Systemische medikamentöse Therapie des Harnblasenkarzinoms

Welche Therapie für welchen Patienten?

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Berlin, 03. 10. 2010

Disclosure of Potential Conflicts of Interest

1. Employment or Leadership Position

none

2. Advisory Role

Novartis, GSK, Pierre-Fabre, Roche, Amgen,

3. Stock Ownership

none

4. Honoraria

Pfizer, Sanofi Aventis, Eli Lilly

5. Financing of Scientific Research

none

6. Expert Testimony

none

7. Other Financial Relationships

none

Standard chemotherapy 2010

First-line treatment for "fit" patients:

Gemcitabine / Cisplatin
MVAC (+ GCSF)
HD-MVAC + GCSF

⇓

Level 1 evidence
Grade of recommendation: A

ESMO CPG 2010

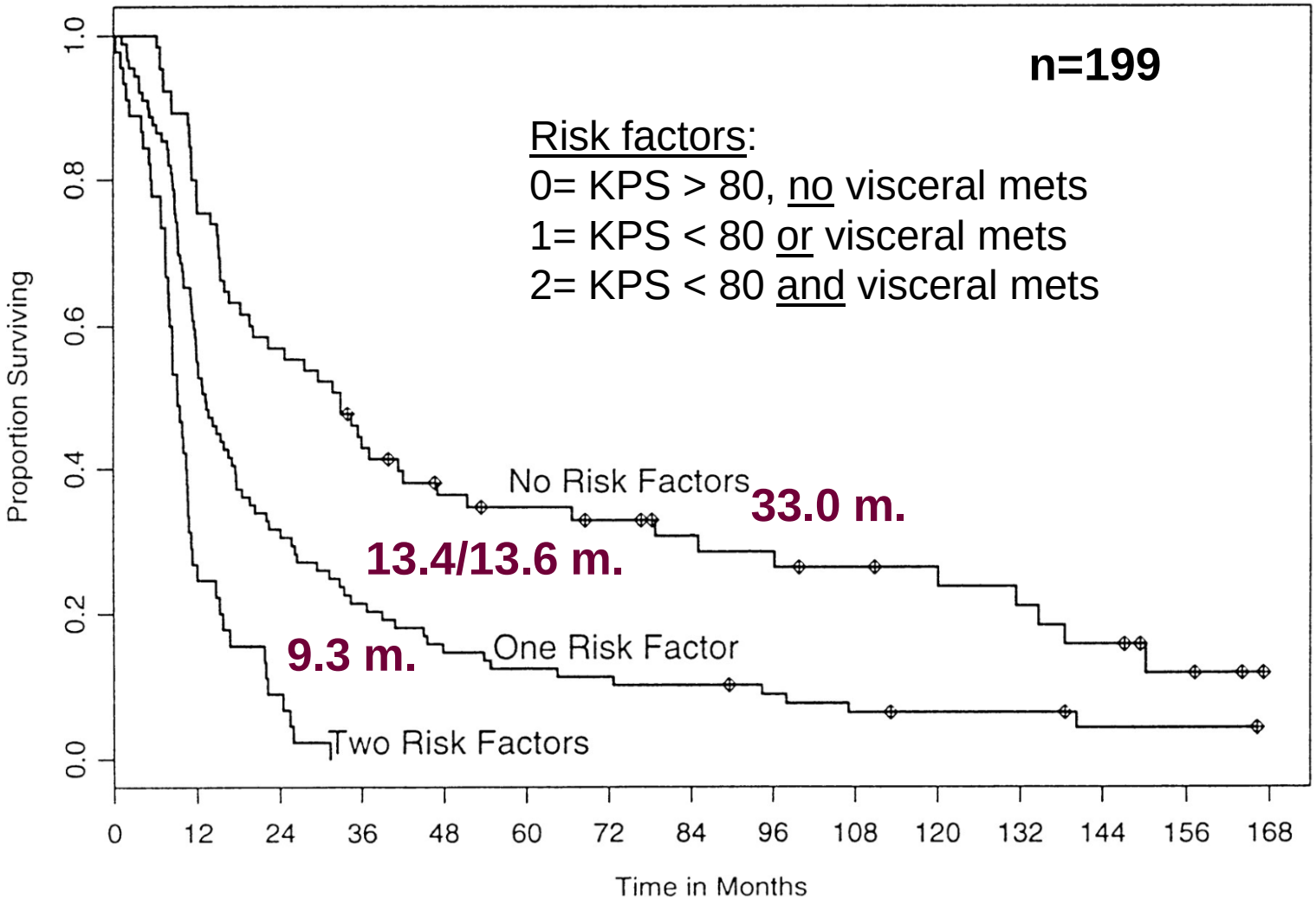
Long term follow-up of cisplatin combination-chemotherapy of the post-MVAC-era

