

# Mesane Kanserlerinde adjuvant-neoadjuvan Kemoterapi

Dr. Mert Bařaran  
İstanbul Üniversitesi, Onkoloji Enstitüsü

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# Mesane Kanseri Hasta Dağılımı

- İleri yaş hastalığı
  - PS düşüklüğü, kemik iliği rezerv azlığı
- Eşlik eden hastalıklar
  - Sigara içiciler; kalp, akciğer ve damar hastalıkları
- Beraberinde böbrek fonksiyon kaybı sıklığı

# Küratif Tedavi

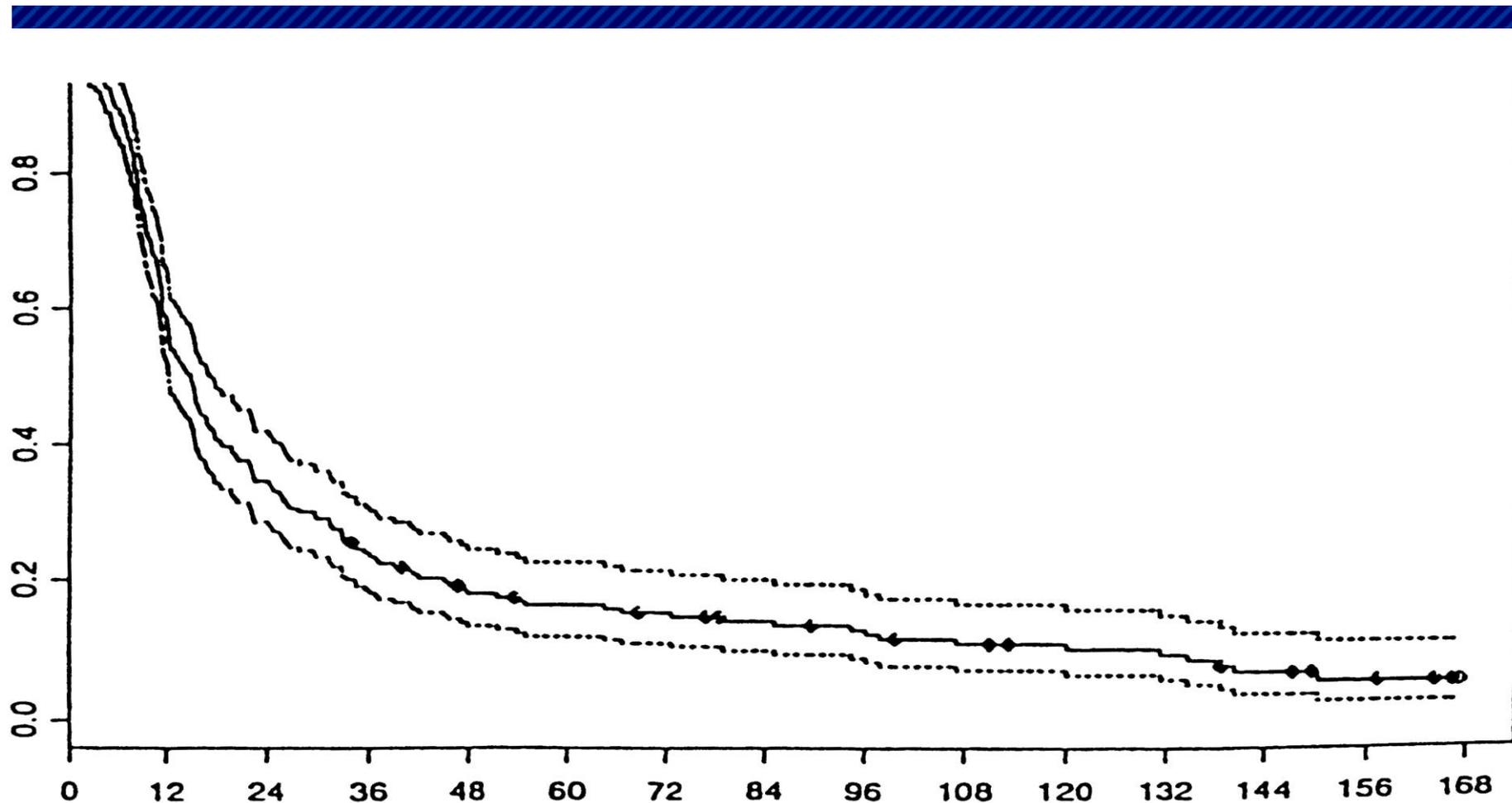
- Ön planda radikal sistektomi
- Seçilmiş hasta grubunda radyoterapi

# Neoadjuvan – Adjuvan Kemoterapi

- Hastada kür şansını artırmalı
  - Rezeksiyon şansını artırmak
  - Nüks oranını azaltmak
  - Uzak metastaz azaltmalı

En Etkili KT Kombinasyonu Hangisidir?

# Survival for 203 Patients Treated with M-VAC at MSKCC (Bajorin, et al., *JCO*, 10/99)



# İleri Evre Mesane Kanseri MVAC tecrübesi

Series	No. of Cases	CR (%)	PR (%)	Total (%)	Survival (mos.)
MSKCC	194	24	43	67	14.8
PMH	30	13	27	43	10.0
Japan	58	17	40	57	8.0
MDAH	55	35	30	65	11.0
France	67	19	38	57	13.0
Inter-GP	120	13	25	38	12.5

EORTC 30924: A Randomized Phase III  
Trial in Advanced Urothelial Tract Tumors  
of High Dose Intensity M-VAC  
Chemotherapy (HD-MVAC) and G-CSF vs.  
Classic M-VAC Chemotherapy

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C.N. Sternberg, P.H.M. De Mulder, J.H.  
Schornagel, C. Theodore, S.D. Fossa, U. Tirelli,  
C.J. van Groeningen, L. Collette and the EORTC  
Genito-Urinary Cancer Group

# HD-MVAC vs. M-VAC Study Design

Standard MVAC

q4w

HD MVAC

q2w

Total dose in 4 w

MTX

30 x 3

30 x 2



VBL

3 x 3

3 x 2



ADR

30

30 x 2



CDDP

70

70 x 2



# HD-MVAC vs. M-VAC Hematologic Toxicity

	grade	M-VAC n=129	HD-MVAC n=134	P
WBC	2	22%	21%	<0.001
	3	46%	12%	
	4	16%	8%	
PLTS	2	12%	16%	0.033
	3	11%	11%	
	4	6%	11%	

# HD-MVAC vs. M-VAC Response Rate

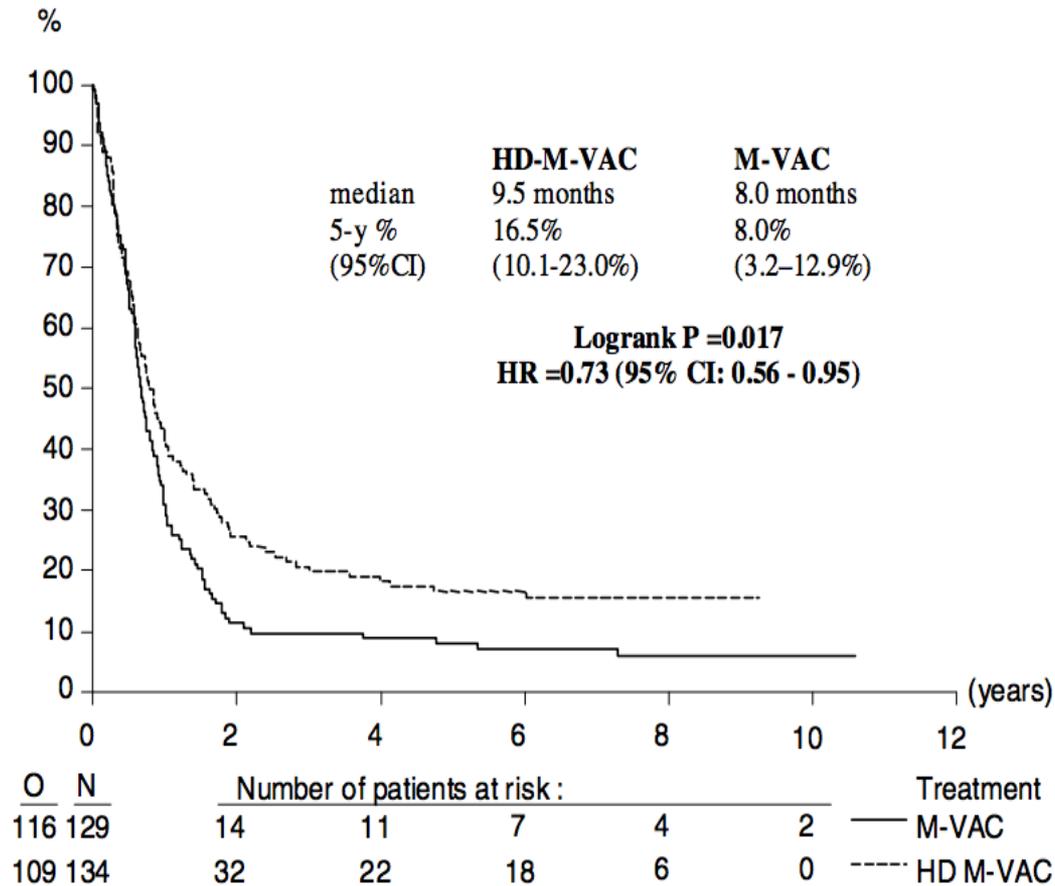
	M-VAC	HD-MVAC
	<u>N (%)</u>	<u>N (%)</u>
n	113 (88)	114 (85)
CR + PR	65 (58)	83 (72)
CR	12 (11)	28 (25)
PR	53 (47)	55 (48)

2 sided p-value difference in CR rate  $p=0.006$  (chi-square test)

2 sided p-value difference in CR + PR rate  $p=0.016$  (chi-square test)

# PFS

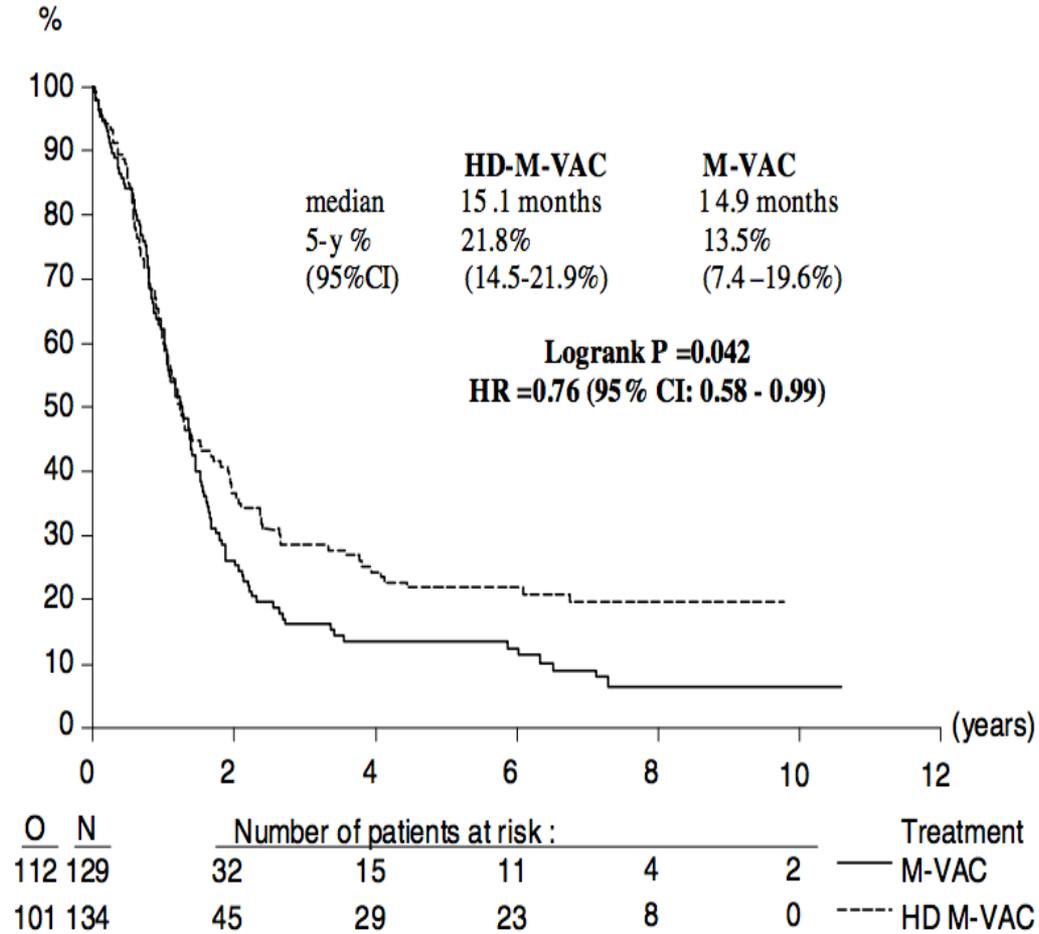
“updated results 2006”



