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Chemotherapy in metastatic bladder cancer

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DISCLOSURES

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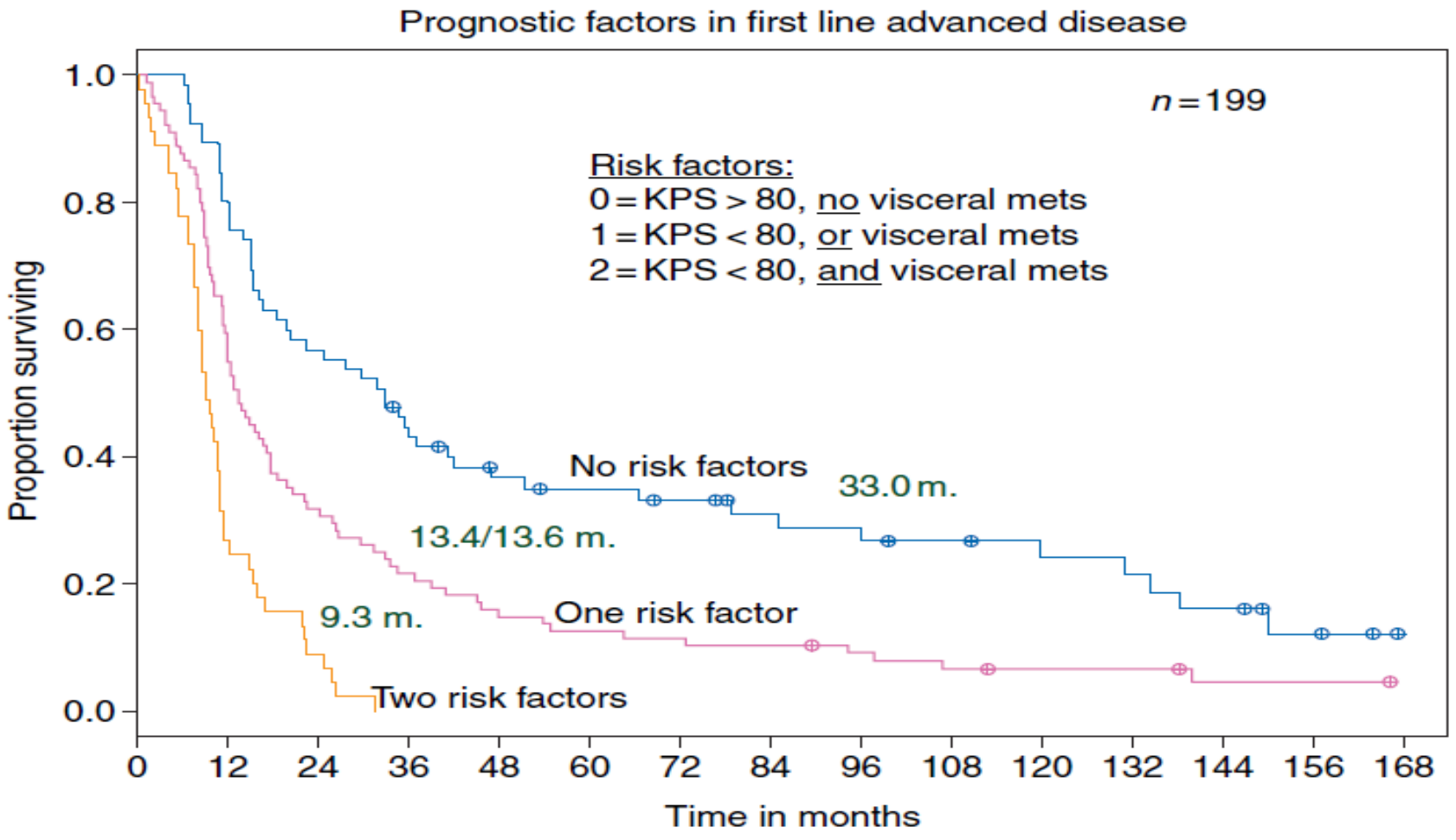
- Speaker’s role: MSD

