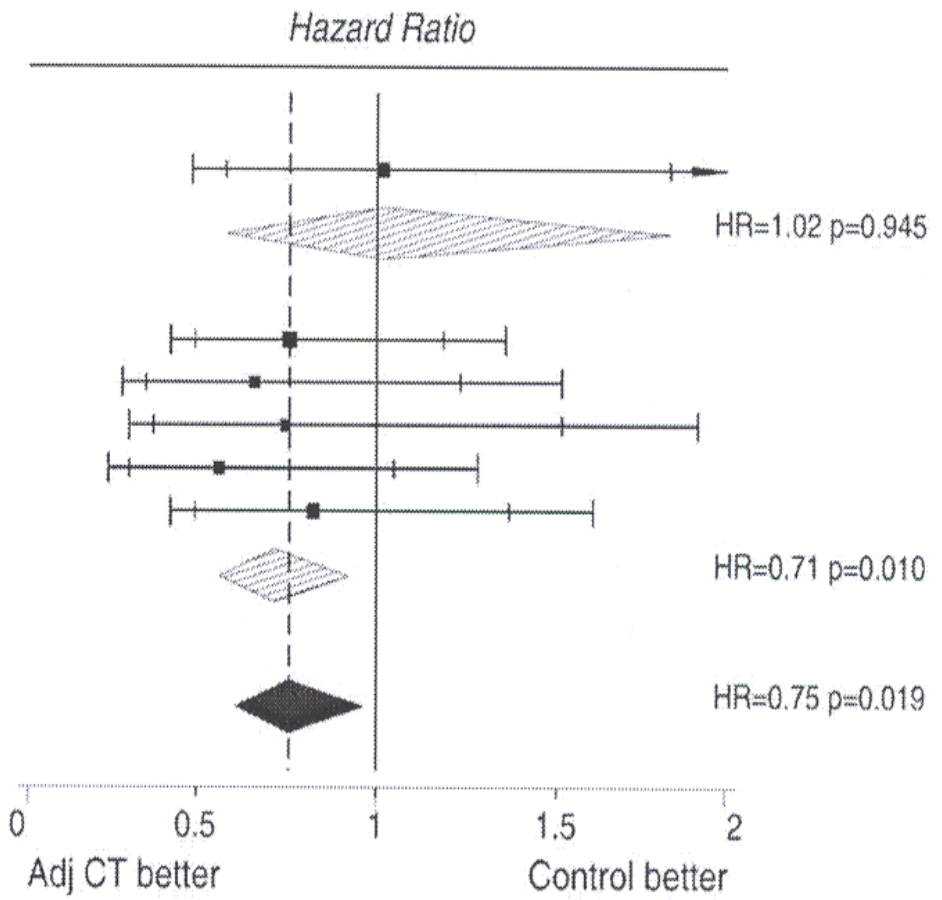


Fig. 1. Hazard ratio plot for survival. Each individual trial is represented by a square, the centre of which denotes hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars mark 95% CI. Size of square is directly proportional to amount of information in the trial. The black diamond gives the overall hazard ratio for combined results of all trials; the centre denotes hazard ratio and the extremities the 95% CI. The shaded diamonds represent hazard ratios for the trial groups; the centre denotes the hazard ratio and the extremities the 95% CI. Trials are ordered chronologically by date of start of trial (oldest first).

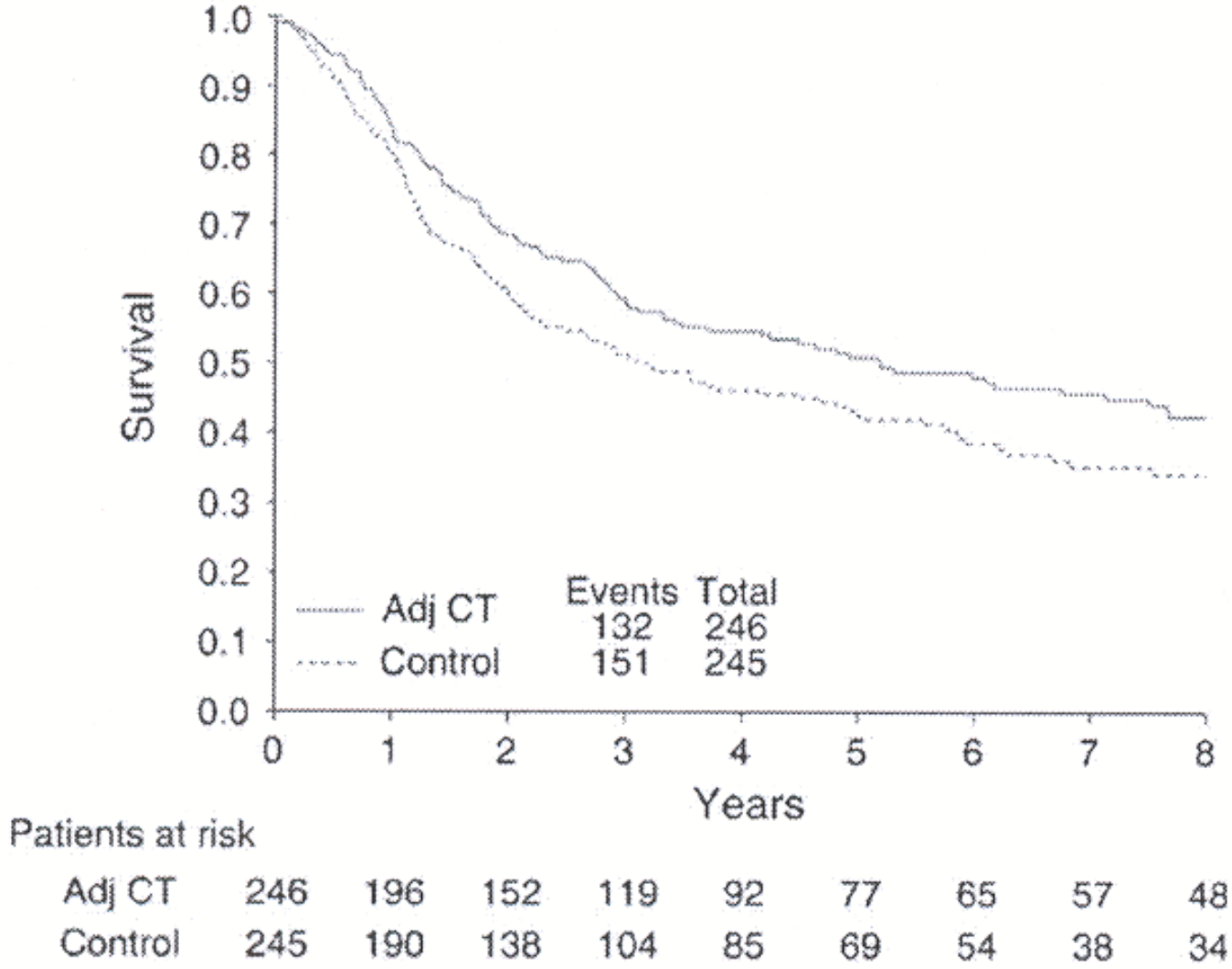


Fig. 2. Kaplan-Meier curve for survival (All trials).