**Fig. 2 – Progression-free survival.**

# OS

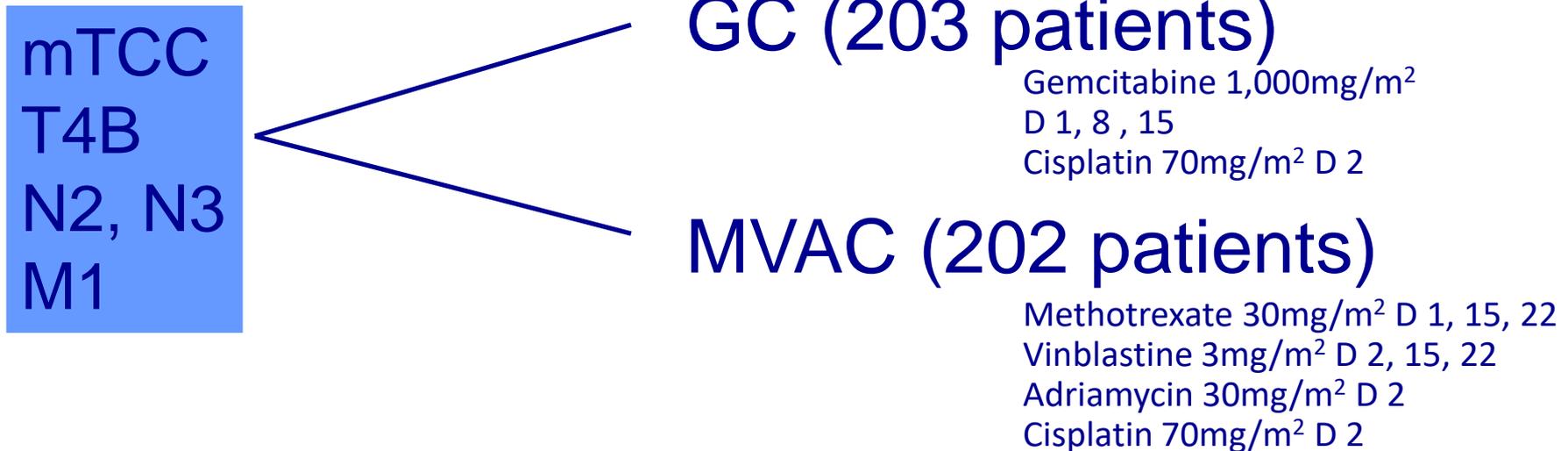
## “uptated results 2006”



**Fig. 3 – Overall survival.**

# Randomize Faz III Çalışma Metastatik Mesane Kanseri

von der Mase, H, Hansen, S., Roberts T, Conte P, Oliver T, Moore M



Study initiated November, 1996 – recruitment  
completed, September, 1998

# Randomized Phase III Study in Metastatic Bladder Cancer

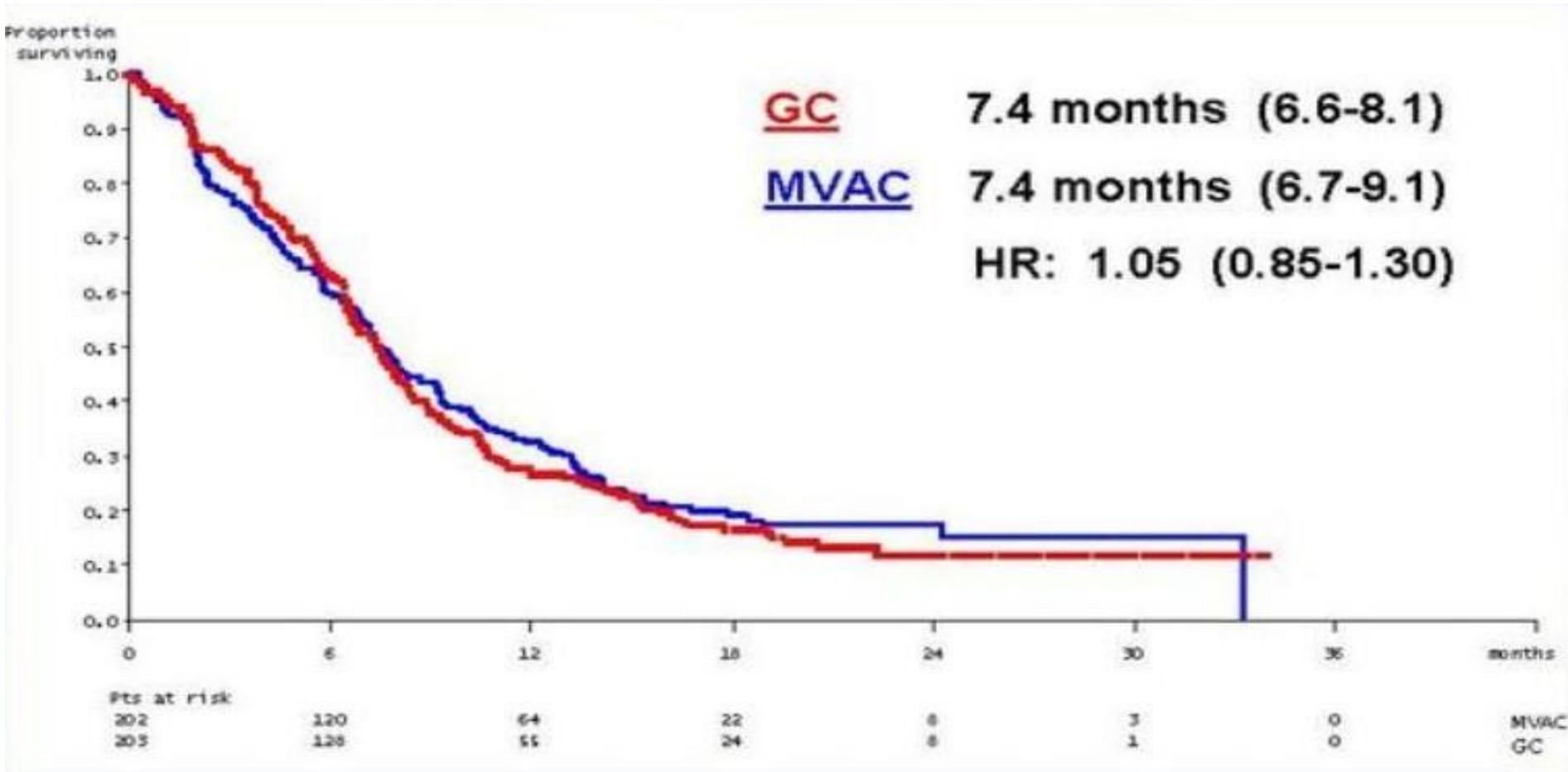
- GC:
    - Gemcitabine 1,000mg/m<sup>2</sup> day 1, 8 and 15
    - Cisplatin 70mg/m<sup>2</sup> day 2
  - MVAC:
    - Methotrexate 30mg/m<sup>2</sup> day 1, 15 and 22
    - Vinblastine 3mg/m<sup>2</sup> day 2, 15, and 22
    - Adriamycin 30mg/m<sup>2</sup> day 2
    - Cisplatin 70mg/m<sup>2</sup> day 2
- every 28 days

# GC vs. MVAC Response

Response	GC (n=164)	MVAC (n=151)
CR	12%	12%
PR	37%	34%
Response Rate	50%	46%

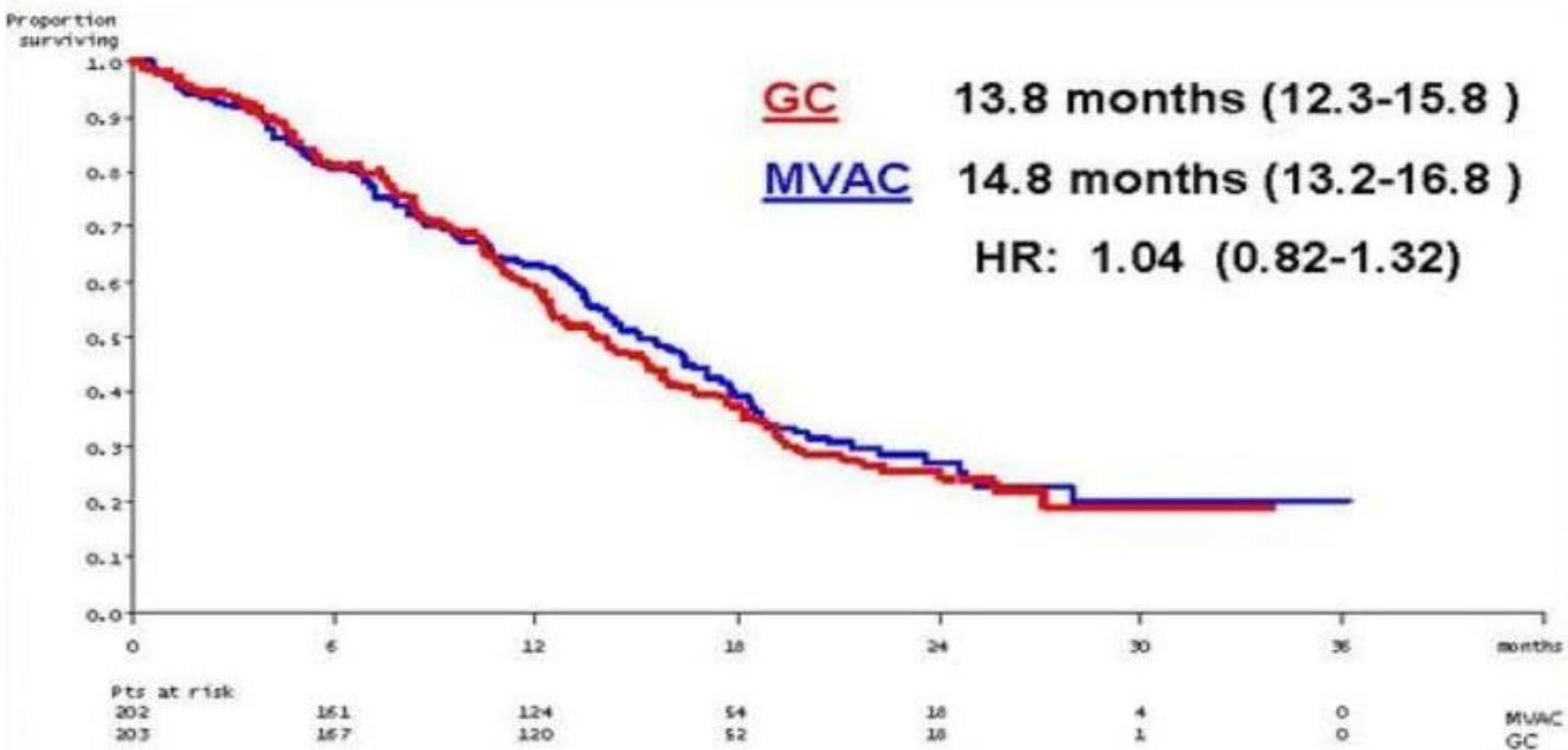
# GC vs. MVAC

## Time to Progressive Disease



# GC vs. MVAC

## Overall Survival



# Maximum Toxicities (Grades 3 and 4) Reported for MVAC or GC

Toxicity	World Health Organization Toxicity Grades			
	GC (%)		MVAC (%)	
	3	4	3	4
<b>Hematologic</b>				
Anemia	23.5	3.5	15.5	2.1
Thrombocytopenia	28.5	28.5	7.7	12.9
Neutropenia	41.2	29.9	17.1	65.2
<b>Nonhematologic</b>				
Mucositis	1.0	0	17.7	4.2
Nausea/vomiting	22.0	0	19.2	1.6
Alopecia	10.5	0	54.2	1.0
Infection	2.0	0.5	9.9	5.2
Diarrhea	3.0	0	7.8	0.5
Pulmonary	2.5	0.5	2.6	3.1
Hematuria	4.5	0	2.3	0
Constipation	1.5	0	2.6	0.5
Hemorrhage	2.0	0	2.1	0
State of Consciousness	0.5	0	3.1	0
Fever	0	0	3.1	0