Chemotherapy

- Prognostic factors
- First line therapy
- Second line therapy

Prognostic factors

- 203 pts, MVAC chemotherapy, retrospective, MSKCC
- 2 risk factors had independent prognosis: Performance status based on KPS (<80), Visceral metastases (liver, lung, bone)
- 0, 1, 2 risk factors



Bajorin et al, JCO 1999;17:3173

First line therapy

- Cisplatin eligible
- Cisplatin ineligible

Eligibility for cisplatin

- Defining medically frail patients
  - ECOG performance status >=2
  - Creatinine clearance < 60ml/min
  - Hearing loss of 25dB
  - Peripheral neuropathy >grade 2
  - NYHA >class III heart failure

Galsky et al. Lancet Oncol 2011;12:211

Cisplatin-eligible:

Methotrexate/ Vinblastine/ Adriamycin/ Cyclophosphamide (MVAC)

- 1984 to 1989, 269 pts
- MVAC vs Cisplatin
- Improvement in RR (39% vs 12%)
- Median PFS (10 mths vs 4 mths)
- Median OS (13 mths vs 8 mths)
- Higher toxicities (neutropenic fever, mucositis, mortality)

Loehrer et al. JCO 1992;10:1066

Gemcitabine/ cisplatin (GC)

- 1996 to 1998, 405 pts
- GC vs MVAC
- Similar ORR (49% vs 46%)
- Similar OS (14 mths vs 15mths); 5-year survival rate (13% vs 15%)
- Less toxicities (2% va 14% neutropenic sepsis, 1% vs 22% mucositis)
- Note: designed for superiority , not powered for equivalence

Von der Maase et al. JCO 2005;23:4602

ddMVAC

- 1996 to 1998, 263 pts
- ddMVAC vs MVAC
- Improvement in ORR (64% vs 50%; p=0.06)
- Median survival 15.1 mths vs 14.9mths
- 5-year survival (21.8% vs 13.5%)
- Bordeline statistically significant relative reduction in risk of death

Sternberg C et al. Eu J Cancer 2006;42:50

Paclitaxel/Gemcitabine/Cisplatin (PGC)

- 2001 to 2004,626 pts
- PGC vs GC
- Increase in ORR (56% vs 44%)
- Trend in OS (16 mths vs 13 mths) but not statistically significant
- Increased toxicities (neutropenia, fatigue, infection)

Bellmunt et al. JCO 2012;30:1107

Cisplatin eligible pts

- Options:
  - MVAC
  - ddMVAC
  - GC
  - PGC
- Outcome –OS/PFS fairly similar

Cisplatin - ineligible

- Carboplatin based
- Non-platinum based
- Single agent taxane
- Single agent gemcitabine

Gemcitabine/ Carboplatin

- 2001 to 2008 , 238 pts, impaired renal function (30ml/min<CCT<60ml/min) and/or ECOG >=2)
- Gem/Carbo vs M-CAVI (Carbo/Methotrexate/Vinblastine)
- Higher but not statistically significant RR (41% vs 30%)
- No difference in median OS (9 mths vs 8 mths)
- Less toxicities with Gem/Carbo

De Santis et al. JCO 2012;30:191

Gemcitabine/ Carboplatin

- Inferior survival as compared to cisplatin based chemotherapy
- For pts with no Bajorin risk factors, the median OS was 12 months
- If renal function can be improved (eg due to obstructive uropathy that is easily reversible), correct and give cisplatin-based chemotherapy if possible