(randomized phase III-trials)

Author Treatment arm	N (ITT)	median f-up (yrs)	Median survival (mos)	5-year (%)
Sternberg, 2006	263			
MVAC	**129**	**7.3**	**14.9**	**13.5**
HD-MVAC	**134**		**15.1**	**21.8**
von der Maase, 2005	405			
MVAC	**203**	**>5**	**14.0**	**15.3**
Gem/Cis	**202**		**15.2**	**13.0**
visc mets				**6.8**
no visc mets				**21.9**

There is long term survival (only) with cisplatin combination-chemotherapy!

Survival for all patients grouped according to number of risk factors present at baseline



Bajorin, D. F. et al. J Clin Oncol; 17:3173-3181 1999

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„Unfit“ for cisplatin

- More than 50% of patients with urothelial cancer are not eligible for cisplatin based chemotherapy.[1-4]

- So far no standard chemotherapy has been established for this patient group.

[1] Dash A, et al., Cancer. 2006 Aug 1;107(3):506-13.
[2] Nogue-Aliguer M, et al., Cancer. 2003 May 1;97(9):2180-6.
[3] Balducci L, Oncologist. 2000;5(3):224-37.
[4] De Santis et al, Curr Opin Urol 17:363–368, 2007

Who are the „unfit“?

Ineligibility for cisplatin:

- **Comorbidities:**
  - renal function impairment
  - congestive heart failure
  - cardiovascular risk factors
  - neuropathy

- **Performance status**

Comorbidity, age and trials

- Incidence and prevalence of comorbidity increase with age. .....Comorbidity is the rule, not the exception.

Boyd CM, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Jama 2005;294(6):716–24

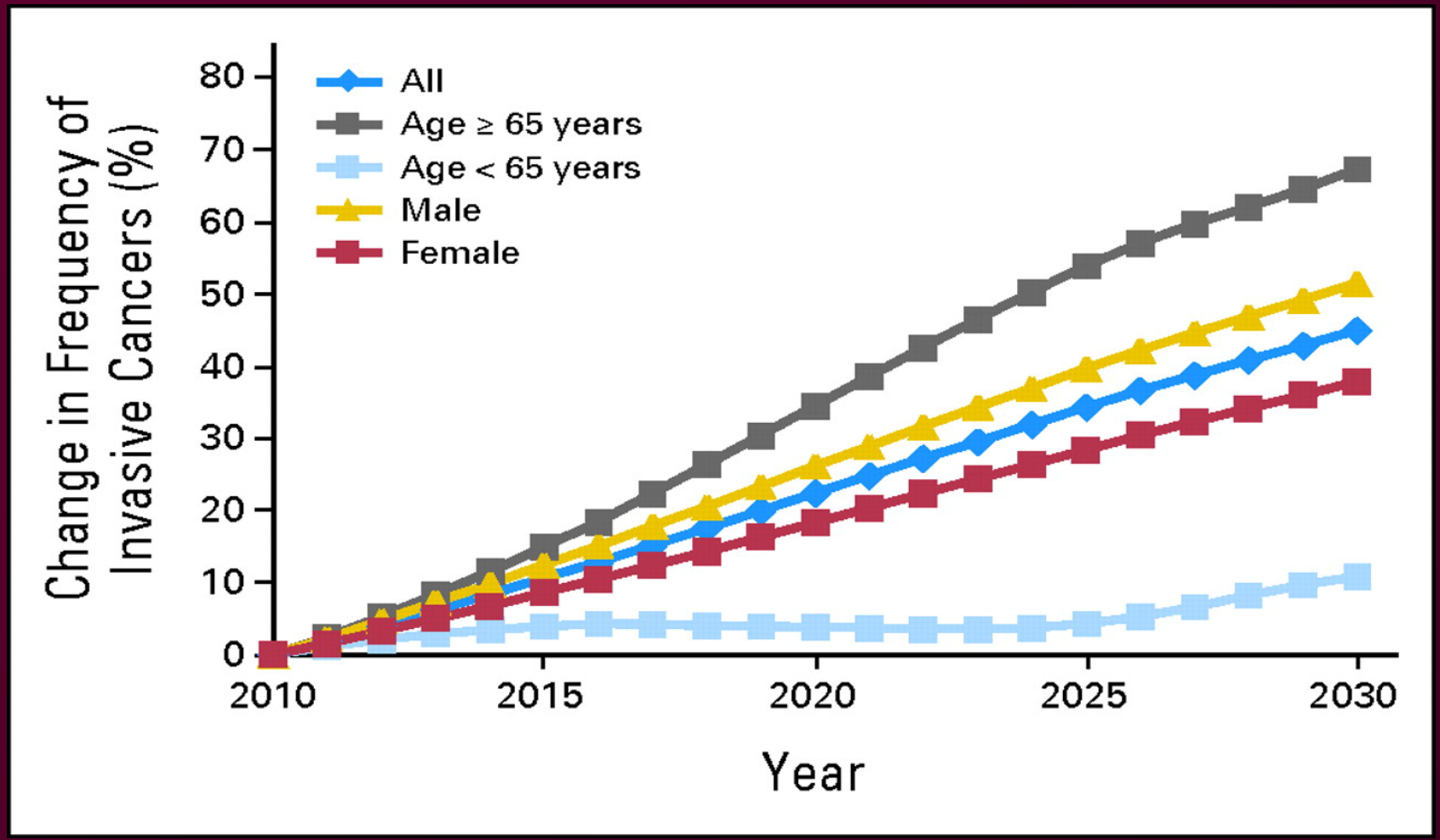
- Patients with a history of cancer have an average of three comorbid conditions.