GC = gemcitabine/cisplatin; MVAC = methotrexate/vinblastine/adriamycin/cisplatin

# Gem/CDDP vs Gem/Carbo

## Randomised Phase II

*Dogliotti et al. Eur Urology 2007*

80 pts

med OS:

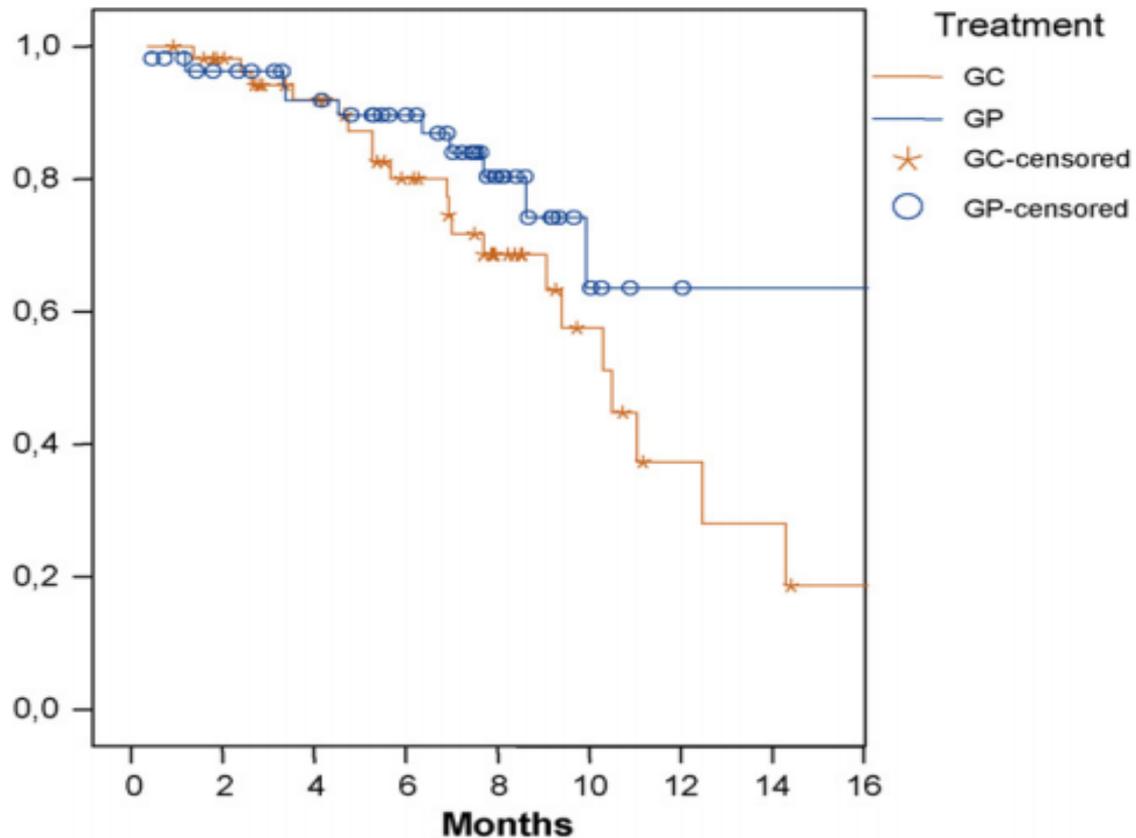
GC 12.8 m

Gcar 9.8 m

ORR

GC 49 %

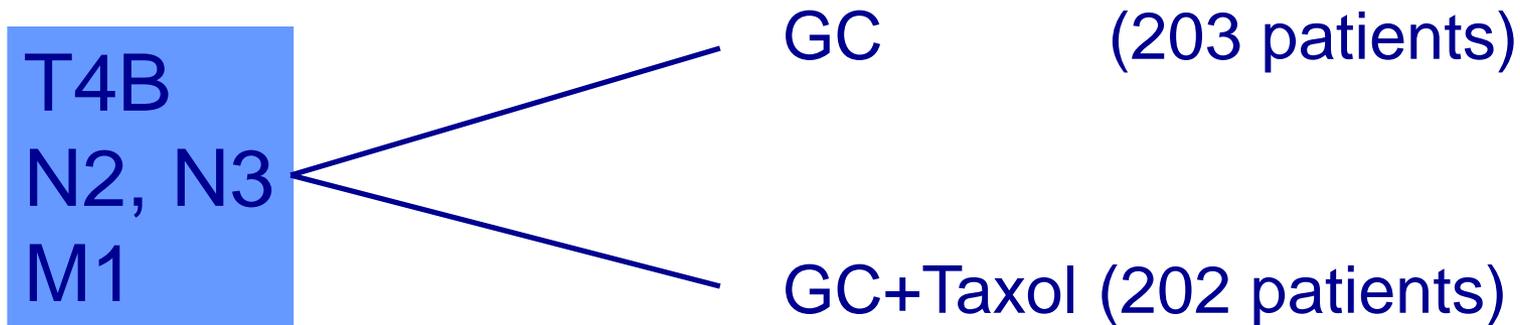
Gcar 40 %



**Fig. 2 - Overall survival for the gemcitabine-carboplatin (GC) arm and the gemcitabine-cisplatin (GP) arm.**

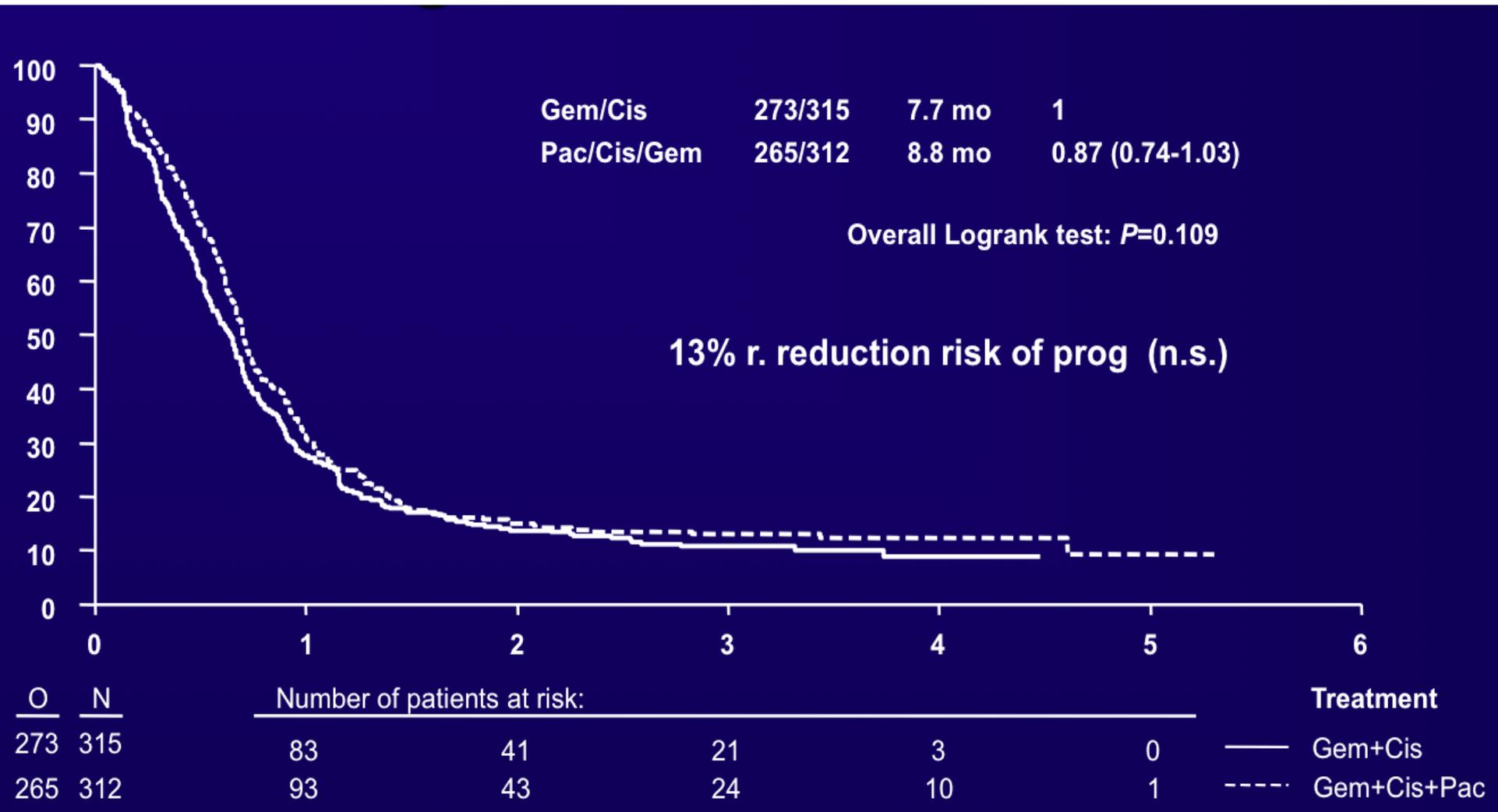
# EORTC/Intergroup Phase III Study in Metastatic Bladder Cancer

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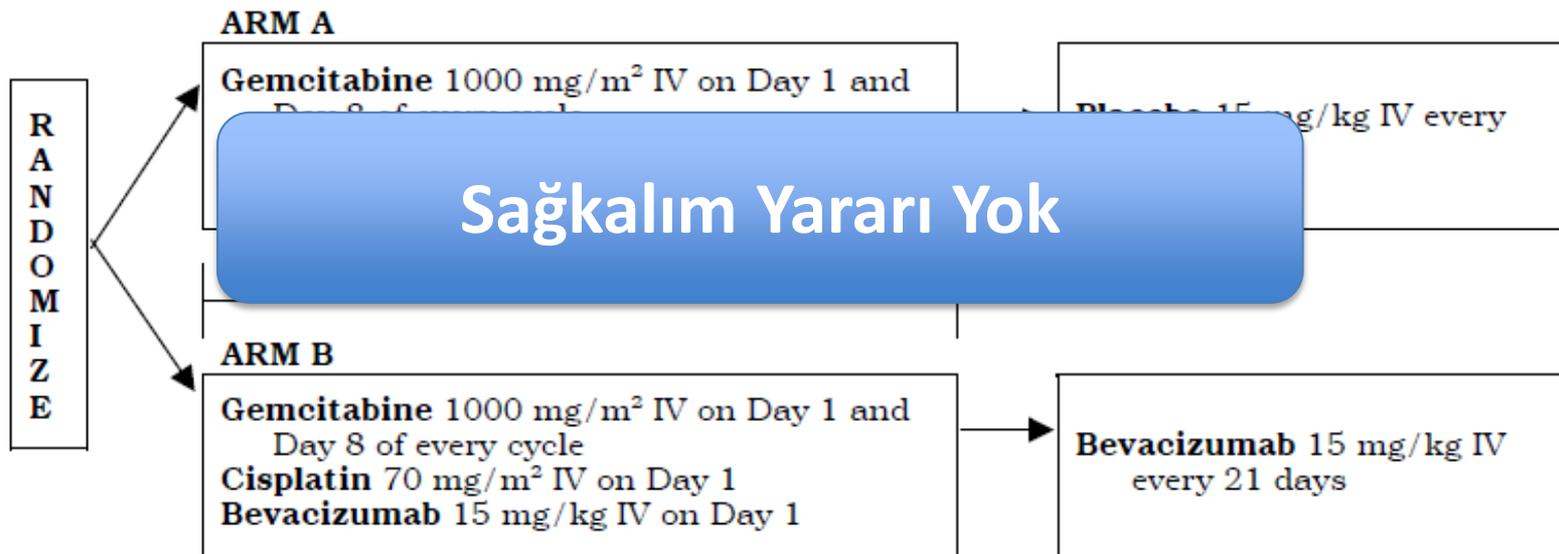
Study initiated November, 2001 – completed  
2006, reported 2007

# Progression Free Survival



# Randomized phase III study of gemcitabine and cisplatin with or without bevacizumab in patients with advanced TCC

Schema  
1 cycle = 21 days



Treatment with gemcitabine and cisplatin should continue for a maximum of 6 cycles. Treatment with bevacizumab/placebo alone will continue until disease progression or unacceptable toxicity.