Meta-Analysis of Adjuvant Chemotherapy for Bladder Cancer: Overall Survival: IPD *vs* AD

	IPD[1]	AD[2]
RR	0.75	0.74
p	*0.019*	*0.001*
Heter. Test	0.81	0.80
Absolute Benefit	9%	11%

[1]Vale, Eur Urol 2005; [2]Ruggeri, Cancer 2006

Una metanalisi su 6 studi randomizzati ha valutato i dati di sopravvivenza di 491 pazienti (11). Nonostante i dati suggeriscano un incremento assoluto in sopravvivenza del 9% a 3 anni, il ruolo della chemioterapia adiuvante è ancora oggetto di discussione e né gli studi randomizzati, né la meta-analisi hanno fornito dati sufficienti per raccomandarne l'utilizzo nella pratica clinica (**Livello di Evidenza2++; Forza della Raccomandazione C).**

adjuvant gemcitabine and cisplatin (GC) and those receiving chemotherapy at relapse.[50]

Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, current data suggest that adjuvant chemotherapy may delay recurrences, which may justify the administration of chemotherapy in those at a high risk for relapse.[51] A minimum of three cycles of a cisplatin-based combination, such as MVAC, or more commonly now GC, may be used in patients undergoing adjuvant therapy. Regimen and dosing recommendations are mainly based on studies in advanced disease. Carboplatin should not be substituted for cisplatin in the perioperative setting. No data support the use of adjuvant chemotherapy for non-urothelial carcinomas, regardless of stage.

Patients with tumors that are pathologic stage T2 or less and have no nodal involvement or lymphovascular invasion are considered to have lower risk and do not necessarily require adjuvant chemotherapy. Some groups suggest stratifying patients based on the p53 status of the tumor, because tumors with more than 20% of positive cells seem to have a higher risk for systemic relapse. Determining the p53 status of the tumor is still considered an experimental procedure and is not part of routine management.

disease.[53] Because local recurrence rates are high for some patients after cystectomy (32% for pT3-T4 patients and 68% for patients with positive surgical margins),[37] adjuvant radiation therapy is reasonable to consider in these patients. Radiotherapy to 40 to 45 Gy, with or without concurrent cisplatin, could be used. The safety of higher doses, especially in the setting of a neobladder, needs to be further studied. Since pT3a to pT4a patients are also at high risk of developing metastatic disease, they are also treated with first-line multidrug chemotherapy if their renal function is adequate for cisplatin. Radiation and multidrug chemotherapy should not be given concurrently.

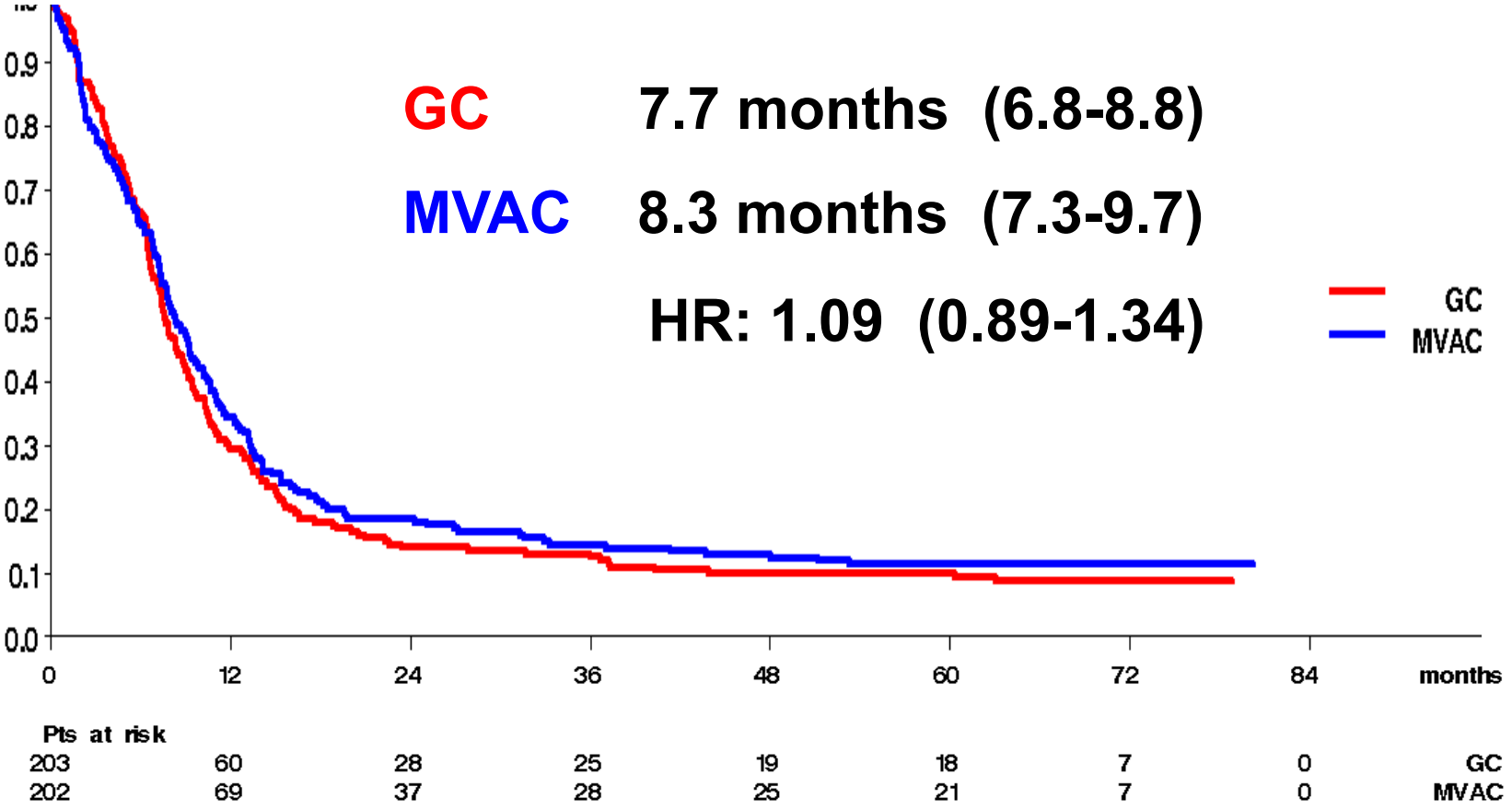
Bladder-Preserving Options

Within the categories of T2 and T3a urothelial carcinomas, selected patients may be considered for bladder-preserving approaches.[54] Options include aggressive endoscopic TUR alone, TUR followed by chemotherapy alone, radiotherapy alone, or a combination of chemotherapy and radiotherapy. Partial cystectomy, also a form of bladder preservation, has been discussed above. No uniform consensus has been reached about the applicability of these approaches to the management of T2 tumors.

Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those

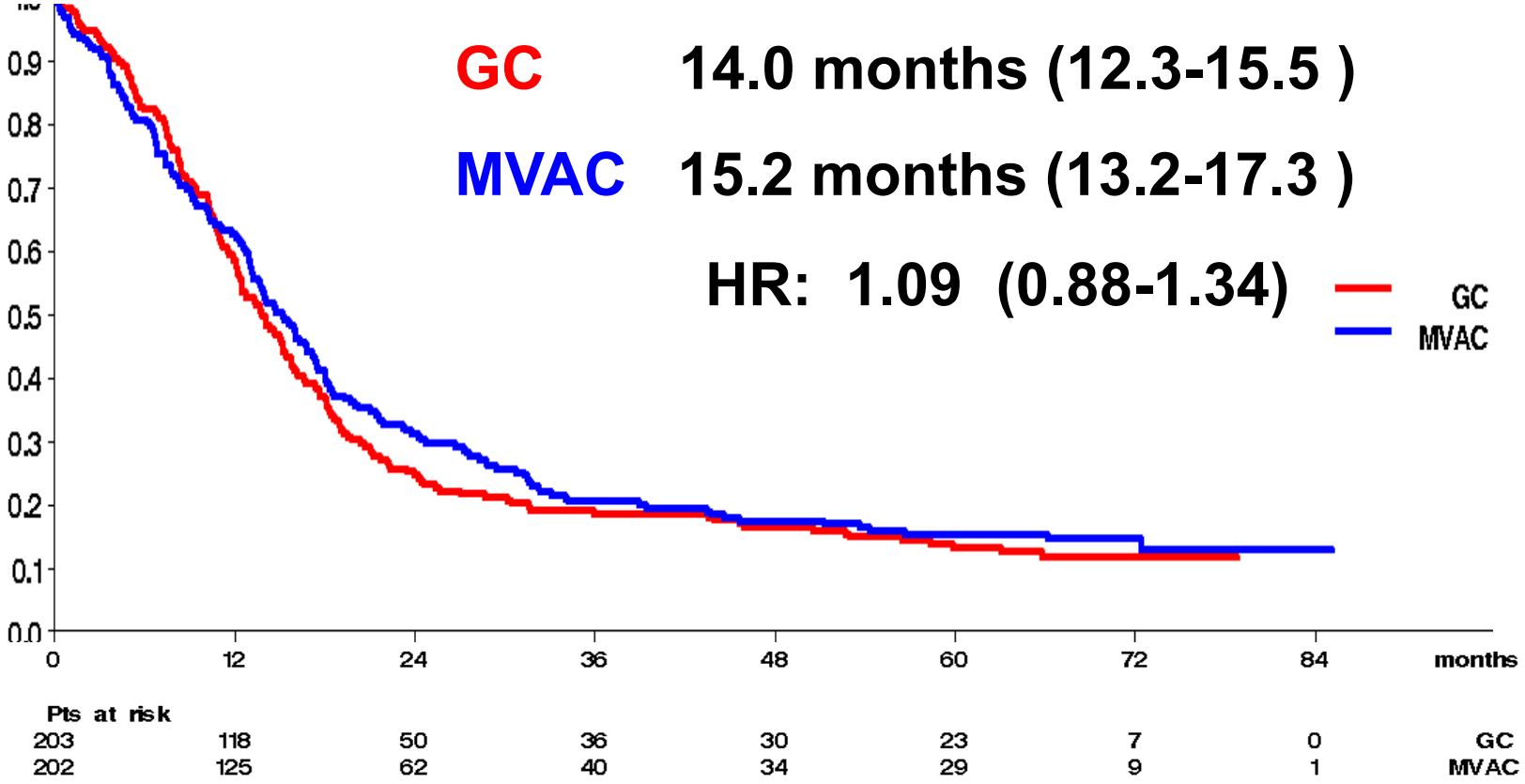
First line

GC *vs.* MVAC trial - 5-year update
Progression-free survival

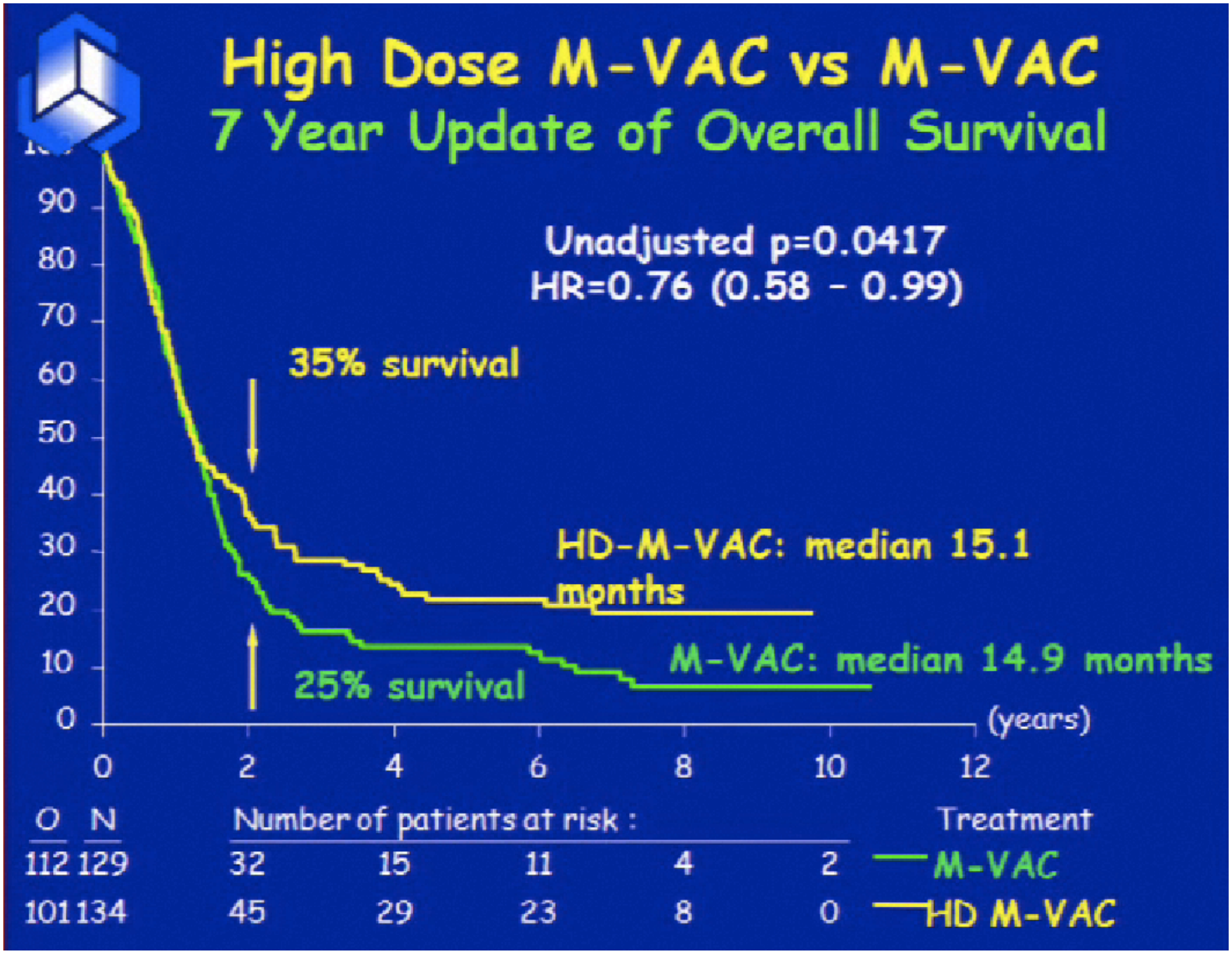


