Muscle invasive bladder cancer:
the good, the bad and the immunologic

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Presenter Disclosure and Mitigation Plan

- **Presenter:** Piotr Czaykowski

- **Relationships with commercial interests:**
  - **Grants/Research Support:** I have participated in clinical trials with Pembrolizumab (Merck); I have received no direct financial remuneration
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

After the next 10 minutes…

- You will be able to:
  - 1. Comment on the indications for systemic therapy in MIBC (metastatic, neoadjuvant, adjuvant, chemoradiotherapy)
  - 2. Explain why treating advanced bladder cancer can often be quite tricky
  - 3. Understand the factors in choosing first line systemic therapy
  - 4. Appreciate the emerging new treatment options

Epidemiology of Bladder Cancer

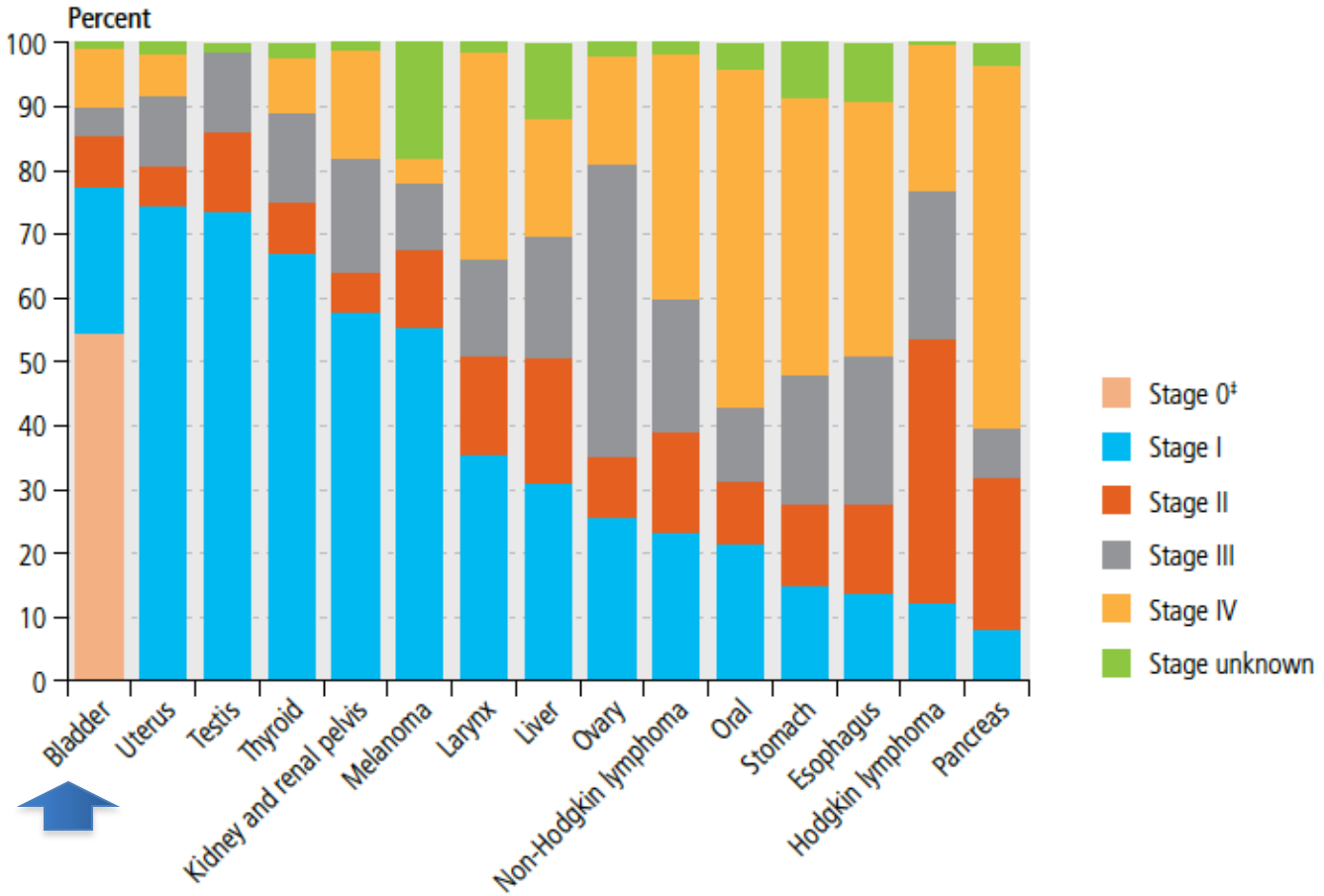
Incidence in Canada:

- 🚹 - 4th most common – 6700/yr (230 in MB)
- 🚺 - 12th most common – 2200/yr (75 in MB)
- 2400 deaths in Canada annually

- Incidence peaks in 7th decade

Canadian Cancer Statistics 2017

FIGURE 11 Percent distribution of cancer stage at diagnosis, selected cancers, Canada,* 2011–2015†



Analysis by: Health Statistics Division, Statistics Canada
Data source: Canadian Cancer Registry database at Statistics Canada

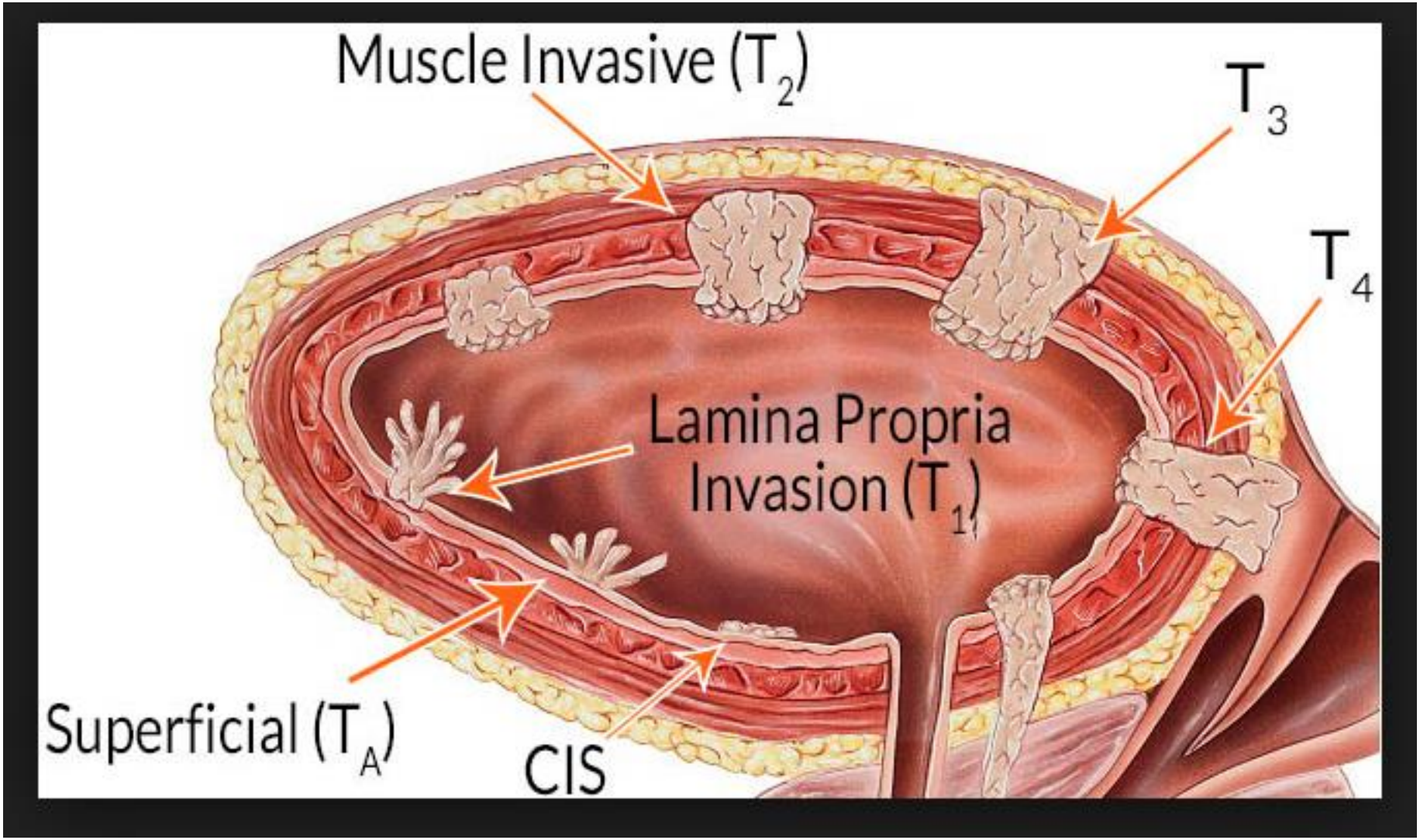
Urothelial carcinoma

- Urothelium = Lining of the urinary collecting system
  - Includes renal pelvis, ureters, urinary bladder and proximal urethra
- Vast majority of malignancies in this area involve the bladder
- 10% present with upper tract disease

- 80% are “transitional cell” cancers

T Stage

- Clinical versus pathological