# Mesane Kanserinde Kemoterapi Seçimi Yorum

- Standard KT rejimi
  - Gem/CDDP
  - MVAC
  - HD MVAC büyüme faktörleri desteği ile
- Hedefe yönelik molekülerden EGFR ve VEGF yolağı blokajı ek yarar getirmedi
- Karboplatin sağkalım ve yanıt anlamında sisplatinden daha az etkilidir

**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

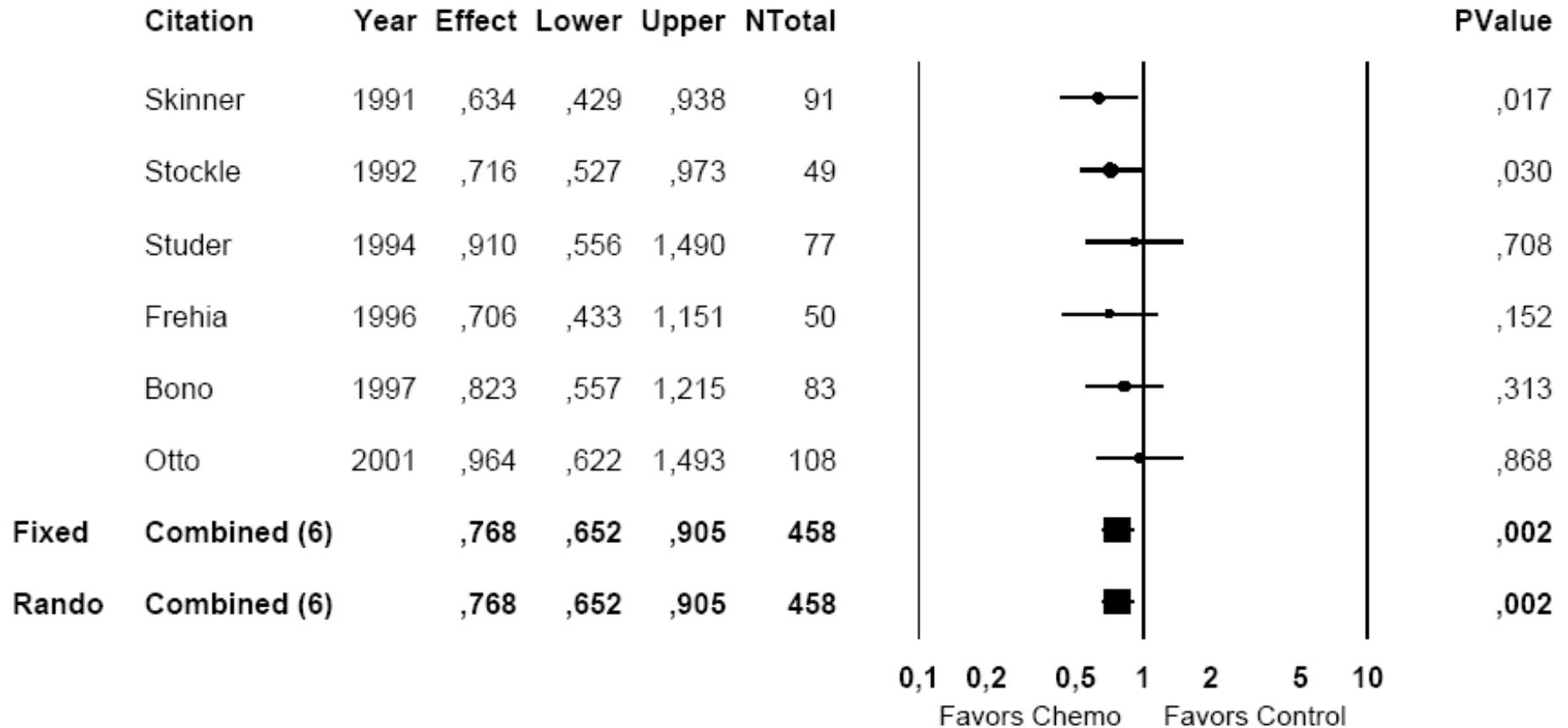
**TABLE 1. Randomized trials of adjuvant chemotherapy for TCC.**

<b>Study</b>	<b>Stages</b>	<b>N &amp; treatment</b>	<b>Results</b>
<b>Skinner et al. (1991)</b> [9]	pT3-4 or N+, M0	91 (44 CISCA; 47 cystectomy alone)	Significant increase in TTP for adjuvant therapy; no significant differences in OS except for subgroups
<b>Stockle et al. (1992)</b> [10]	pT3b-4a or N+	49 (26 M-VAC/M-VEC; 23 observation)	Stopped early due to a significant increase in DFS for adjuvant therapy
<b>Studer et al. (1994)</b> [13]	T1 (G2) – T4	77 (37 cisplatin; 40 observation)	No advantage for adjuvant therapy
<b>Freiha et al. (1996)</b> [15]	pT3b-4, any N, M0	50 (25 CMV immediately after cystectomy; 25 CMV at relapse)	Stopped early because of a significant increase in TTP for adjuvant therapy; not significant differences in OS
<b>Bono et al. (1997)</b> [14]	T2-T4a, N0, M0	83 (48 CM; 35 cystectomy only)	No benefit for adjuvant therapy
<b>Otto et al. (2001)</b> [15]	T3, N1-2, M0	108 (55 M-VEC; 53 observation)	No advantage for adjuvant therapy in terms of survival
<b>Lehmann et al (2005)</b> [16]	pT3-4a and/or N+	327 (163 CM; 164 M-VEC)	No inferiority of CM; better tolerability for CM

R – randomization; TTP – Time to progression; OS – overall survival; CISCA – cisplatin; cyclophosphamide, doxorubicin; M-VAC – methotrexate, vinblastine, doxorubicin, cisplatin; M-VEC - methotrexate, vinblastine, epirubicin, cisplatin; CMV – cisplatin, methotrexate, vinblastine; CM – cisplatin, methotrexate;

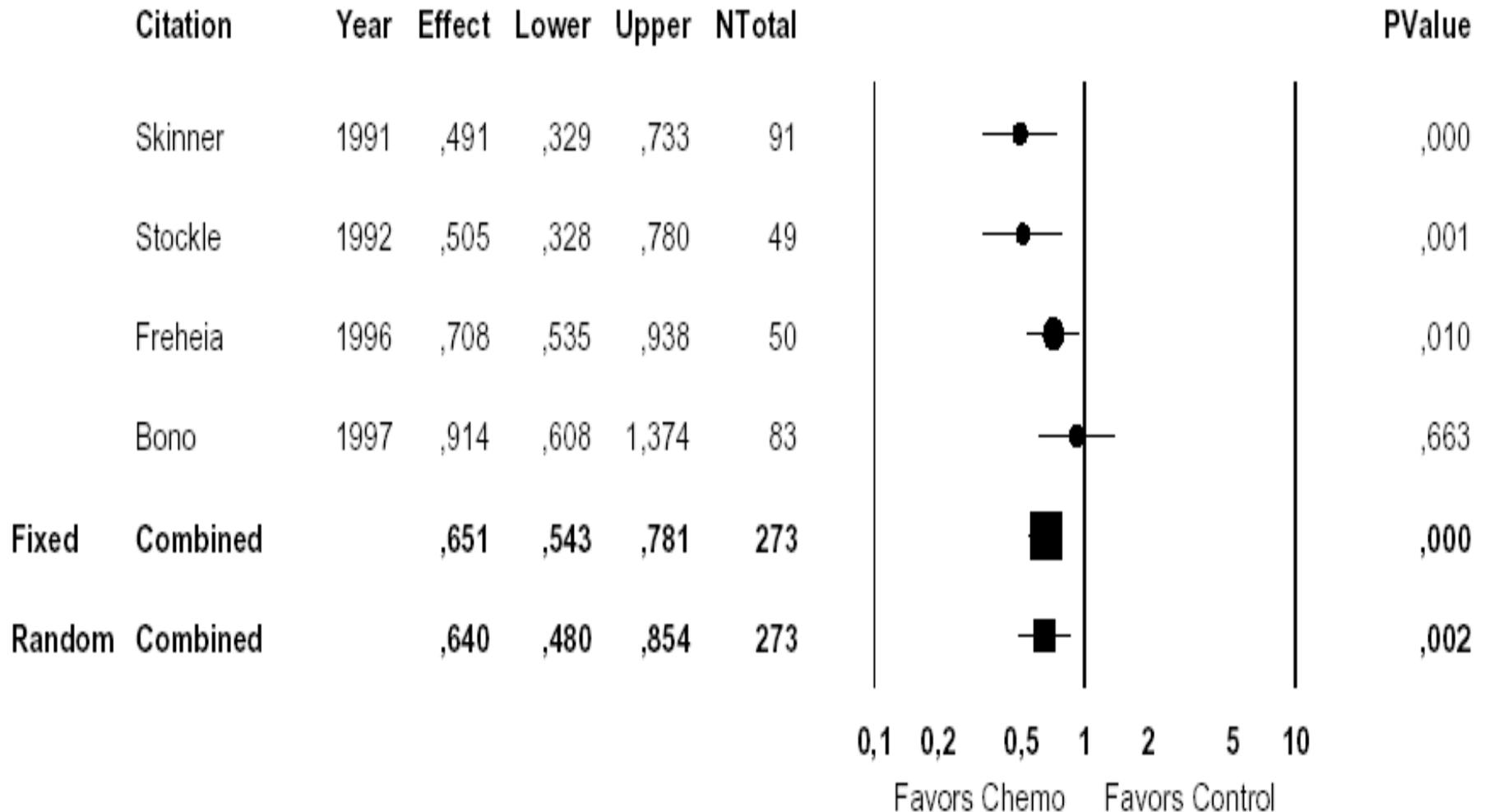
# Adjuvant Chemotherapy In Muscle-invasive Bladder Cancer: A Pooled Analysis From Phase III Studies.