Seo PH,et al, Cancer 2004;101(10):2276–84.

- „Despite the importance of comorbidity in clinical practice, it has not gained a considerable role in clinical trials, medical statistics and clinical practice“.

Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis **1970**;23:455–69.

Projected change in frequency of invasive cancers in the United States by age and sex.



Pal S K , Hurria A JCO 2010;28:4086-4093

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Inconvenience of cisplatin

- **time consuming**
  (need for overnight hospitalization, prolonged outpatient i.v. hydration)
- **Quality of life-reduction**
- **Nausea**
- **Fatigue**
- **Fluid overload**
- **Cardiovascular risk**
- **Renal toxicity**
- **Neurotoxicity**

Do we need cisplatin?

- **A matter of debate.....**

1. Sonpavde G, Galsky MD, Vogelzang NJ: First-line systemic therapy trials for advanced transitional-cell carcinoma of the urothelium: Should we stop separating cisplatin-eligible and -ineligible patients? J Clin Oncol doi:10.1200/JCO.2010.29.1047

2. REPLY TO G. SONPAVDE ET AL
JCO SEP 1, 2010:E443E444; PUBLISHED ONLINE ON JULY 19, 2010; 10.1200/JCO.2010.29.3779

Cisplatin vs Carboplatin in cisplatin - eligible patients

- **No data from randomised phase III studies**
  - Dreicer, 2004

MVAC vs Carbo/Ptx: Early termination due to slow accrual

- **Randomized phase II studies**

regimens	CR %	OS mos	source
MVAC vs MVECa	25 11	13 9.5	Petrioli, 1996
MVAC vs Carbo/ MV	13 0	16 9 (DSS)	Bellmunt, 1997
Cis/ Gem vs Carbo/Gem	14.5 1.8	12.8 9.8	Dogliotti, 2007

→ **Carbo: CR ↓ Survival ↓**

- **Phase II studies with Carboplatin/ Paclitaxel**
  - Redman, 1998
  - Vaughn, 1998
  - Small, 2000

→ **RR 21 - 50%**
CR 0 - 20%
OS 8.5 - 9.5 mos

EORTC definition of „fit“ and „unfit“ for cisplatin

„fit“	„unfit“
GFR ≥ 60 ml/min and PS 0-1	GFR < 60 ml/min and /or PS 2

Purpose of study strategy - developement

EORTC:
First randomized phase II/III trial for „unfit“ TCC patients

Randomized phase II/III trial assessing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI) in patients (pts) with advanced urothelial cancer (UC) “unfit” for cisplatin based chemotherapy: updated phase II results and risk group analysis of EORTC study 30986

M. De Santis[1], J. Bellmunt[2], R. de Wit[3], G. Mead[4], J.M. Kerst[5], M. Leahy[6], P. Maroto[7], I. Skoneczna[8], S. Marreaud[9], R. Sylvester[10]