- Ta – non-invasive papillary tumor
- Tis – carcinoma in situ (flat tumor)
- T1 – tumor invades subepithelial connective tissue
- T2a – tumor invades muscularis (inner half)
- T2b – tumor invades muscularis (outer half)
- T3a – microscopic invasion of perivesical tissue
- T3b – extravesical mass (macroscopic)
- T4a – invades prostate, uterus or vagina
- T4b – invades pelvic or abdominal wall

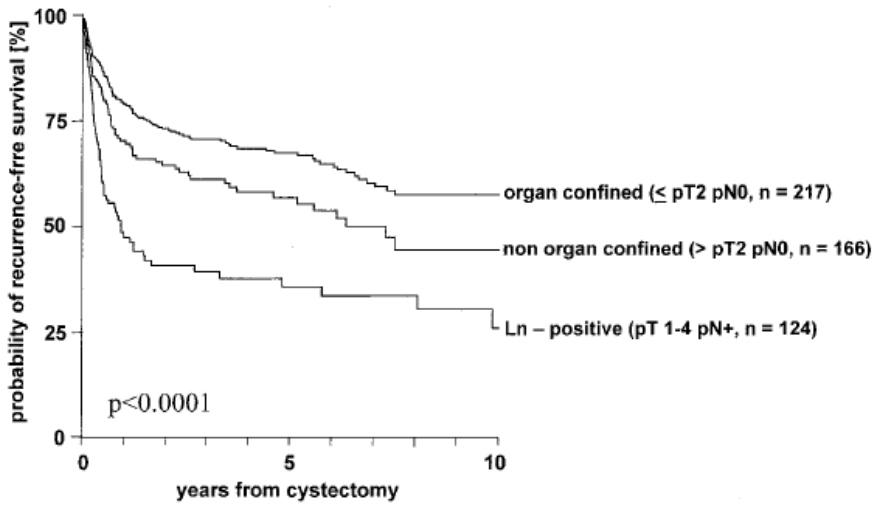

Muscle Invasive (T_2)
T_3
T_4
Lamina Propria Invasion (T_1)
Superficial (T_A)
CIS

Natural History

- 75% - superficial at presentation
  - 50-80% relapse after local management
  - Relapsed disease is muscle invasive in 10-25% of cases
- 25% - muscle invasive at presentation
- Muscle invasion → grim prognosis
  - 50% risk of distant metastases