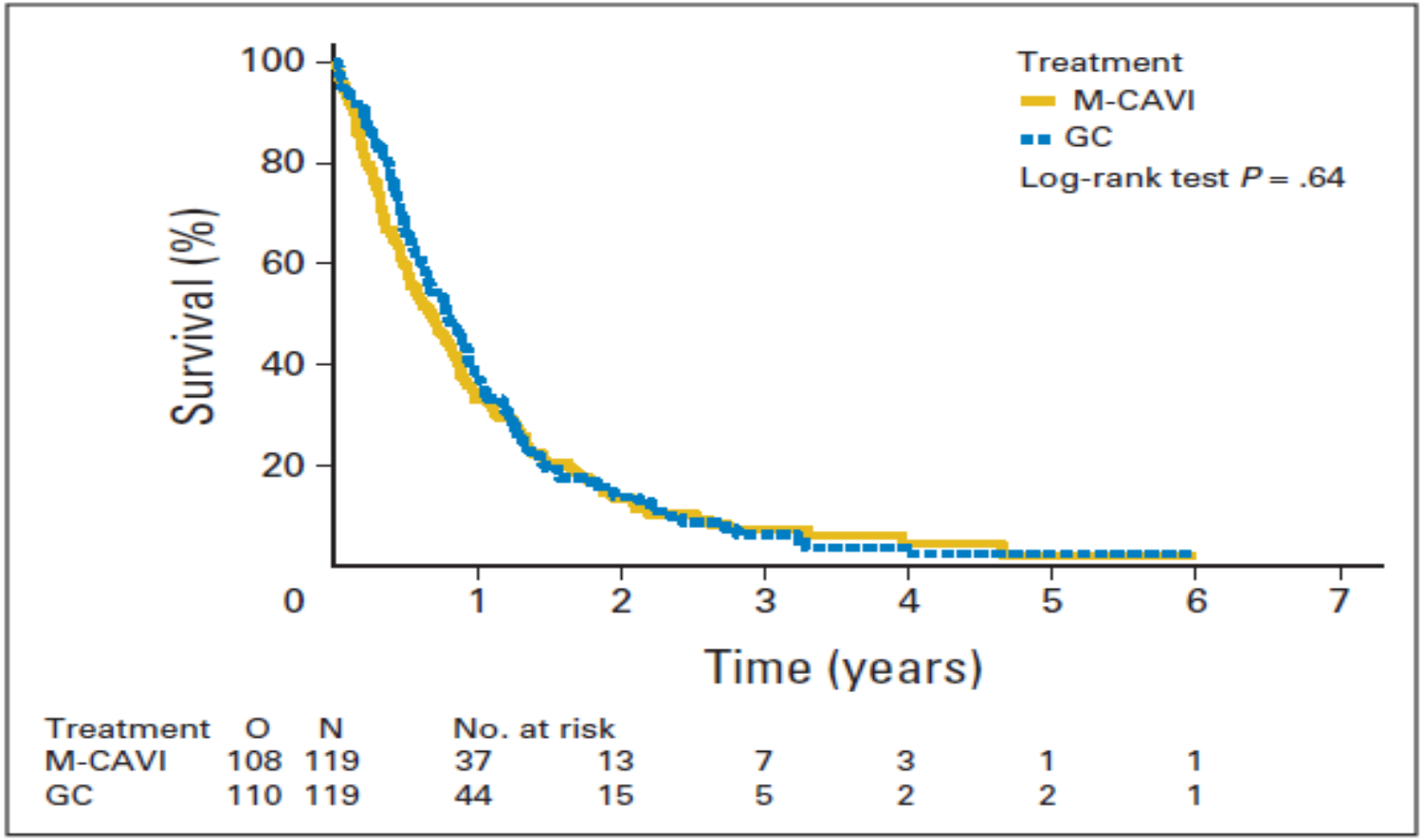


Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

Non-platinum combination

- Paclitaxel/Gemcitabine
  - Phase II
  - Response rates between 54 to 70%
  - Median OS between 13 to 16 months
- Docetaxel/Gemcitabine
  - Phase II
  - RR between 33 to 53%
  - Median OS between 13 to 15 months