[1] Kaiser Franz Josef - Spital and ACR-ITR VIEnna, Vienna; [2] Hospital Vall d'Hebrón, Barcelona; [3] Erasmus Univ Med Center, Rotterdam, [4] Royal South Hants Hospital, Southampton;[5] Netherlands Cancer Institute, Amsterdam; [6] St James Hospital, Leeds; [7] Hospital Santa Creu, Barcelona; [8] Warsaw; Maria Sklodowska-Curie Memorial Cancer Centre, [9] EORTC Data Center, Brussels

phase II, JCO 2009
phase III, ASCO 2010

Phase III results of EORTC study 30986
Patient characteristics

		GC (n=119)	M-CAVI (n=119)
Male, n (%)		90 (75.6)	96 (80.7)
Female, n (%)		29 (24.4)	23 (19.3)
Age (yrs)	Median	70	72
	Range	36 - 87	34 - 86
	≥71 yrs, n (%)	57 (47.9)	67 (56.3)
WHO – PS	0, n (%)	20 (16.8)	19 (16.0)
	1, n (%)	46 (38.7)	46 (38.7)
	2, n (%)	53 (44.5)	54 (45.4)
Associated chronic disease, n (%)		60 (50.4)	55 (46.2)

Phase III results of EORTC study 30986
Disease characteristics

	GC (n=119) n (%)	M-CAVI (n=119) n (%)
Liver mets	20 (16.8)	29 (24.4)
Visceral mets	55 (46.2)	66 (55.5)
Bladder primary	90 (75.6)	87 (73.1)
- Bladder primary target	*24 (26.7)*	*33 (37.9)*