Post-cystectomy outcomes

A



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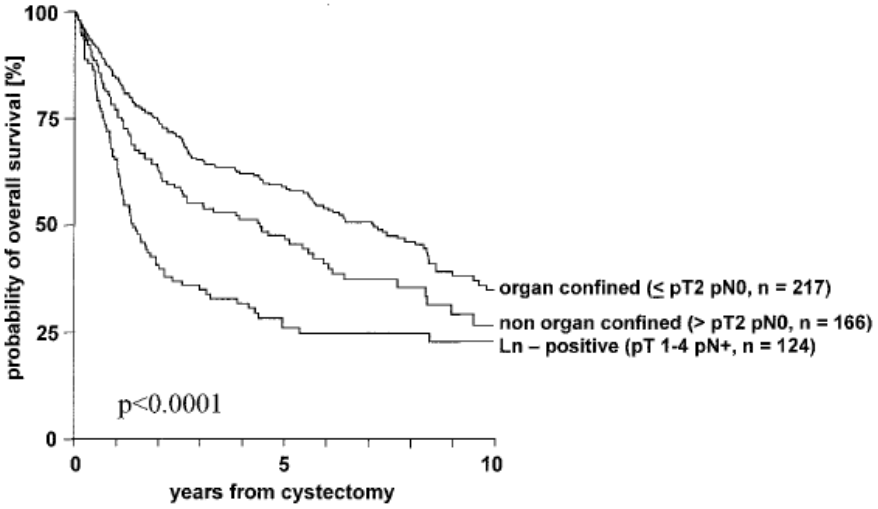


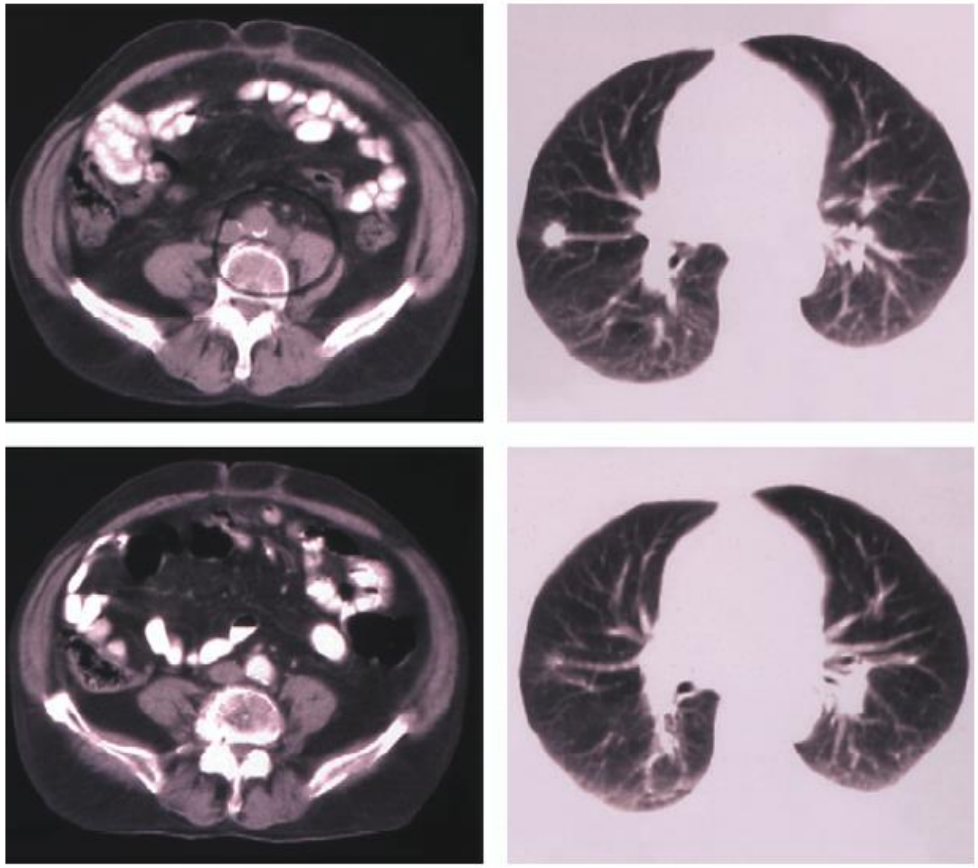
507 patients
Surgery 1985-2000
Despite negative staging (cN0), 24% have nodal metastases at surgery

J Clin Oncol 21:690-696.