von der Maase H et al. J Clin Oncol. 2005

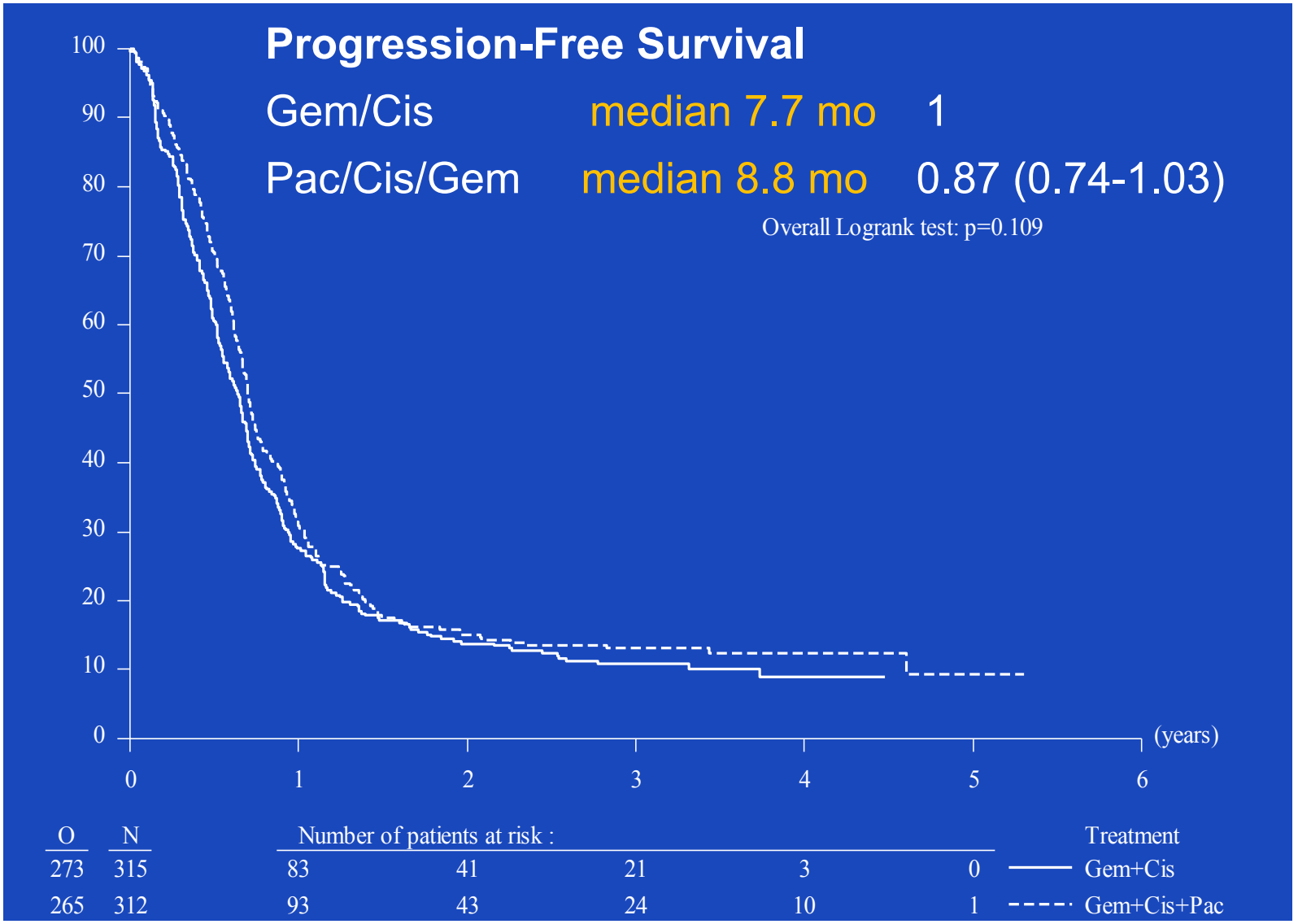
GC *vs.* MVAC trial - 5-year update
Overall survival



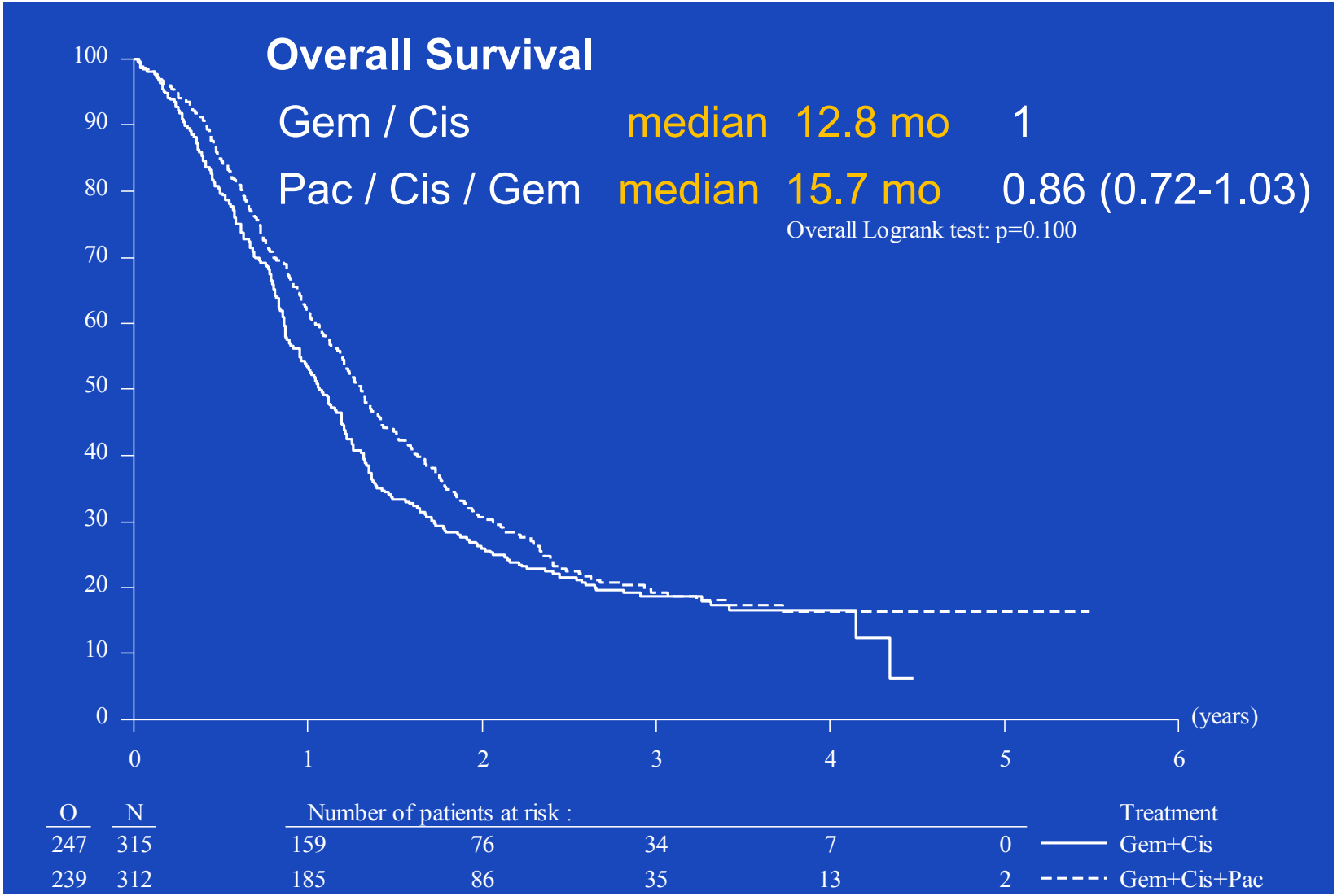
von der Maase H et al. J Clin Oncol. 2005