Li J et al. JCO 2005;23:1185, Meluch AA et al. JCO 2001;19:3018
Ardavanis A,et al. Br J Cancer 2005;92:645, Gitlitz BJ et al. Cancer 2003;98:1863

Single agent gemcitabine

- Phase II studies
- RR 23-29%

Table 1
Responses to single-agent gemcitabine in bladder cancer[a]

Investigator (reference)	Phase	Gemcitabine dose (mg/m^2)	Prior therapy	Evaluable patients (n)	CR/PR (n)	RR% (CR%)	Median survival (months)
Pollera et al. 1994 [22]	I	875–1370	Prior MVAC except for 1 patient	15	1/3	27% (7%)	NR
Lorusso et al. 1998 [23]	II	1250[b] days 1, 8, 15 every 28 days	One prior cisplatin-based regimen	31	4/3	23% (13%)	5
Stadler et al. 1997 [24]	II	1200 days 1, 8, 15 every 28 days	Adjuvant >6 months prior to study entry	39	4/7	28% (10%)	13.5
Moore et al. 1997 [25]	II	1200 days 1, 8, 15 every 28 days	Adjuvant >12 months prior to study entry	37	3/6	24% (8%)	8
Gebbia et al. 1999 [26]	II	1000 3 consecutive weeks every 28 days	One prior cisplatin-based regimen	24	1/6	29% (4%)	13.0+

[a] CR, complete response; PR, partial response; RR, overall response rate; NR, not reported.
[b] In the publication of this study, the dosage was erroneously published as 1200 mg/m^2; the actual dosage used was 1250 mg/m^2.

Von der Maase . Crit Reviews Hematology & Oncology 2000;175

Single agent taxanes

- Paclitaxel -42% RR (23% -63%)
- Docetaxel – 31% RR (14-48%)

Galsky. The oncologist 2005;10:792

Cisplatin ineligible pts

- Options:
  - Gemcitabine/Carboplatin
  - Gemcitabine/paclitaxel
  - Gemcitabine
  - Paclitaxel
  - Docetaxel

2nd line therapy

- Prognostic factors
- Progression-free interval >12 months, can re-challenge with platinum based regimen
- Progression-free <12 months

Prognostic factors

- 370 pts on the phase III vinflunine vs BSC clinical trial
- 3 adverse OS prognostic factors: PS>0, Hb<10g/dL, liver mets
- 4 subgroups: 0,1,2, 3 Risk factors