- Bladder primary only target	*14 (15.6)*	*12 (13.8)*
Cystectomy / Cytoprostatectomy	25 (21.0)	23 (19.3)

Phase III results of EORTC study 30986

Results: Toxicity

	GC (n=118) n (%)	M-CAVI (n=118) n (%)
Leucopenia G 3/4 [a]	53 (44.9)	55 (46.6)
Neutropenia G 3/4 [a]	62 (52.5)	75 (63.5)
Thrombocytopenia G 3/4 [a]	57 (48.3)	23 (19.4)
Febrile Neutropenia G 3/4	5 (4.2)	17 (14.4)
Infection G 3/4 [a]	14 (11.8)	15 (12.7)
Severe Acute Toxicity (SAT)*	11 (9.3)	25 (21.2)

[a]not a SAT ; *patients with at least 1 SAT

SAT= severe acute toxicity (death due to toxicity, G4 thrombocytopenia with bleeding, G 3/4 renal toxicity, neutropenic fever G 3/4 or mucositis G 3/4 at least possibly related to study drug)

Phase III results of EORTC study 30986

Results: Best Overall Response

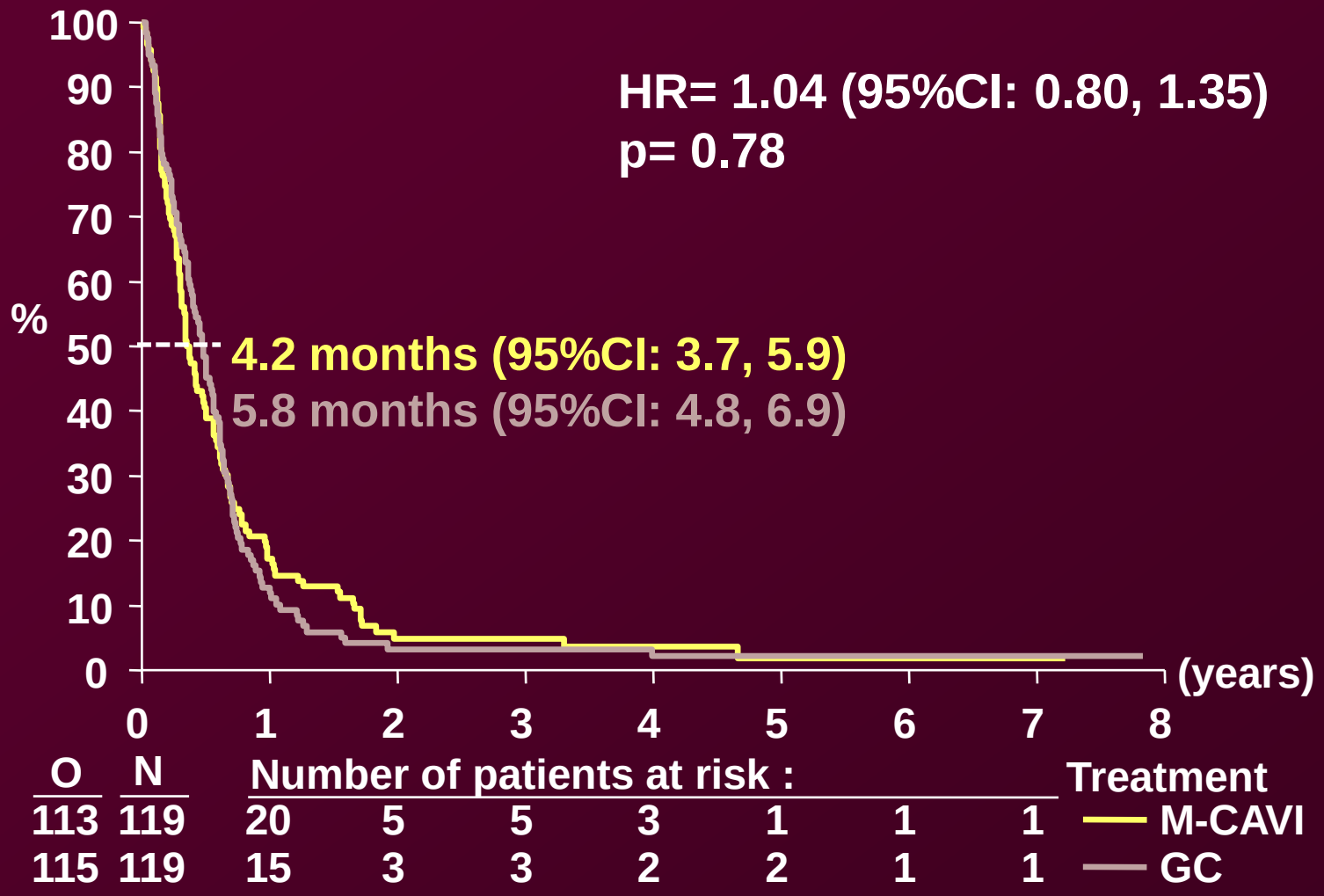
	GC (n=119) n (%)	M-CAVI (n=119) n (%)
CR+PR *Confirmed response*	49 (41.2) *43*	36 (30.3) *25*
No change	39 (32.8)	41 (34.5)
Progression	18 (15.1)	17 (14.3)
Early death	4 (3.4)	10 (8.4)
Not assessable	9 (7.6)	15 (12.6)