Sternberg CN, Eur J Cancer 2006



Bellmunt J et al. ASCO 2007



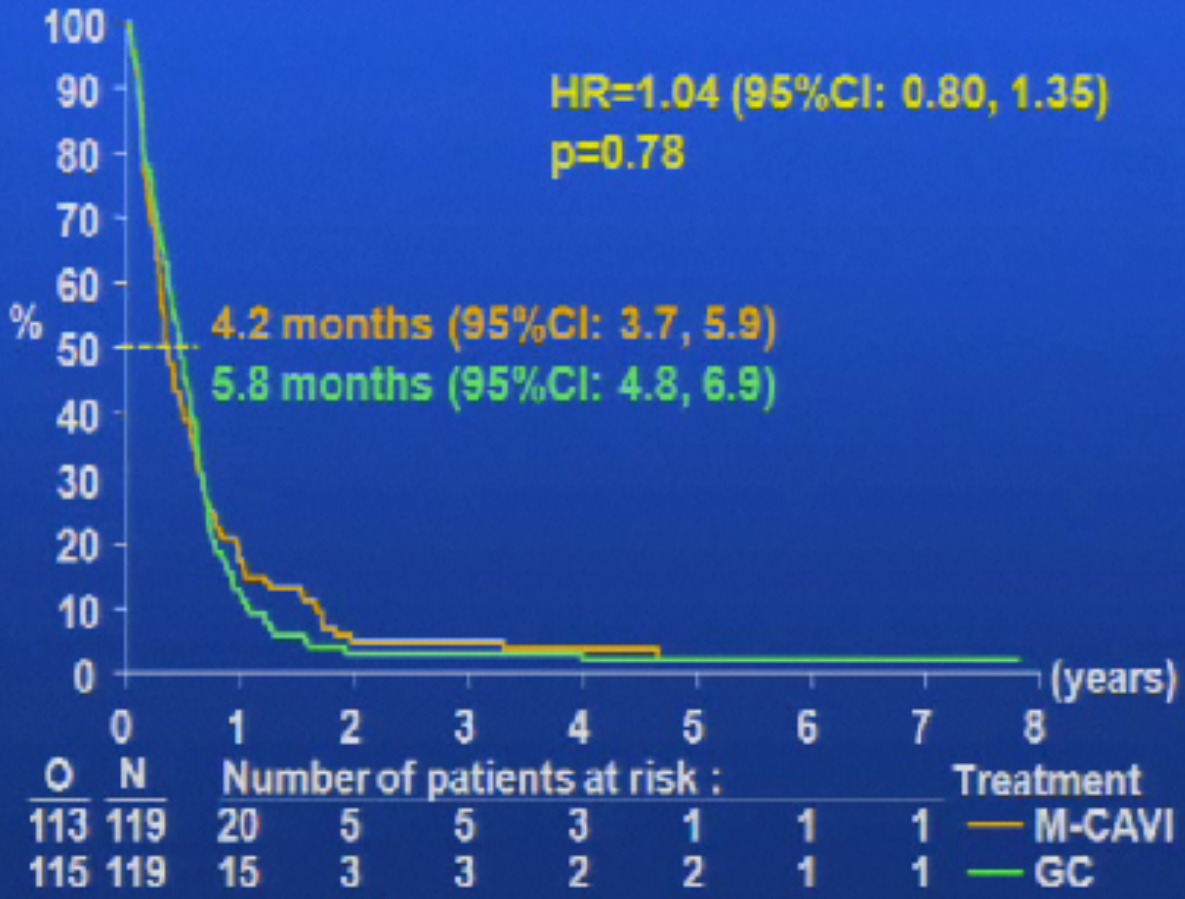
Bellmunt J et al. ASCO 2007

Unfit for Cisplatin

Who is unfit for cisplatin ?

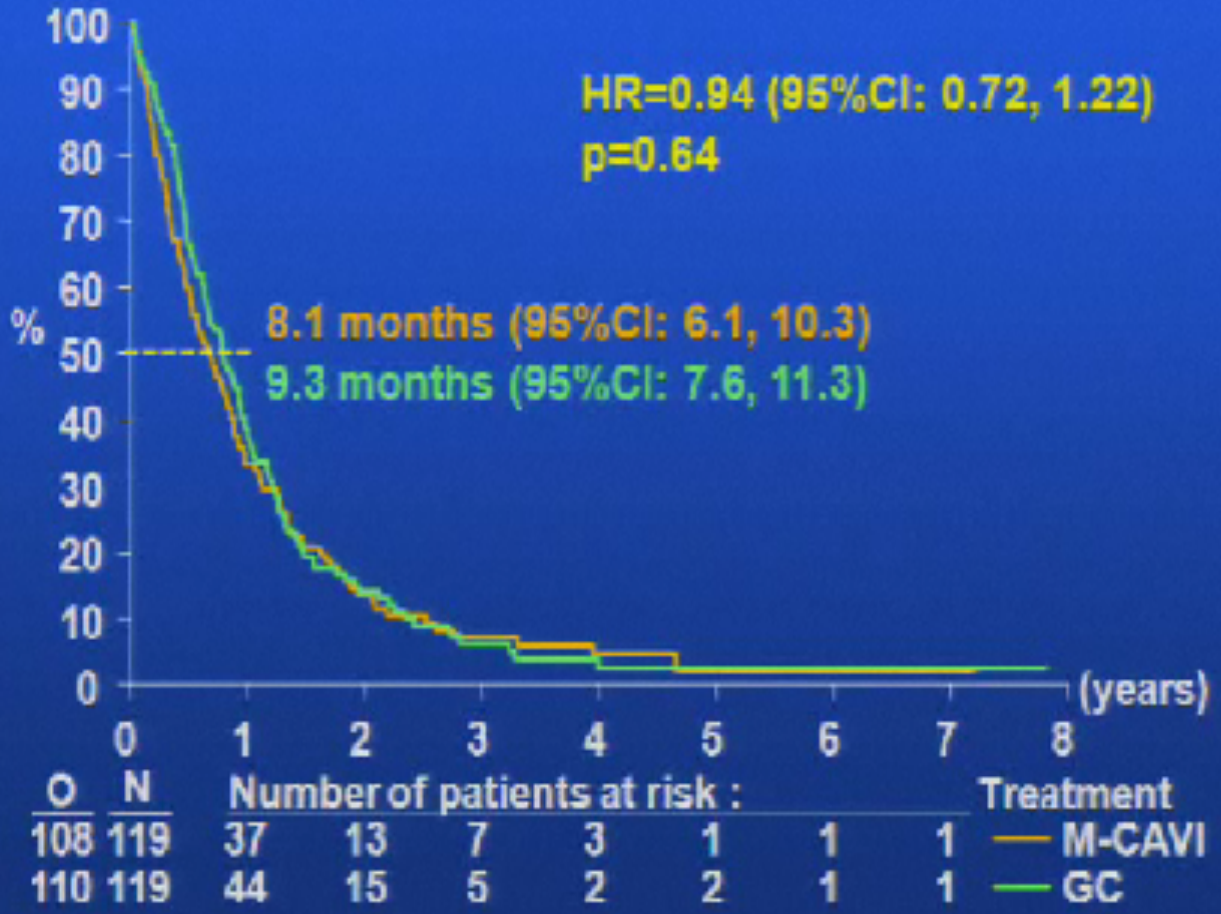
- Patients meeting at least one of the following criteria were considered unfit for cisplatin:
- ECOG performance status of 2
- creatinine clearance below 60 mL/min
- grade 2 or greater hearing loss
- grade 2 or greater neuropathy
- and/or New York Heart Association Class III heart failure.