## Genel Sağlıkım

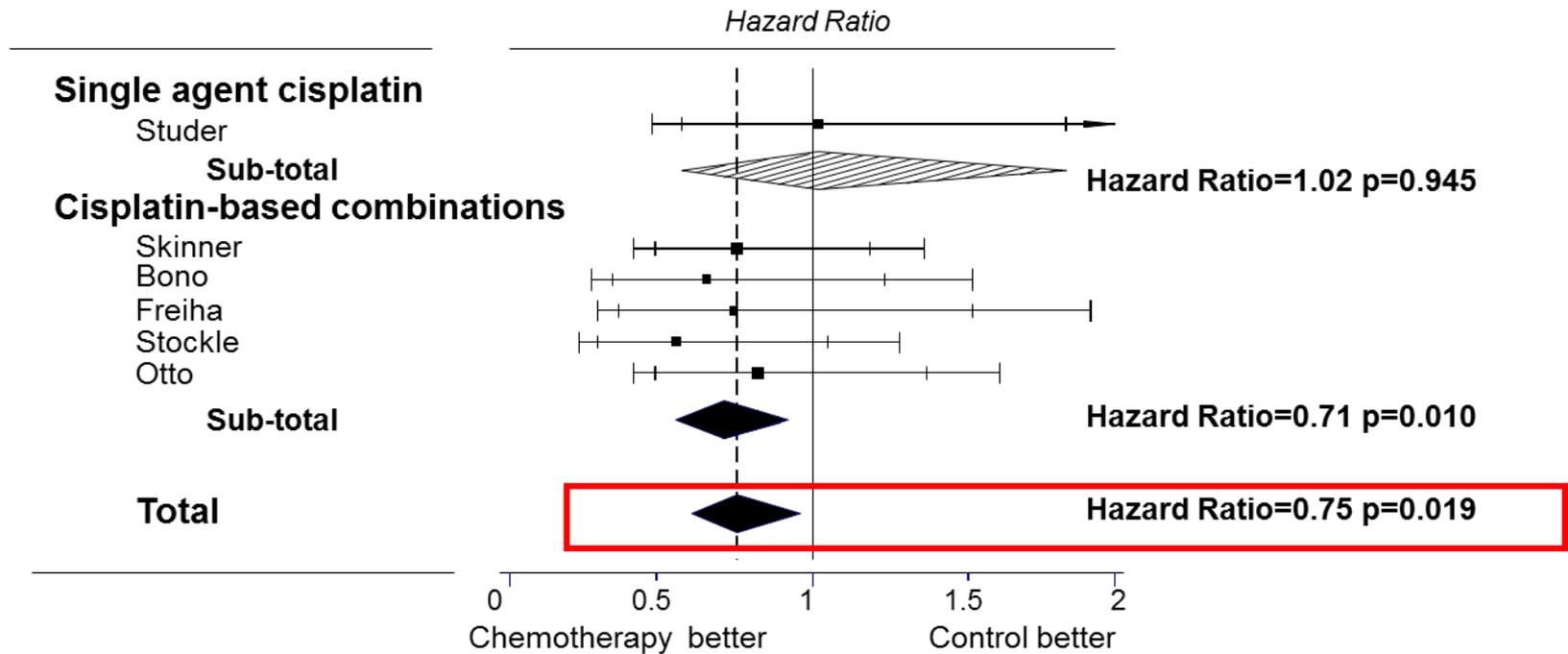


# Adjuvant Chemotherapy In Muscle-invasive Bladder Cancer: A Pooled Analysis From Phase III Studies.

## Hastalıksız Sağlık



# Advanced Bladder Cancer (ABC) Meta-analysis Collaboration Survival



Test for interaction  $\chi^2=1.20$ ,  $p=0.237$

**Very wide confidence intervals!**

# EORTC TRIAL 30994

*Lancet Oncol 2015; 16: 76–86*

## International Intergroup Randomized Phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and /or N+ M0 transitional cell carcinoma (TCC) of the bladder

Study coordinated by the EORTC GU Cancers Group, with collaboration from GETUG, NCRI, NCIC and AUO

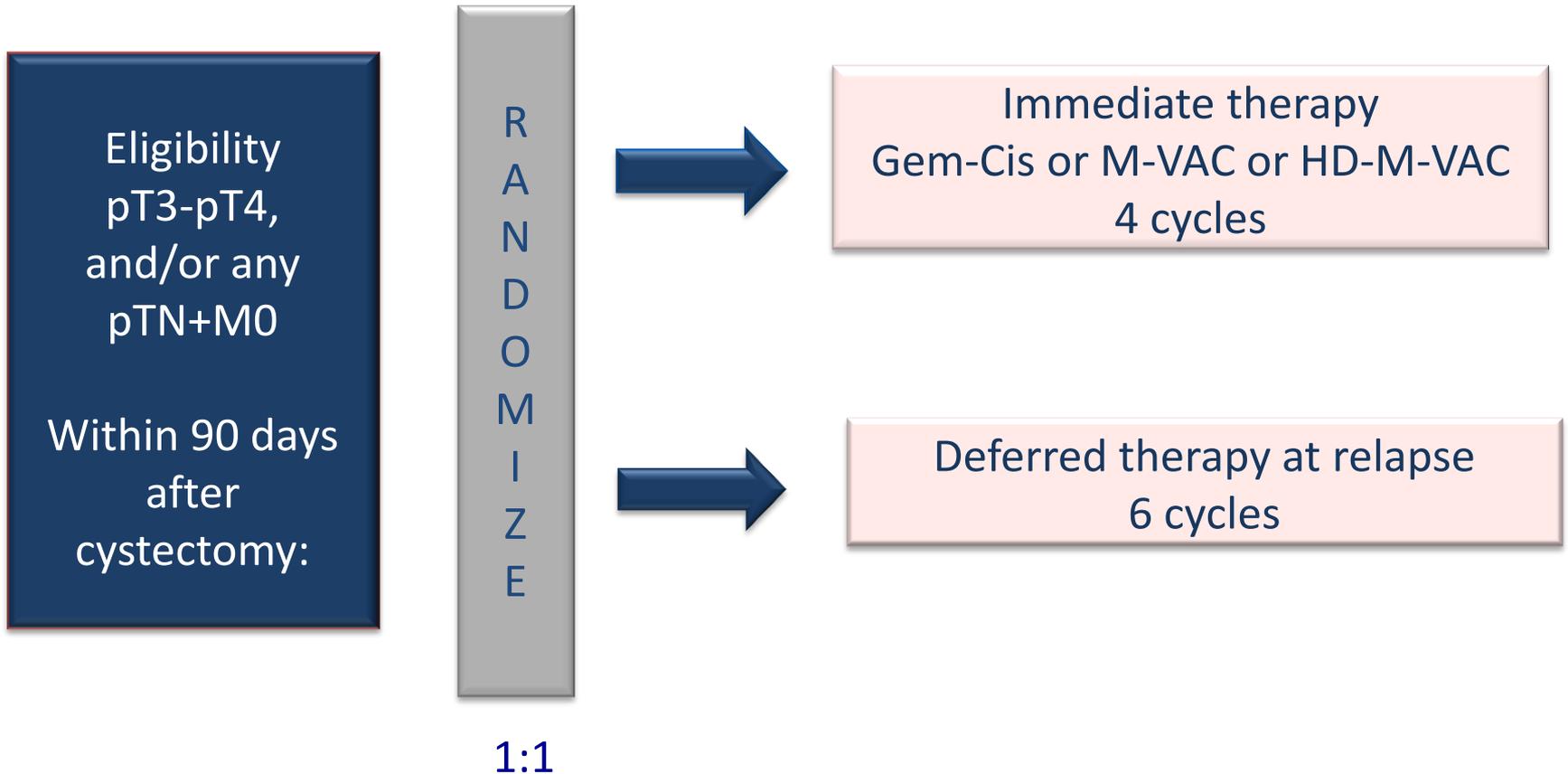
Cora N. Sternberg<sup>1</sup>, Iwona Skoneczna<sup>2</sup>, J.M.Kerst<sup>3</sup>, Sophie Fossa<sup>4</sup>, Peter Albers<sup>5</sup>, Mads Agerbaek<sup>6</sup>, Herlinde Dumez<sup>7</sup>, Maria De Santis<sup>8</sup>, Christine Theodore<sup>9</sup>, Michael Leahy<sup>10</sup>, J.D. Chester<sup>10</sup>, Antony Verbaeys<sup>11</sup>, Armelle Caty<sup>12</sup>, Gedske Daugaard<sup>13</sup>, Sandrine Marreaud<sup>14</sup>, Samantha Cambier<sup>14</sup>, Richard Sylvester<sup>14</sup>

<sup>1</sup>San Camillo and Forlanini Hospitals, Rome, Italy, <sup>2</sup>Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland, <sup>3</sup>The Netherlands Cancer Institute, Amsterdam, The Netherlands, <sup>4</sup>Oslo University Hospital, Oslo, Norway, <sup>5</sup>Klinikum Kassel, Kassel, Germany and University Clinic Bonn, Bonn, Germany,

<sup>6</sup>Aarhus University Hospital, Aarhus, Denmark, <sup>7</sup>U.Z. Gasthuisberg, Leuven, Belgium, <sup>8</sup>Kaiser Franz Josef Spital, Vienna, Austria, <sup>9</sup>Institut Gustave Roussy, Villejuif, France, <sup>10</sup>St James's University Hospital, Leeds, United Kingdom, <sup>11</sup>University Hospital Gent, Gent, Belgium, <sup>12</sup>Centre Oscar Lambret, Lille, France, <sup>13</sup>Rigshospitalet, University of Copenhagen, Denmark,

<sup>14</sup> EORTC Headquarters, Brussels, Belgium.

# Trial Design



Primary endpoint: Overall survival  
Secondary endpoint: Progression free survival

# Hasta Alınma Kriterleri

- ✓ TCC of the bladder: pT3-4 and/or and pTN1-3, M0 disease
- ✓ No pure squamous cell or adenocarcinoma
- ✓ No microscopic residual disease
- ✓ WHO Performance status 0 - 1
- ✓ GFR > 60 ml/min