The difference in response rate between the two treatment arms is not significant (p=0.08)

The difference in confirmed response rate between the two treatment arms is significant (p=0.01)

Phase III results of EORTC study 30986

Progression-Free Survival



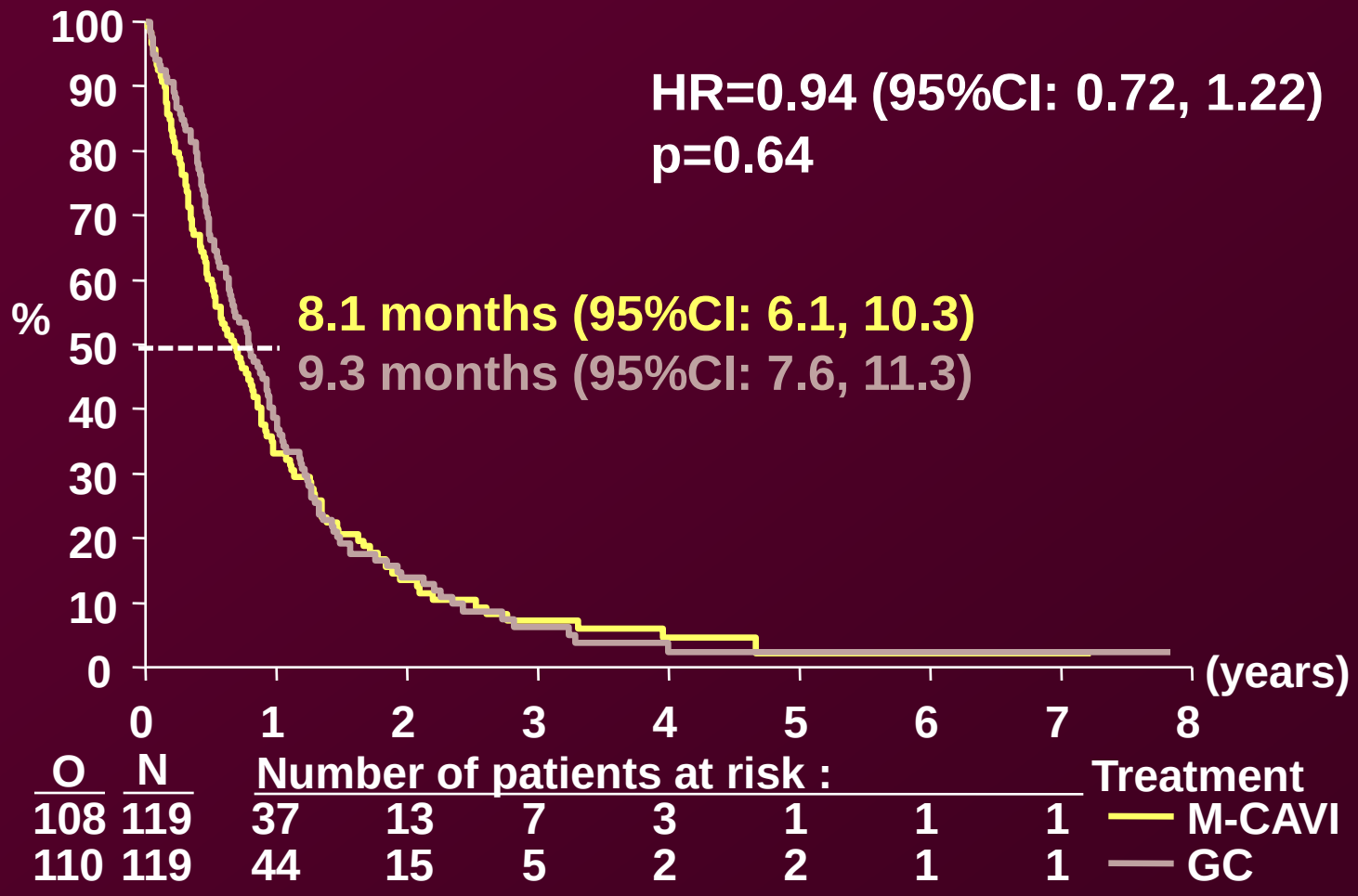
Phase III results of EORTC study 30986

Results: Survival Status

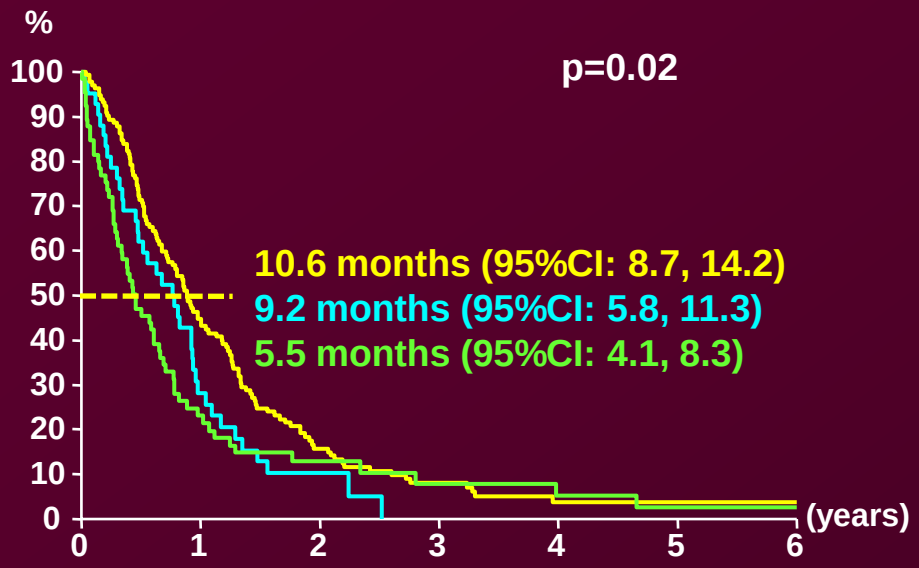
	GC (n=119) n (%)	M-CAVI (n=119) n (%)
Alive	**9 (7.6)**	**11 (9.2)**
Death, cause:	**110 (92.4)**	**108 (90.8)**
- Progression	***82***	***75***
- Toxicity	***3***	***4***
- Chronic disease	***2***	***3***
- Other	***12***	***16***
- Unknown	***11***	***10***