First valid PFS data in this patient population



De Santis M et al, J Clin Oncol 2010 (suppl: abstr LBA 4519)

First valid OS data in this patient population

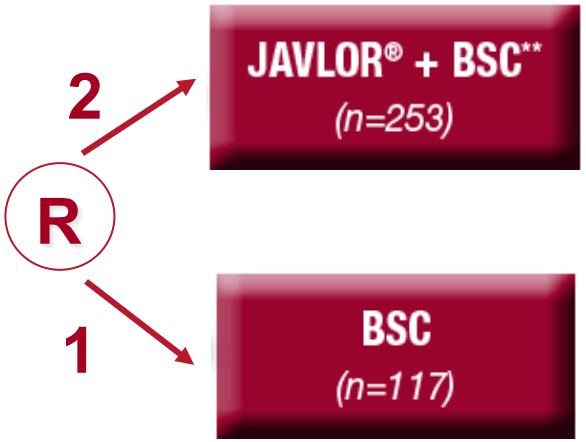


De Santis M et al, J Clin Oncol 2010 (suppl: abstr LBA 4519)

Second line

Second-line phase III trial: Vinflunine + BSC vs. BSC
Bellmunt J, JCO 2009

▶ **370 pazienti, 83 centri, 21 nazioni**



- **PS 0: 320 mg/m² q3w**
- **PS1 o PS0 con RT pelvica: 280 mg/m² q3w**

(Ciclo 1) 320 mg/m² q3w dal Ciclo 2 in assenza di tossicità ematologica che causi ritardo o riduzione di dose durante il Ciclo 1

Obiettivi dello Studio:

▶ **Primario**
Sopravvivenza globale

▶ **Secondario**
Sopravvivenza libera da progressione, Risposte obiettive, Controllo di malattia, Beneficio clinico, QoL

Second-line phase III trial: Vinflunine + BSC vs. BSC
Bellmunt J, JCO 2009

ITT Population

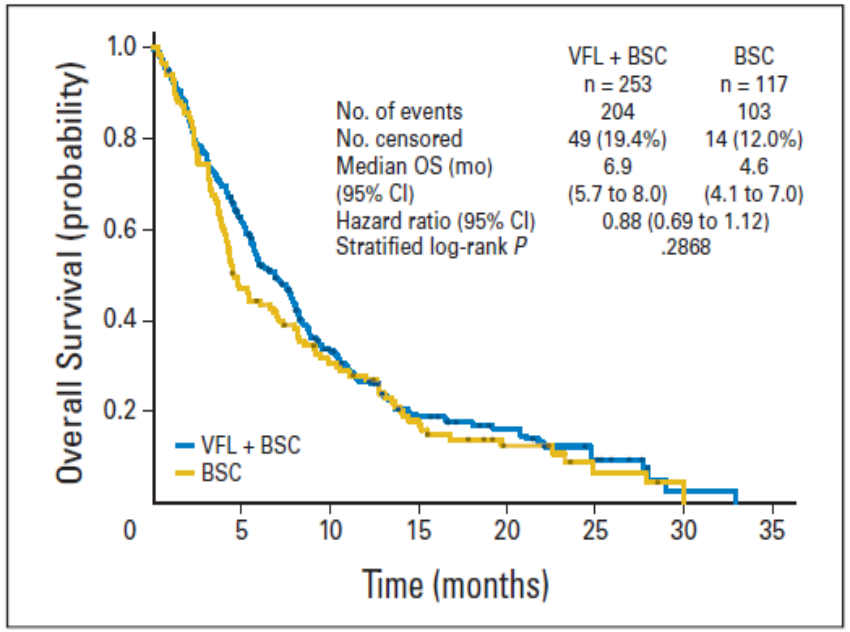


Fig 2. Overall survival (OS) in the intent-to-treat population (n = 370). VFL, vinflunine; BSC, best supportive care.

The ITT population includes 13 patients (9 in BSC arm and 4 in treatment arm) with major inclusion criteria violations that could have bettered survival curves for ITT population (i.e. all 9 pts in BSC arm were not progressing after platinum CT, while only 3 out of 4 were in this condition in JVL+BSC arm).

Eligibile population

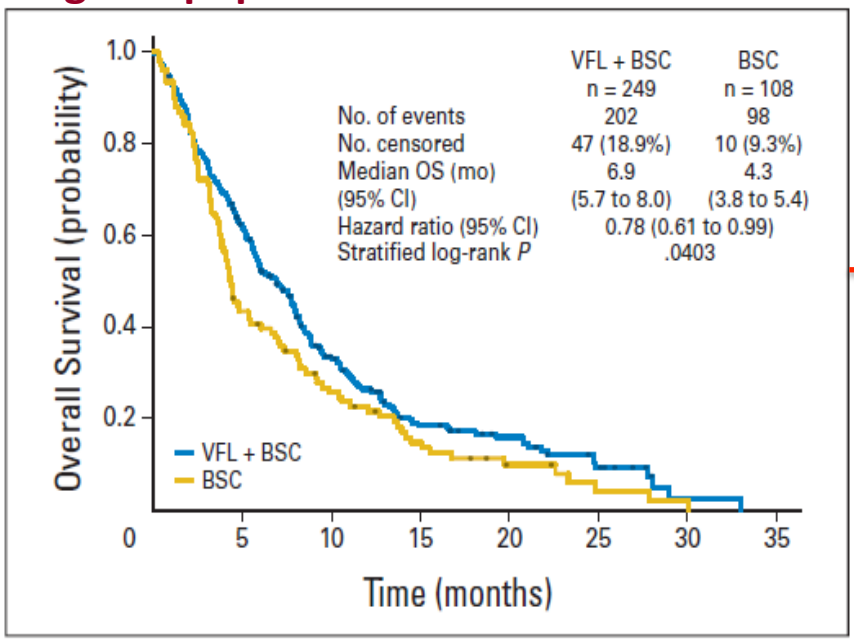
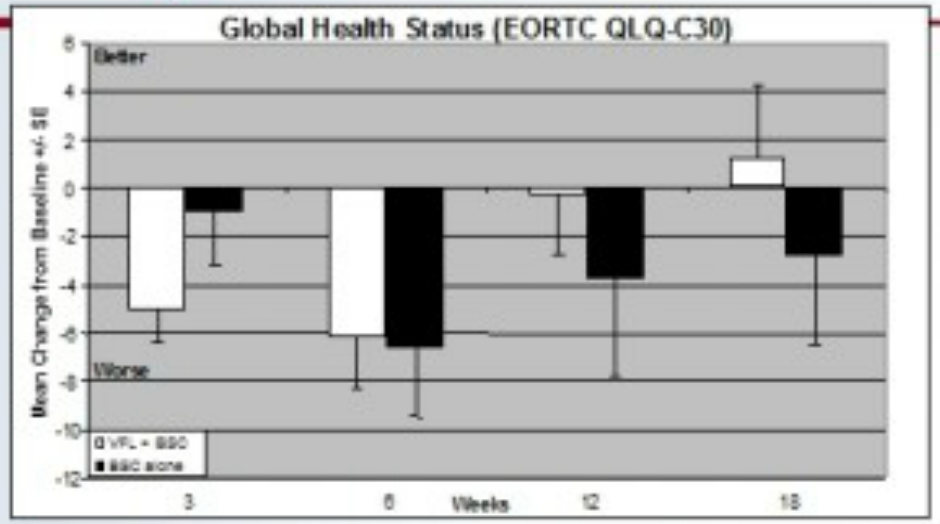


Fig 3. Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.