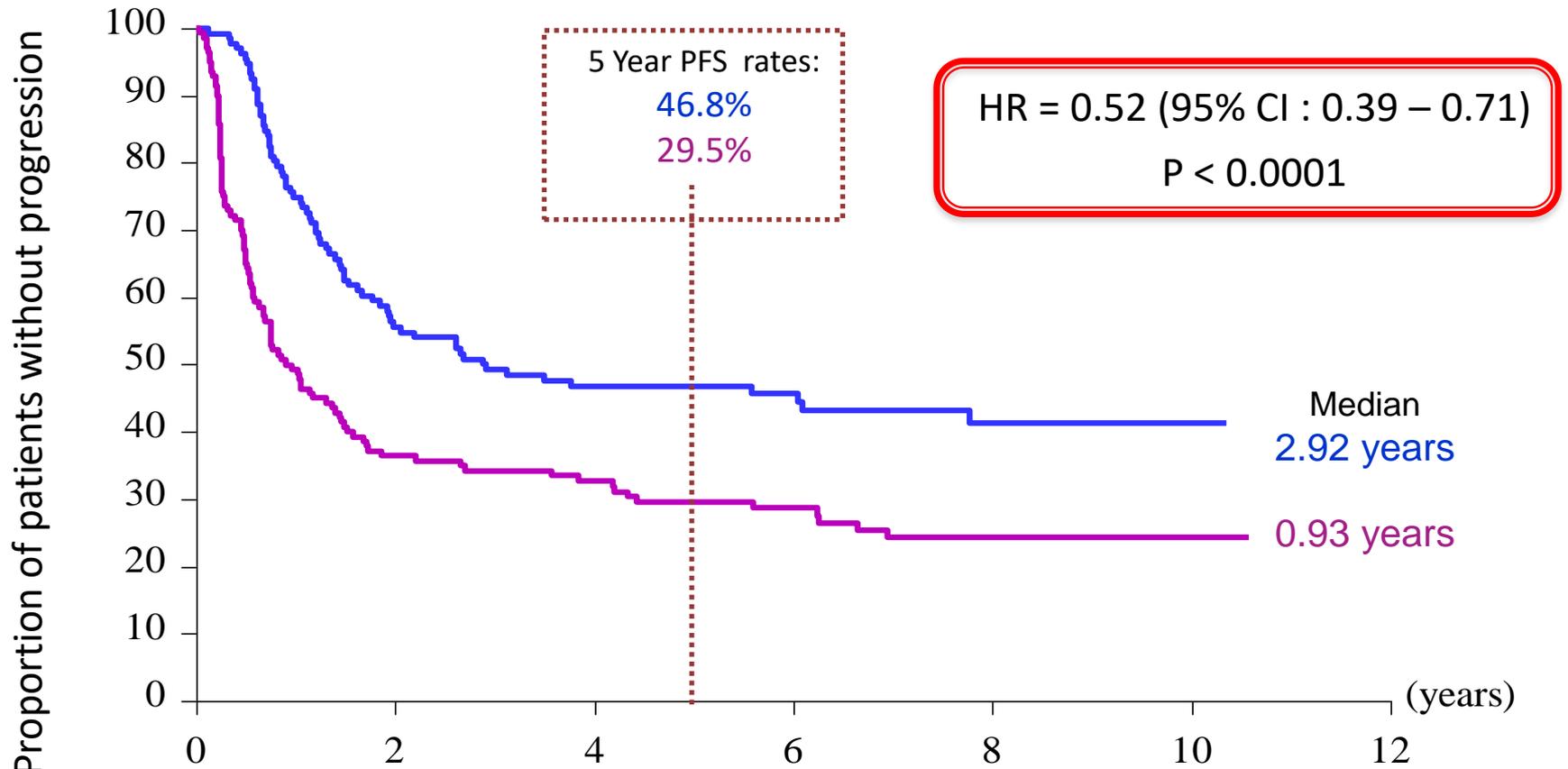
# Patient Characteristics

	Immediate Chemo (n=141)	Deferred Chemo (n=143)
Median age (range)	61 (37-76)	61 (35-82)
Gender		
Male	112 (79.4)	114 (79.7)
Female	27 (19.1)	27 (18.9)
T Category		
pTaT1T2	32 (22.7)	31 (21.7)
pT3T4	109 (77.3)	112 (78.3)
Nodal Status		
pN-	42 (29.8)	44 (30.8)
pN+	99 (70.2)	99 (69.2)
Pathological stage		
pTaT1T2 pN+	32 (22.7)	31 (21.7)
pT3T4 pN+	67 (47.5)	68 (47.5)
pT3T4 pN-	42 (29.8)	44 (30.8)

# Treatment Regimen

Treatment Regimen	Immediate Chemo (n=128)	Deferred Chemo (n=67)
GEM-CIS	108 (84.4)	57 (85.1)
HD-MVAC	19 (14.8)	8 (11.9)
M-VAC	1 (0.8)	2 (3.0)

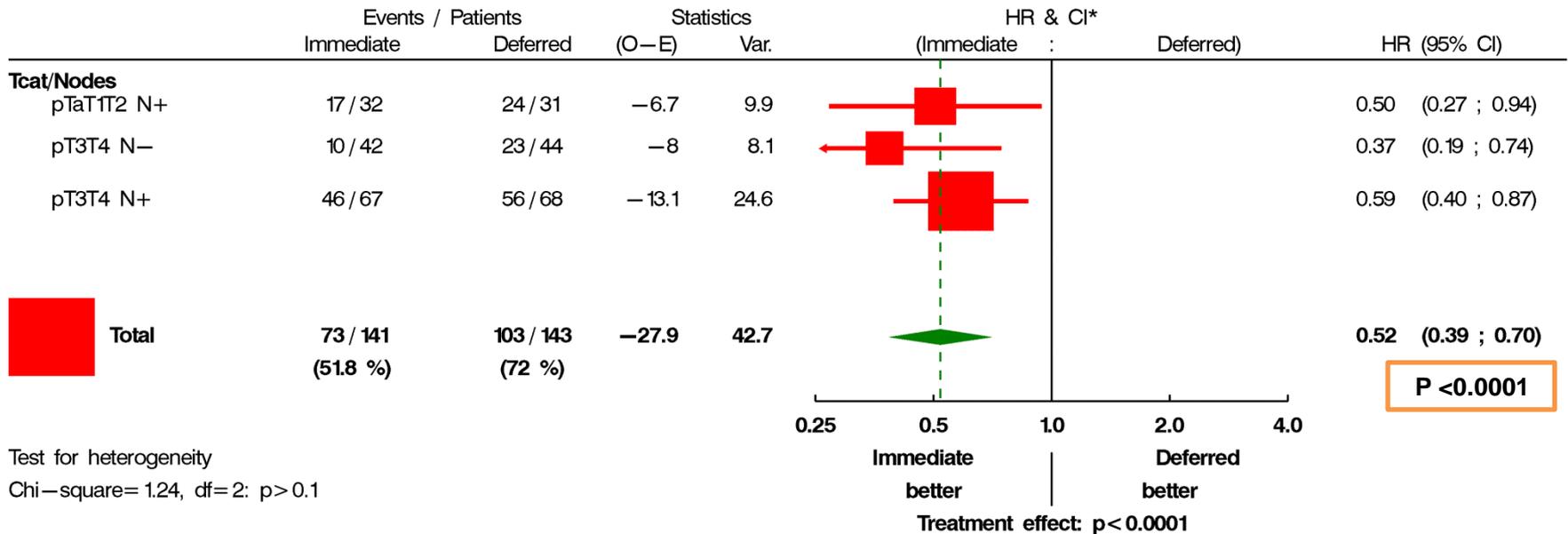
# A Significant Improvement in PFS (ITT)



O	N	Number of patients at risk :					Treatment
73	141	71	56	39	21	3	— Immediate
103	143	50	43	30	18	4	— Deferred

# Exploratory Analysis

## Progression Free Survival According to Disease Stage



Test for heterogeneity  
 Chi-square= 1.24, df= 2:  $p > 0.1$

\*95% CI everywhere

# Nodal Tutulumuna Göre Sağkalım

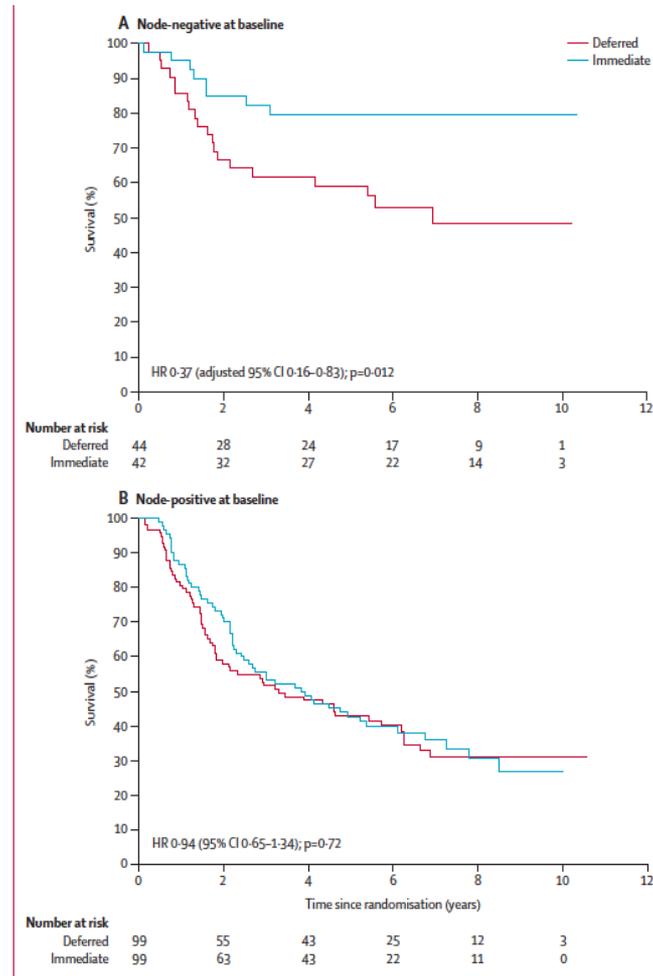
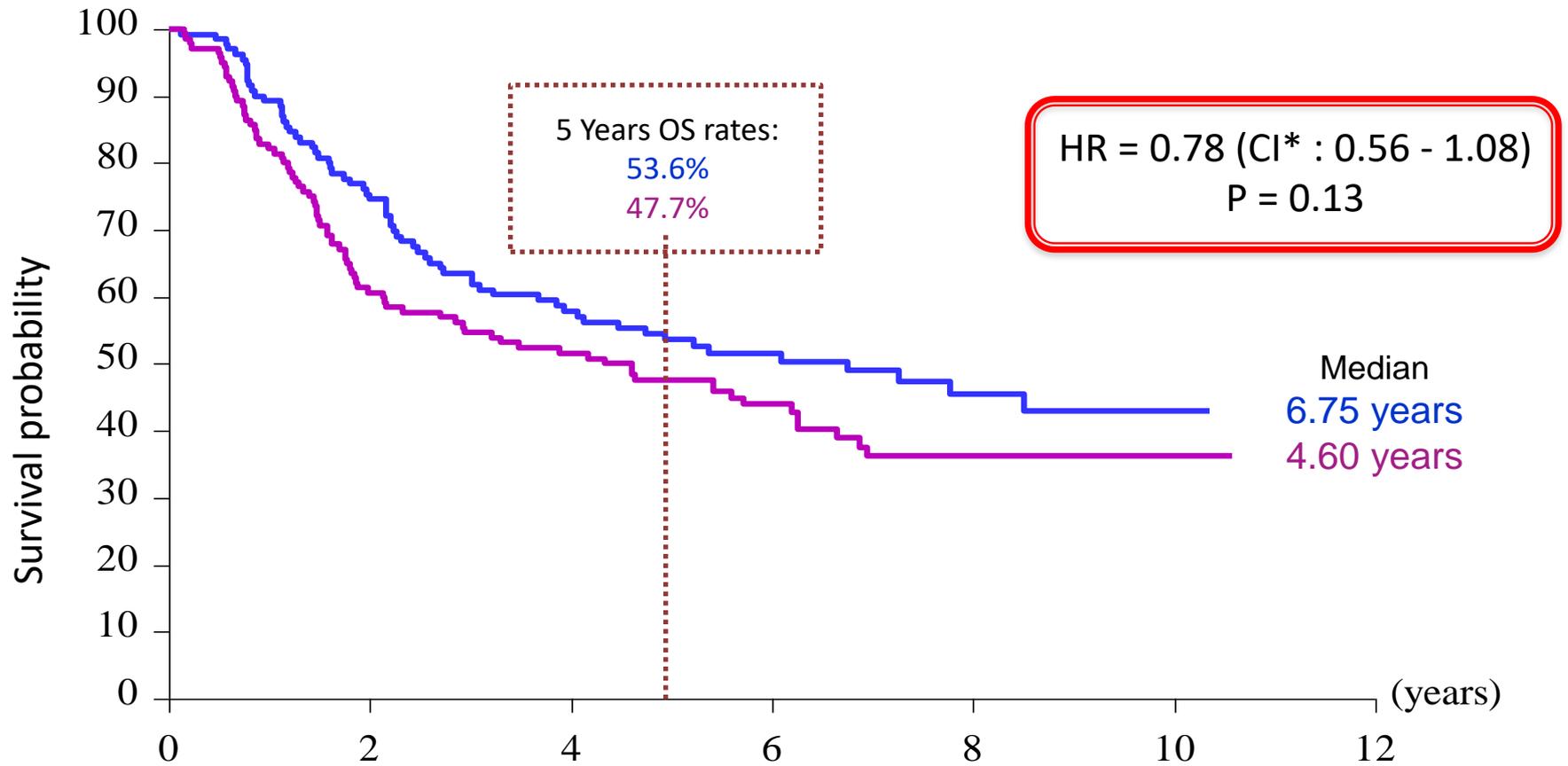


Figure 4: Kaplan-Meier overall survival curves in patients who were node negative at baseline

# Overall Survival (ITT)

A non-significant reduction of 22.2% in the risk of death



O	N	Number of patients at risk :						Treatment
66	141	95	70	44	25	3	— Immediate	
82	143	83	67	42	21	4	— Deferred	