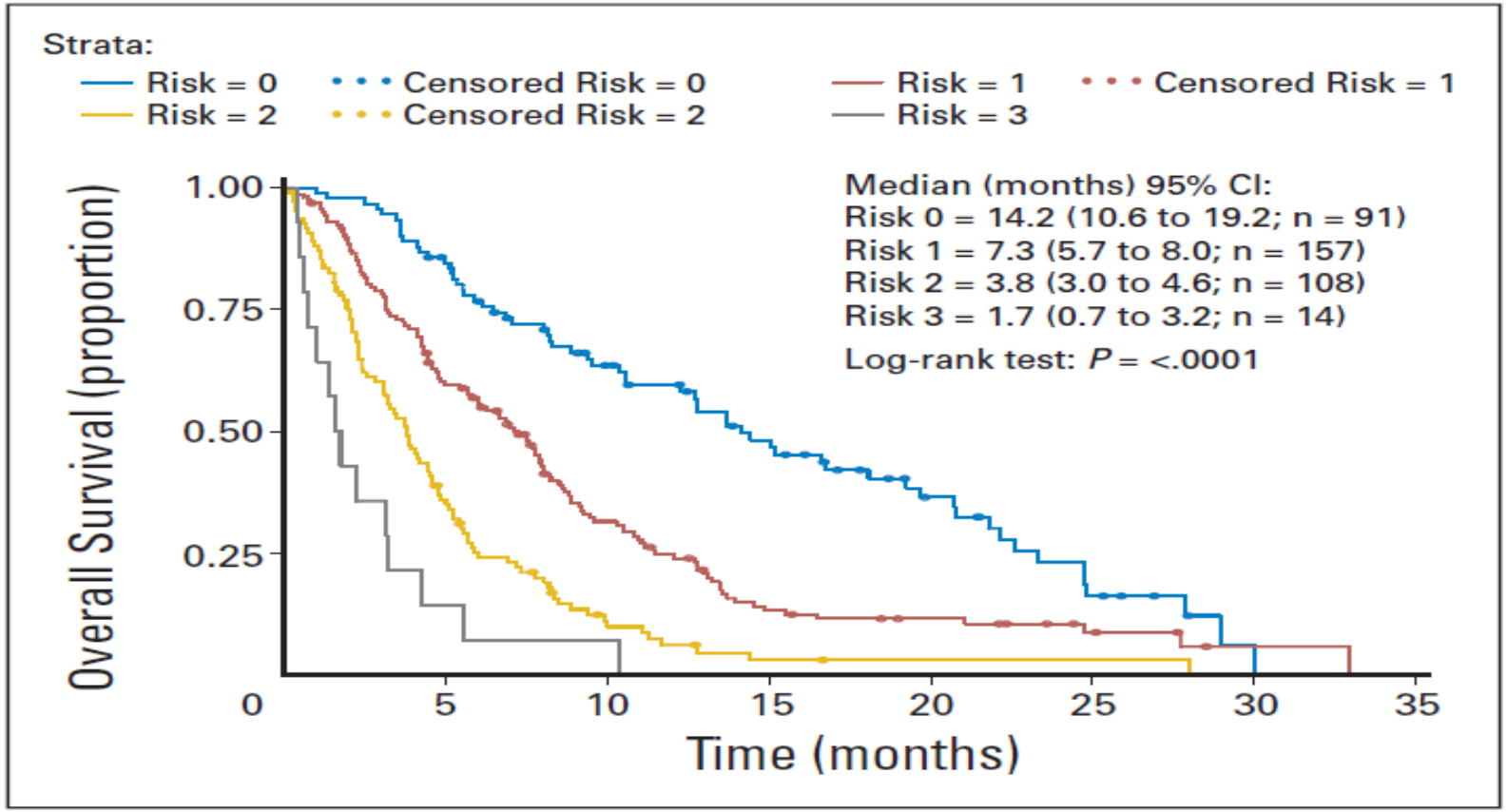


Fig 1. Kaplan-Meier estimates for each risk group (zero, one, two, or three risk factors).

Bellmunt et al. JCO 2010;28:1850

vinflunine

- 2003 to 2006, 370 pts, phase III randomized trial
- Progression after first line platinum-based chemotherapy, CCT>=40ml/min
- 9% objective RR
- ITT group – OS was 6.9 vs 4.6mths (HR-0.88, 95% CI 0.69-1.12)
- Eligible group (357pts) – OS was 6.9 vs 4.3 mths (HR-0.78, 95% CI 0.61-0.99)