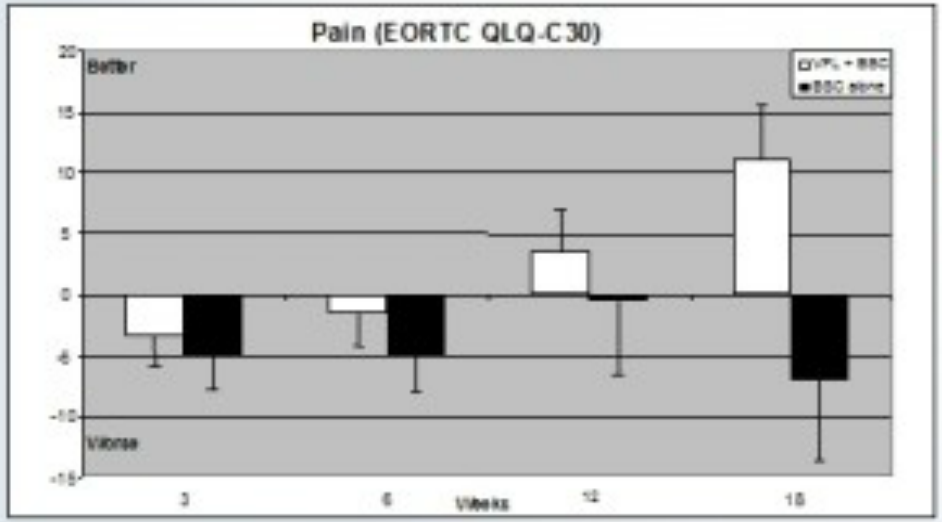
In the eligible population are excluded the 13 patients with major inclusion criteria violations.
Eligible population analysis of survival is granted by EMA ICH.

Quality of Life and Pain Scores

Bellmunt J, JCO 2009



- Trend towards better quality of life for VFL+BSC compared to BSC alone, starting from week 6 (p= 0.658)



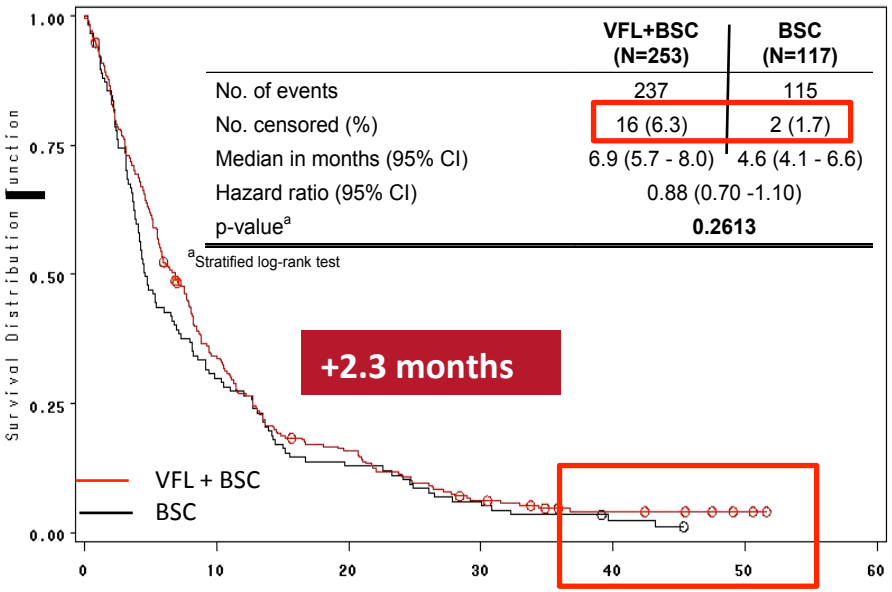
- Different evolution of the pain scale between VFL +BSC compared toBSC alone (p = 0.046)

Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy

J. Bellmunt, R. Fougeray, J.E. Rosenberg, H. von der Maase, F.A. Schutz, Y. Salhi, S. Culine & T.K. Choueiri

Ann Oncol. 2013 Feb 17. [Epub ahead of print]

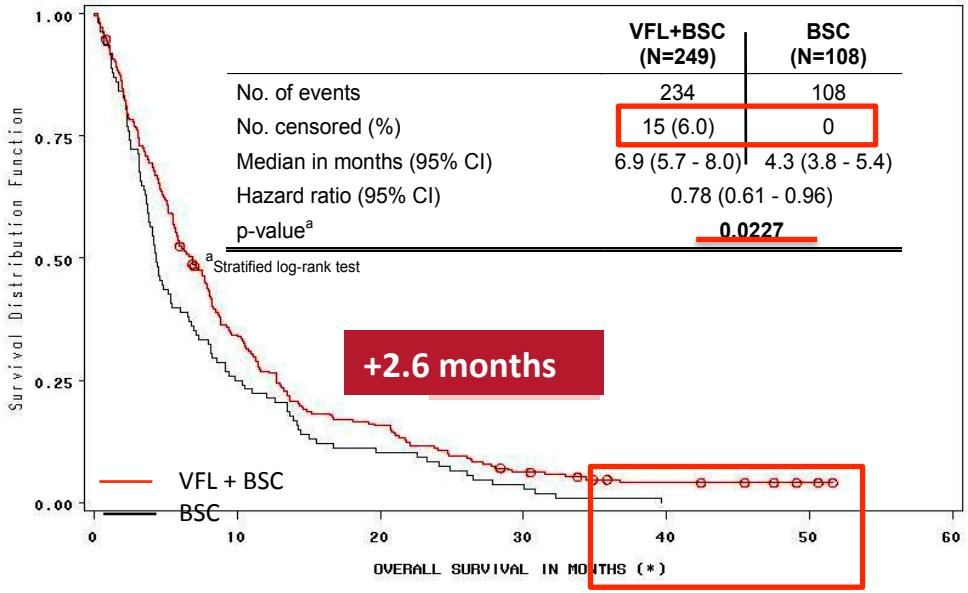
▶ Overall Survival



	VFL+BSC (N=253)	BSC (N=117)
No. of events	237	115
No. censored (%)	16 (6.3)	2 (1.7)
Median in months (95% CI)	6.9 (5.7 - 8.0)	4.6 (4.1 - 6.6)
Hazard ratio (95% CI)	0.88 (0.70 -1.10)	
p-value[a]	**0.2613**	

[a]Stratified log-rank test

ITT Population



	VFL+BSC (N=249)	BSC (N=108)
No. of events	234	108
No. censored (%)	15 (6.0)	0
Median in months (95% CI)	6.9 (5.7 - 8.0)	4.3 (3.8 - 5.4)
Hazard ratio (95% CI)	0.78 (0.61 - 0.96)	
p-value[a]	**0.0227**	

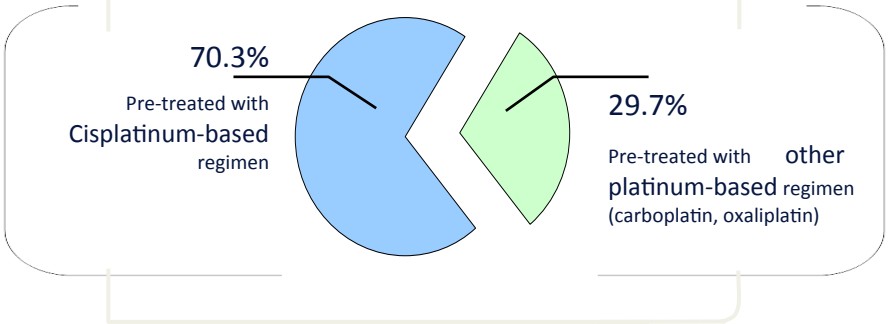
[a]Stratified log-rank test

Eligibile population

>2 months, maintained at > 3.5 yr FUP

Sub-analysis of Phase III – Vinflunine + BSC vs BSC (N=357)
Impact of prior therapy on survival
Fougeray R, ASCO 2012

- Multivariate analysis including prognostic factors (liver involvement, hemoglobin, PS) and prior platinum administration, did not show effect of CDDP on OS.
- Differences in prognostic factors between CISPLATIN and NO CISPLATIN groups may explain the differences in OS in patients who undergo 2nd line therapy.