\*95.09%, adjusted for interim analysis

# Neoadjuvant Kemoterapi

## PROS

- Erken sistemik kontrol
- Mesane koruma şansı
- KT etkinlik testi

## KONTRA

- Lokal kontrolde gecikme
- Kür şansını kaçırma
- Yanlış patolojik evreleme
- Fazla tedavi

# Evidence supporting the efficacy of neoadjuvant chemotherapy

Investigator/Group	Type of evidence	Benefit (% reduction mortality vs cystectomy alone)	Remarks
SWOG (NEJM, 2003)	Multicentric randomized study (317 pts)	HR 0.67 5yrΔ 14% p=0.06 (two sided)	Benefit more evident in T3 or T4a pts
NORDIC (Eur Urol, 2004)	Metanalysis of 2 randomized trial (Nordic I and II) (620 pts)	HR 0.80 5yrΔ 8% (0.64-0.99) p=0.05	Benefit more evident in T3 or <65 yr pts
ABC Collaboration (Lancet, 2003)	Metanalysis of 9 randomized trials (including MRC/EORTC) (2688 pts)	HR 0.91 5yrΔ 3% 0.87 5% p=0.01	Benefit for combination chemotherapy only
CANCER CARE ONTARIO PROGRAM (J Urol, 2004)	Metanalysis of 11 randomized trials (including MRCEORTC) (2605 pts)	HR 0.90 5yrΔ p=0.02 0.87 6.5% p=0.006	Benefit for combination chemotherapy only

# Neoadjuvan Kemoterapi

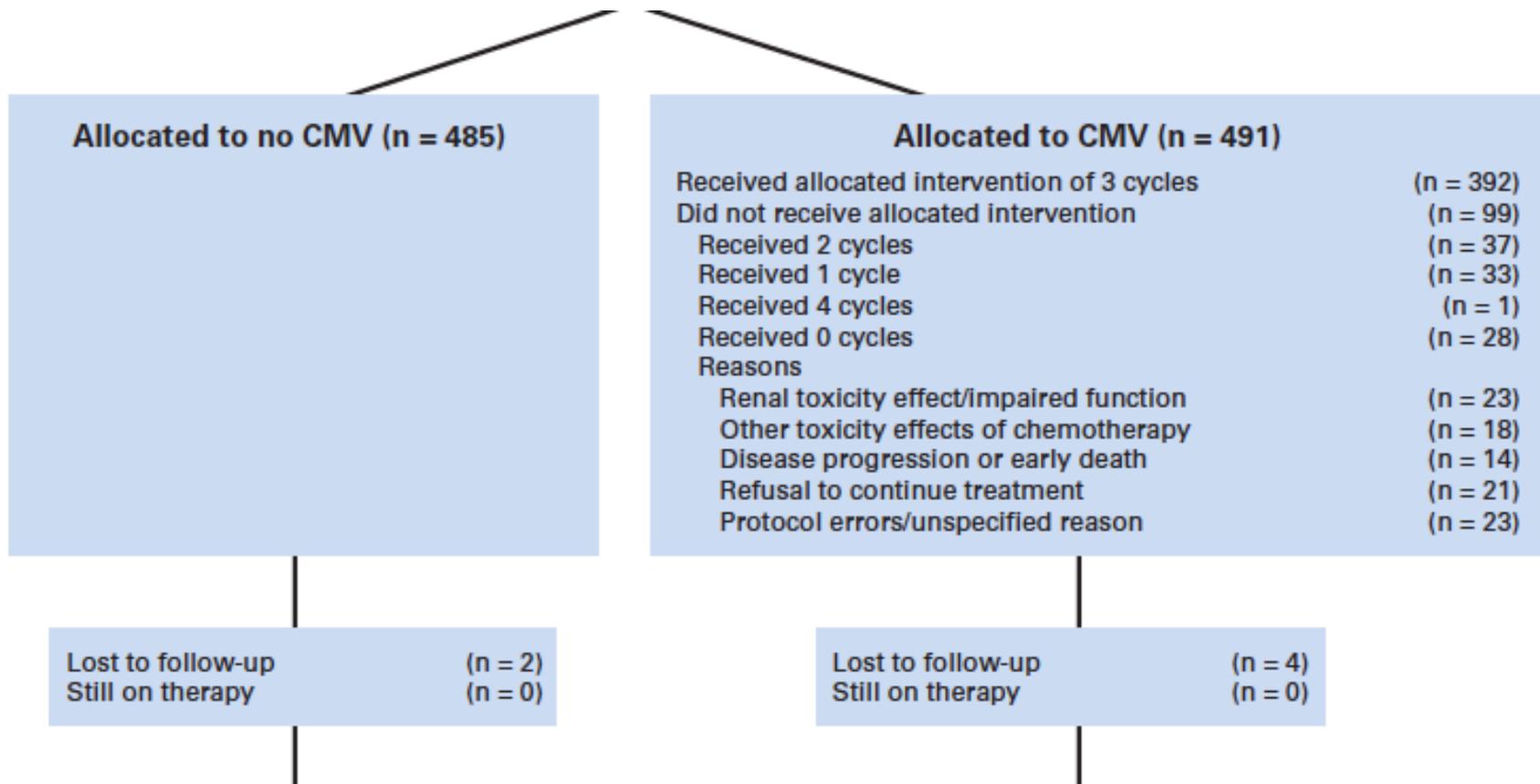
- Meta-analiz: 10 randomize çalışma (2688 hasta)

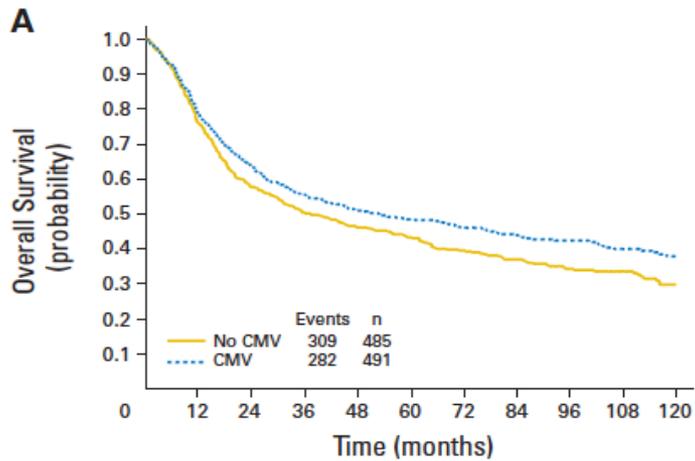
% 13 ölüm riskinde azalma

5 yıllık sağkalımda + % 5 absolut yarar

GS % 45'den % 50'e çıkmaktadır

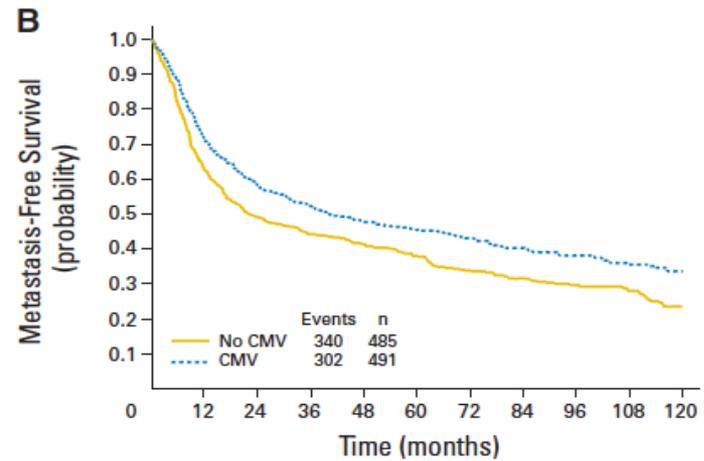
# International Phase III Trial Assessing Neoadjuvant CMV Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial





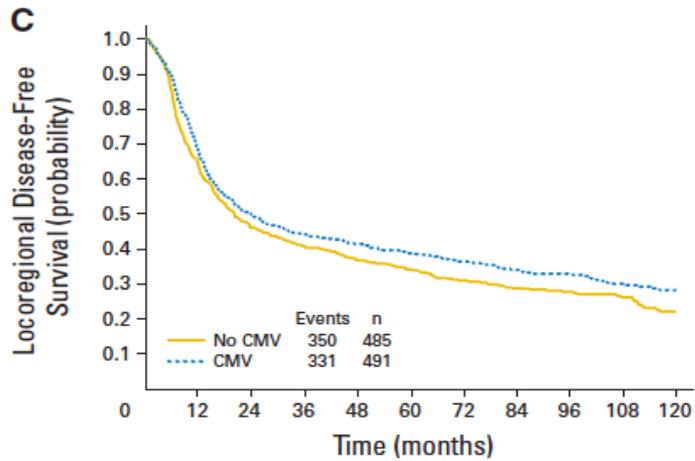
No. at risk

	0	12	24	36	48	60	72	84	96	108	120
No CMV	485	360	270	232	201	179	151	119	93	71	48
CMV	491	377	301	257	228	212	185	150	121	96	60



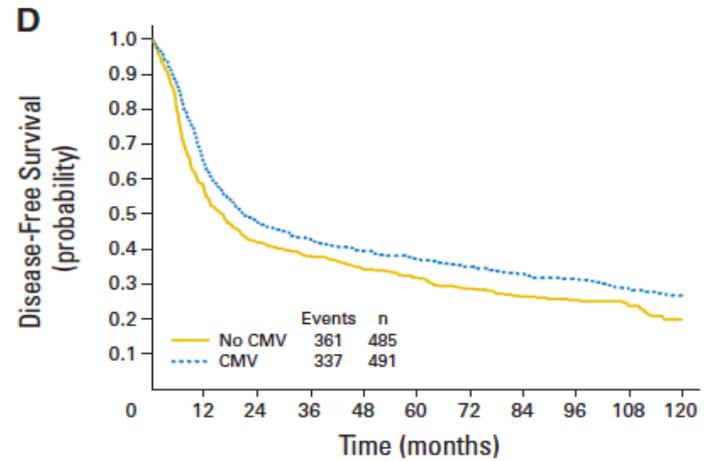
No. at risk

	0	12	24	36	48	60	72	84	96	108	120
No CMV	485	298	230	205	181	158	130	103	83	64	40
CMV	491	339	275	241	213	198	173	142	115	91	56



No. at risk

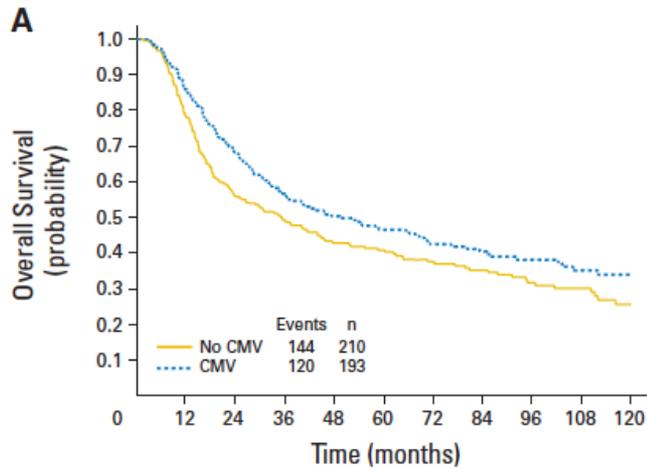
	0	12	24	36	48	60	72	84	96	108	120
No CMV	485	299	216	189	161	142	119	97	79	57	40
CMV	491	321	237	207	188	173	149	122	100	78	48