Phase III results of EORTC study 30986

Overall Survival

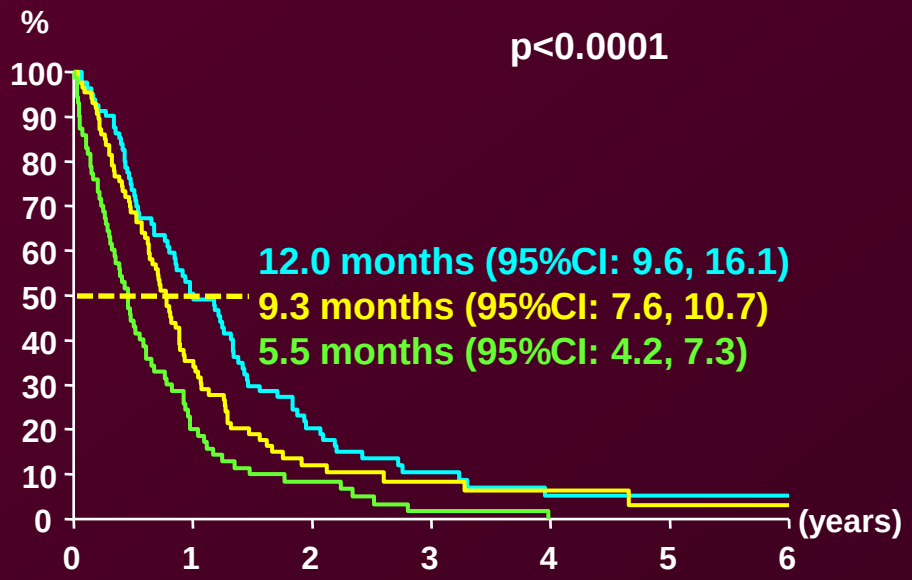


Phase III results of EORTC study 30986
Overall Survival



O	N	Number of patients at risk :					
39	42	11	2	0	0	0	WHO - PS = 2
120	131	56	19	9	3	2	GFR < 60
59	65	14	7	3	2	1	Both

Stratification factors



O	N	Number of patients at risk :					
72	81	39	15	7	3	2	0
77	86	28	8	4	2	1	1
69	71	14	5	1	0	0	2

Bajorin risk group

Options for patients with PS 2 and GFR < 60 ml/min or Bajorin risk group 2?

	PS 2 and GFR < 60ml/min*	Bajorin risk group 2*
OS (mos)	5.5	5.5
RR (%)	26	21
SAT (%)	26	24
Only one chemo-cycle* N (%)	9/46 (20)	10/49 (20)

*phase II data

- Monochemotherapy (gemcitabine, oxaliplatin, taxanes,.....)
- Clinical trial setting (novel agents, monochemotherapy…….)
- Best supportive care (therapeutic goal in unfit and elderly?)

* EORTC 30986 phase II/III results, JCO 2009; LBA, ASCO 2010

How to better select patients for chemotherapy?

- Performance status
  - Valuable, not accurate enough for elderly (>75y)
- Rating of comorbidity?
  - Charlson score, no standard
- Renal function assessment
  - GFR calculation or measurment?
- Comprehensive geriatric assessment, functional status
  - Most probably helpful, but no standard, not validated

Pending results or ongoing trials in unfit or elderly urothelial cancer patients, first-line

- **M-CAVI vs. Gem/Carbo, EORTC 30986-study in unfit TCC patients**
  (phase III results LBA, **ASCO 2010**)

- **Gemcitabine/ vinflunine**
  [closed prematurely due to strategic reasons by company]
  - front-line placebo controlled phase II/III in cisplatin ineligible pts
    [BMS, NCT00389155]

- **Paclitaxel/ gemcitabine (old vs. younger, but NOT unfit)**
  - Pts **aged 70 years or older** (and pts younger than 60 years)
    [SWOG, NCT00022633] → **ASCO 2010**

- **Gemcitabine/ oxaliplatin**
  - Pts unable to receive cisplatin-based chemotherapy due to crcl 30-60 ml/min or PS 2
    [France; NCT00627432]

- **Carboplatin/ gemcitabine/ bevacizumab (ineligible for cisplatin)**
  - KPS>60%, creat <2,0 or GFR>30ml/min
    [MSKCC; NCT00588666]

“Ready to go“ trial in unfit urothelial cancer patients

(Pierre-Fabre)

Randomized phase II trial

vinflunine / gemcitabine

vs

vinflunine / carboplatin

→ Phase III will compare the „winner“ with gem/ carbo

Urothelkarzinom: welche Therapie für welchen Patienten?