The choice of Cisplatin or no Cisplatin chemotherapy in the first line did not impact subsequent benefit of vinflunine over best supportive care.

→ Subsequent benefit of Vinflunine over BSC is the same whatever the platimum-based combination used as prior treatment

Targeted therapies

Selected Phase 2 studies with targeted agents alone or with chemotherapy

Author, year of publ.	Agent	N (evaluable)	ORR (%)	PFS (mo)	OS (mo)
Petrylak (SWOG), 2009	Gefitinib	29	3	NR	NR
Wulfing, 2009	Lapatinib	59 (34)	1.7	2.0	4.2
Dreicer, 2009	Sorafenib	27	0	2.2	8
Gallagher, 2010	Sunitinib 50 mg/d: 4w/2w 37.5 mg/d (cont)	 45 (41) 32 (28)	 7 3	 2.4 2.3	 7.1 6.1
Necchi, 2012	Pazopanib	41	17 (conf.)	2.6	4.7
Stadler, ASCO GU 2011	Volasertib	50	14	1.4	NR
Milowski, ASCO GU 2011	Everolimus	37	5	3.3	10.3
Hahn, 2011	Gemcitabine +Carboplatin +Bevacizumab	43	72	8.2 (median)	19.1 (median)
Wong, 2012	Cetuximab Paclitaxel + Cetuximab	11 (closed) 28	NR 25	NR 3.8	NR 9.5
Choueiri, 2012	Docetaxel +Vandetanib Docetaxel	70 72	7 11	2.6 1.6	5.9 7.0

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Summary for bladder cancer 2012: Targeted agents and biomarkers

- EGFR targeting agent combined with chemotherapy, so far, showed no benefit[1]
- Recent data with sunitinib, pazopanib and bevacizumab confirm the potential role of angiogenic pathway as a target for therapy in advanced urothelial cancer patients[2,3]
  - Bevacizumab plus chemo phase III trial on the way
- Biomarkers: IL-8 (prognostic/predictive) deserves further prospective evalution and validation[3,4]

[1] Grivas P, et al. ASCO 2012, abstr.4506
[2] Gallager DJ, et al. J Clin Oncol. 2010
[3] Bellmunt J, et al, Ann Oncol 2011
[4] Necchi A, et al, ASCO2012, abstr 4507

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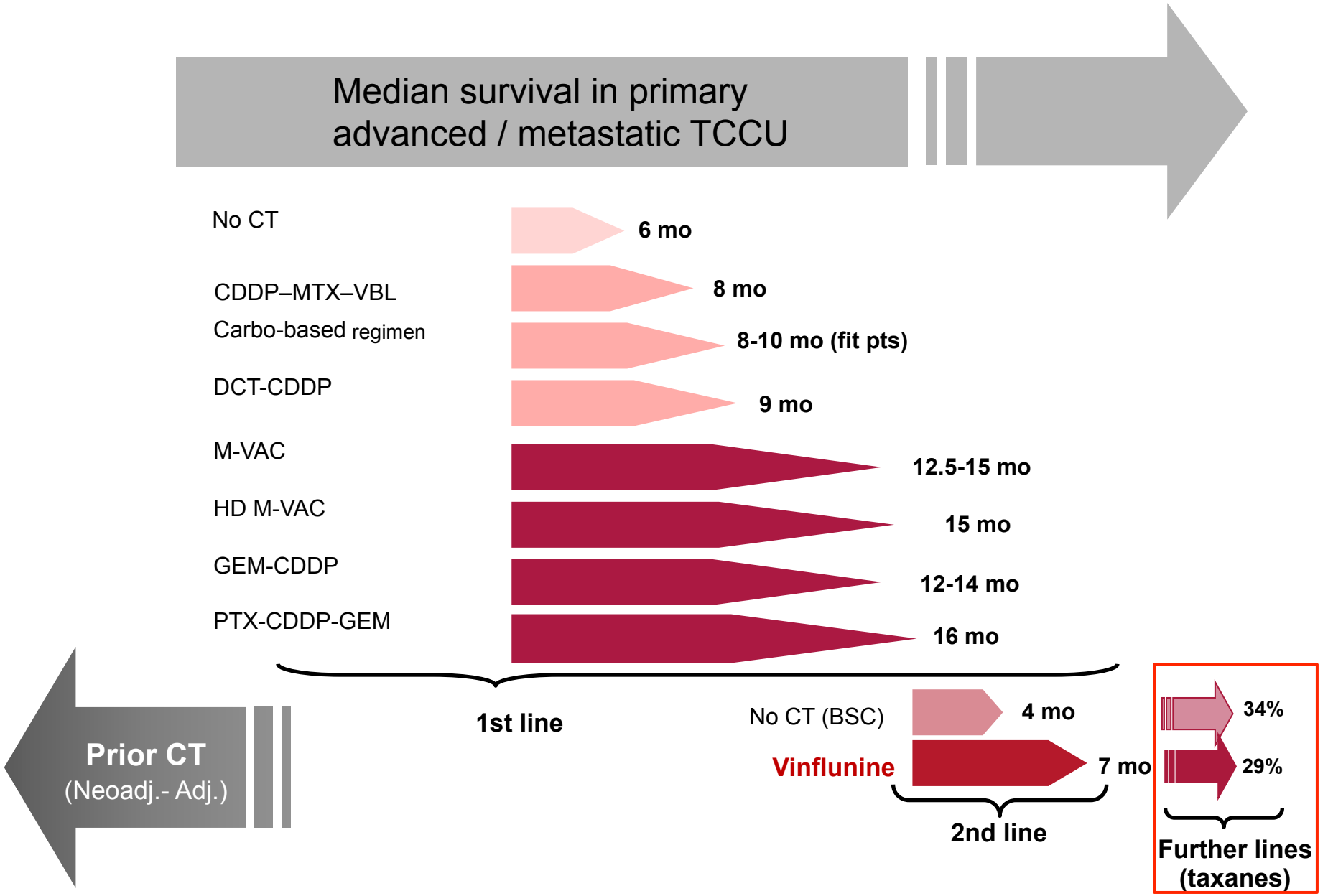
A trend to increasing lines in Advanced/Metastatic TCCU



Bellmunt, J. Clin. Oncol. 2009, appendix on-line

Multi-disciplinary team

"La chiave di tutte le scienze è, senza dubbio, il punto di domanda"

Honorè de Balzac
(1799-1850)