No. at risk

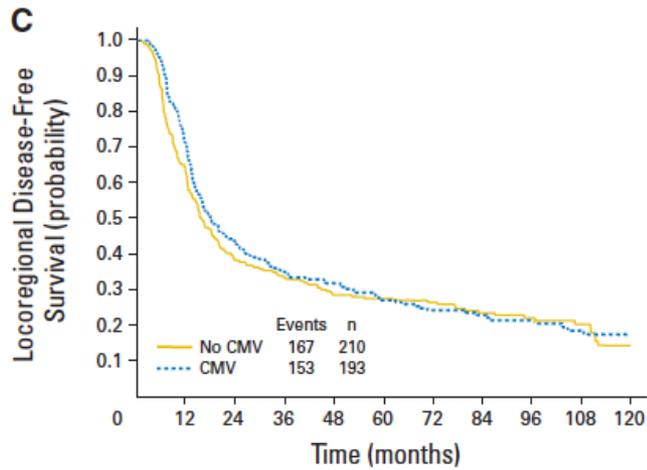
	0	12	24	36	48	60	72	84	96	108	120
No CMV	485	266	196	176	150	132	110	88	73	54	37
CMV	491	304	226	200	180	166	144	119	97	75	45

# Radyoterapi



No. at risk

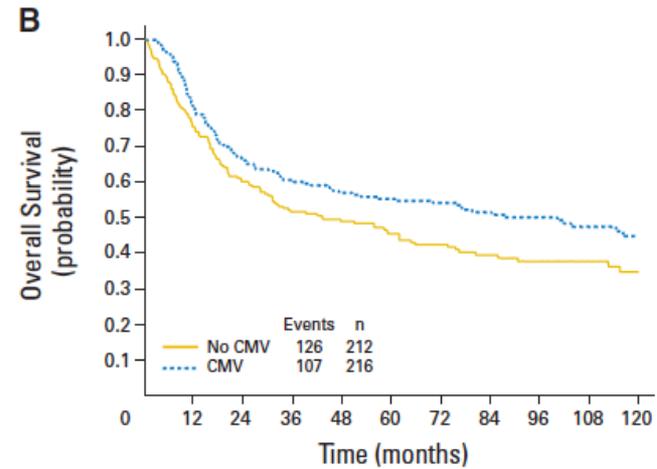
	0	12	24	36	48	60	72	84	96	108	120
No CMV	210	163	116	101	86	78	66	55	40	31	18
CMV	193	165	130	108	94	86	70	56	43	34	21



No. at risk

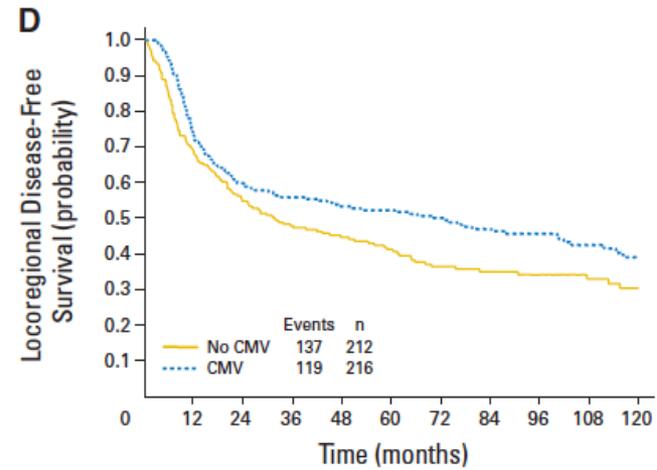
	0	12	24	36	48	60	72	84	96	108	120
No CMV	210	127	79	69	57	52	47	37	27	19	11
CMV	193	134	82	67	60	51	40	32	24	18	11

# Sistektomi



No. at risk

	0	12	24	36	48	60	72	84	96	108	120
No CMV	212	157	122	102	88	76	64	47	38	28	21
CMV	216	169	138	119	106	99	89	73	63	49	29



No. at risk

	0	12	24	36	48	60	72	84	96	108	120
No CMV	212	141	111	95	81	70	55	45	38	28	21
CMV	216	151	124	112	102	97	85	72	63	49	28

# Neoadjuvan - Adjuvan Tedavi

- Hastada kür şansını artırmalı
  - Rezeksiyon şansını artırmak
  - Nüks oranını azaltmak
  - Uzak metastaz azaltmalı
- KLİNİK ÇALIŞMALARDAKİ SONUÇLAR HER HASTAYA UYGULANAMAZ

# Genel Toplumda Tedavi Yaklaşımı

Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

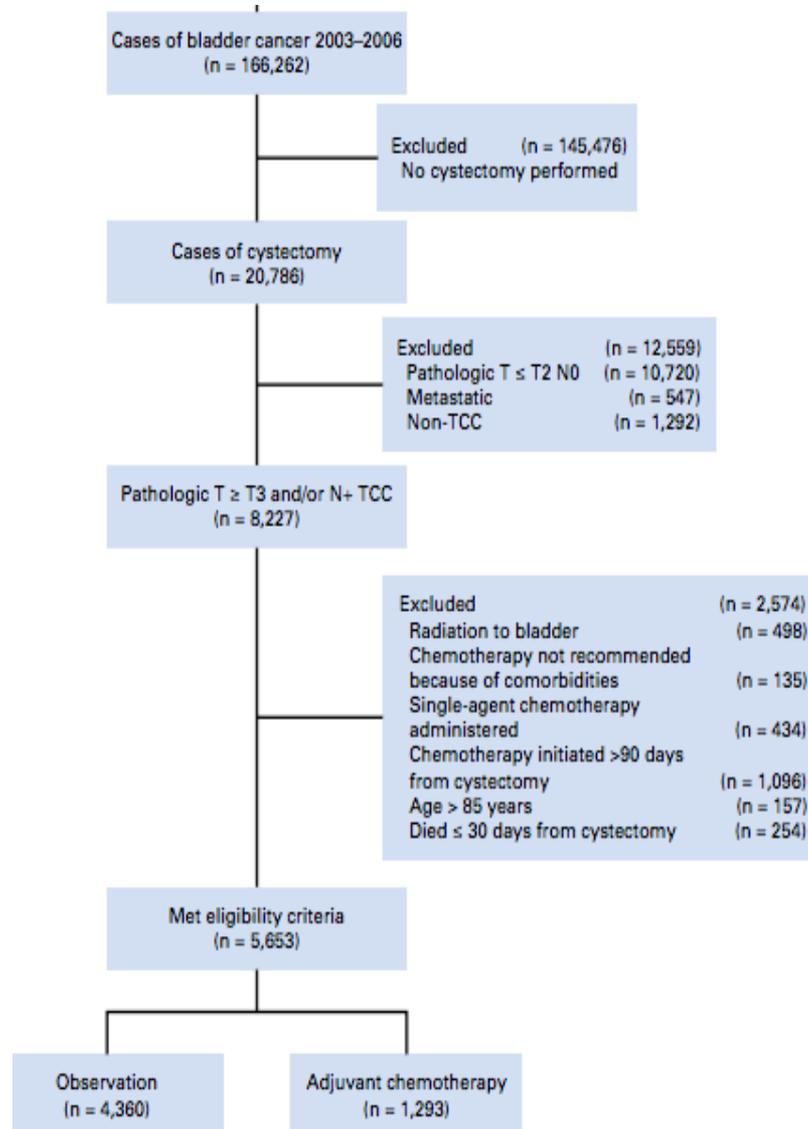
- Galsky MD ve ark.

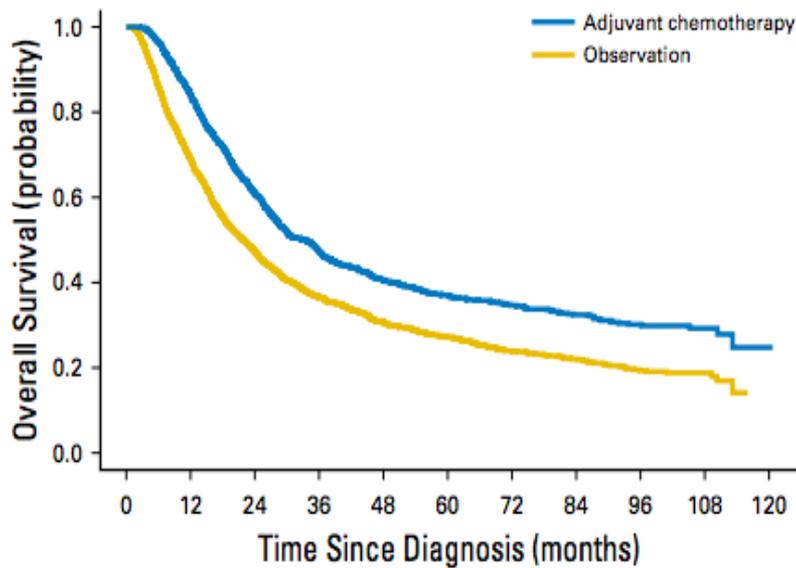
*J Clin Oncol. 2016, 34:825-32*

Amerika B.D'de Kanser Bilgi Toplama Kayıtları

2003- 2006 yılları arasında en az 5 yıl takip süresi olabilecek hastalarda gözlemsel çalışma

# Hasta Alımı

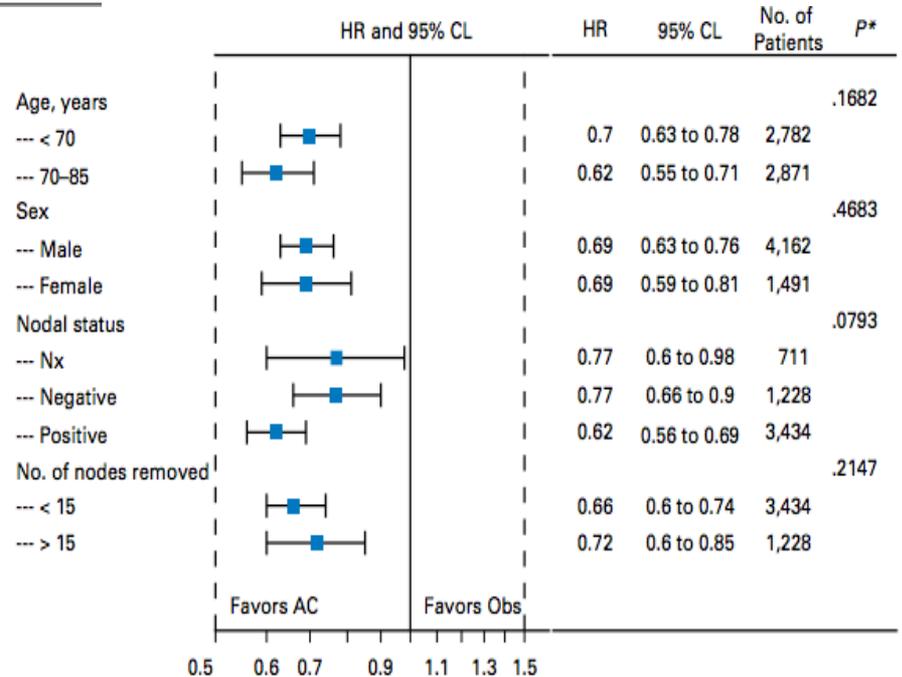




No. of patients	0	12	24	36	48	60	72	84	96	108	120
Adjuvant chemotherapy	1,293	1,067	762	584	495	427	326	193	102	30	1
Observation	2,080	1,395	931	703	571	464	320	178	87	28	

## KT alan hasta grubu ( $P < 0.05$ )

- Genç
- Özel sağlık sigortalı
- Ortalama geliri daha yüksek bölgeler
- Daha yüksek eğitilmişler
- Lenfatik tutulumu ve/veya cerrahi sınır pozitif olan hastalar



# Sonuçlar

- Lokal ileri mesane kanserinde sistektomi öncesi veya sonrası kemoterapi ile sağkalım artmaktadır
- Genel durum iyi (ECOG PS 0-1)
- Ciddi komorbiditesi olmayan
- $\geq$  T3 veya nodal tutulumu olan hastalara kemoterapi verilmelidir.
- Genel yaklaşım kemoterapinin ameliyat öncesi verilmesidir.
  - Böbrek fonksiyonları
  - Postop komplikasyonlar tedaviyi önlememeli

*Teşekkür ederim*