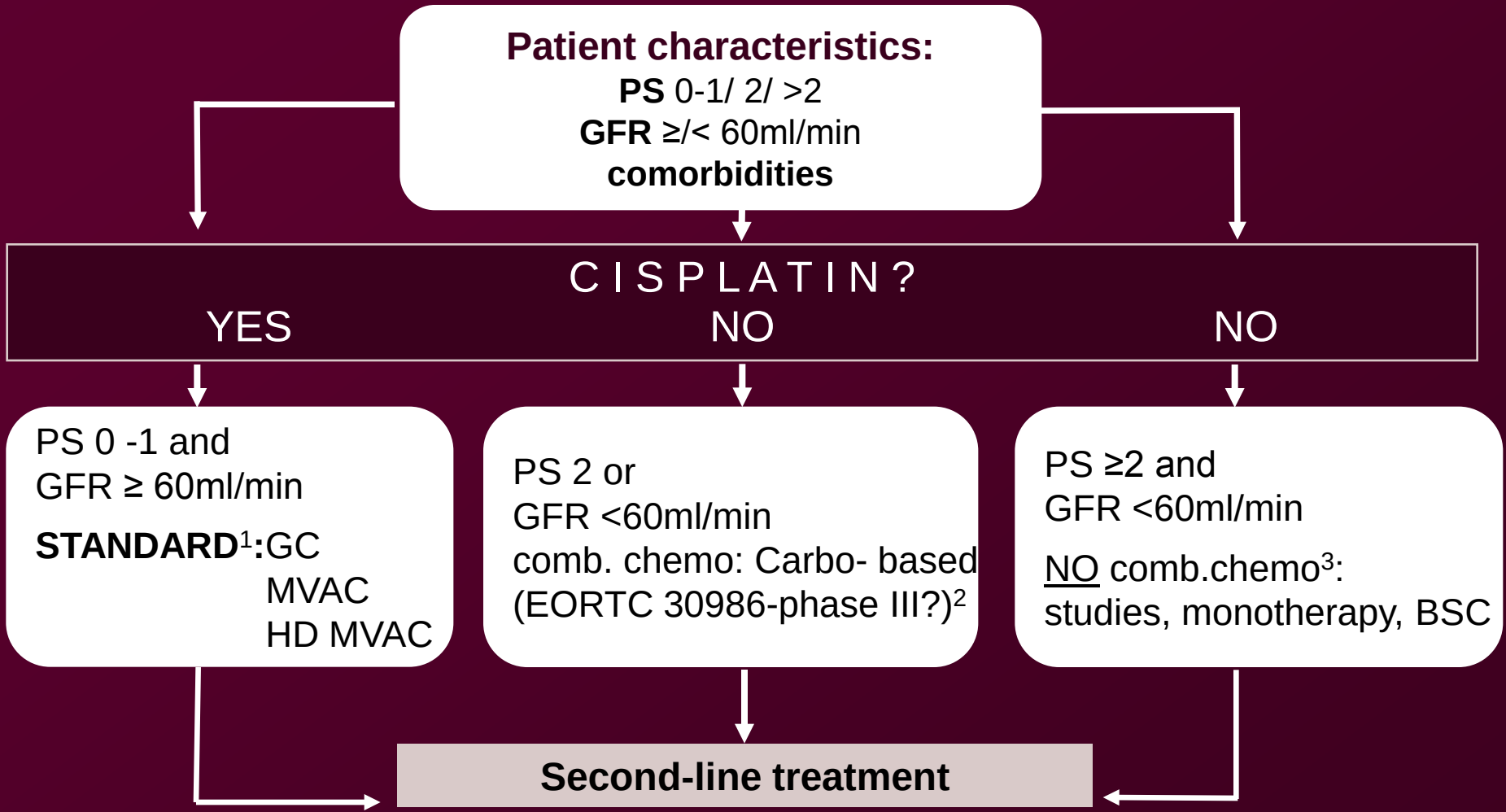
Zusammenfassung (1)

- Komorbidität ist die Regel und nicht die Ausnahme beim Harnblasenkarzinompatienten.
- Cisplatin basierte Kombinationschemotherapie ist der Standard, ABER: > 50%der Patienten sind nicht “fit” für Cisplatin.
- EORTC Definition von “unfit”: PS 2 und/oder GFR <60 ml/min
- In der ersten randomisierten Phase II/III – Studie für „nicht fitte“ Patienten waren M-CAVI und Gem/Carbo wirksam.
- Schwere akute Toxizitäten waren etwas häufiger unter M-CAVI.

Zusammenfassung (2)

- **Nicht „fitte“ Patienten sind keine einheitliche Gruppe**

Metastatic Urothelial Cancer – Treatment - Algorithm



GFR = Glomeruläre Filtrationsrate; PS = Performance Status; CHT=Chemotherapie; BSC = best supportive care
GC = Gemcitabin, Cisplatin; MVAC = Methotrexat, Vinblastin, Adriblastin, Cisplatin; HD= Hochdosis; Carbo = Carboplatin;

[1] Stenzl, Eur Urol 2009; [2] EORTC 30986 study, De Santis, ASCO 2010; [3] De Santis, JCO 2009

Zusammenfassung (3)

- **Dringend erforderlich:**
  - **bessere Selektionskriterien**
  - **bessere Therapieoptionen für Patienten mit Komorbiditäten**
  - **klinische Studien für Subgruppen („unfit“)!**

DANKE !!!