Bellmunt et al. JCO 2009;27:4454

Vinflunine

- Objective RR 8.6%, PFS-3.0 vs 1.5 mths
- Limitations: toxicities

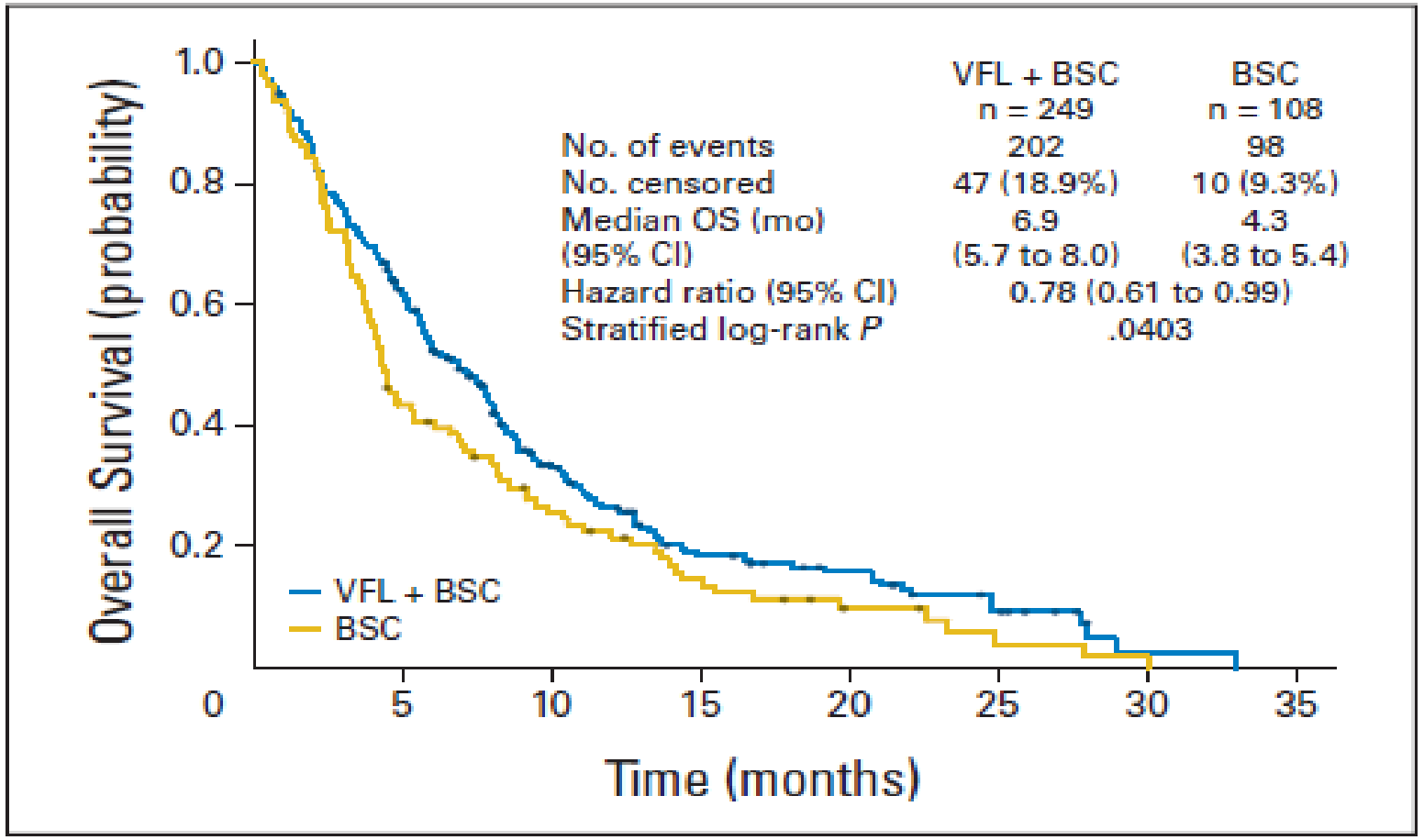


Fig 3. Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.

Taxanes

- No randomized phase III trials
- Paclitaxel 9% RR
- Docetaxel 13% RR

Galsky. The oncologist 2005;10:792

2nd line therapy

- Vinflunine
- Taxanes
- Others: pemetrexed, gemcitabine, ifosfamide, oxaliplatin

Conclusion

- Cisplatin based chemotherapy is std of care for treatment naïve met urothelial carcinoma who are cisplatin eligible
  - Long term survival in small proportion of pts
- Carboplatin based chemotherapy/single agent chemotherapy are options for cisplatin-ineligible pts
- For second line therapy, vinflunine or taxanes are chemotherapeutic options

THANK YOU