Role of Systemic Drug Therapy in MIBC

- Prevent recurrence post definitive therapy
  - Neoadjuvant before radical cystectomy
  - Adjuvant after radical cystectomy
  - Combined modality therapy – “radiosensitizer” with radical radiotherapy
- Control advanced (usually metastatic) disease
  - Cure occasionally?

Advanced Urothelial Carcinoma



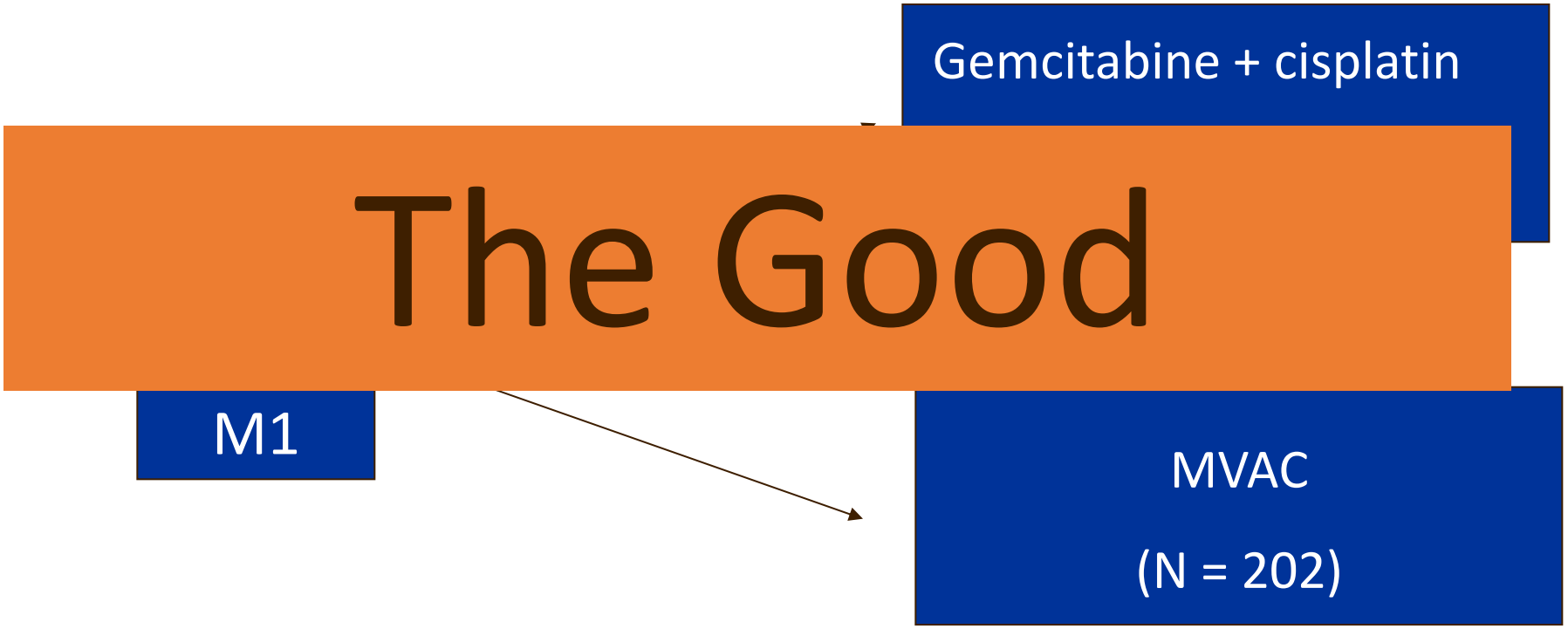
Sites of Metastases

- Common
  - Nodes, bone, lung, liver
- Uncommon
  - Skin, brain, meninges, vagina, peritoneal carcinomatosis

Advanced Bladder Cancer

Treatment	Med. Surv. (mo.)	3-Year Surv. (%)
Supportive Care	4-6	0
Single Agent Chemo.	7-8	0
Multi-agent Chemo.	12	20-25%

GC versus MVAC – Phase III RCT



von der Maase et al. JCO 2000; 18: 3068

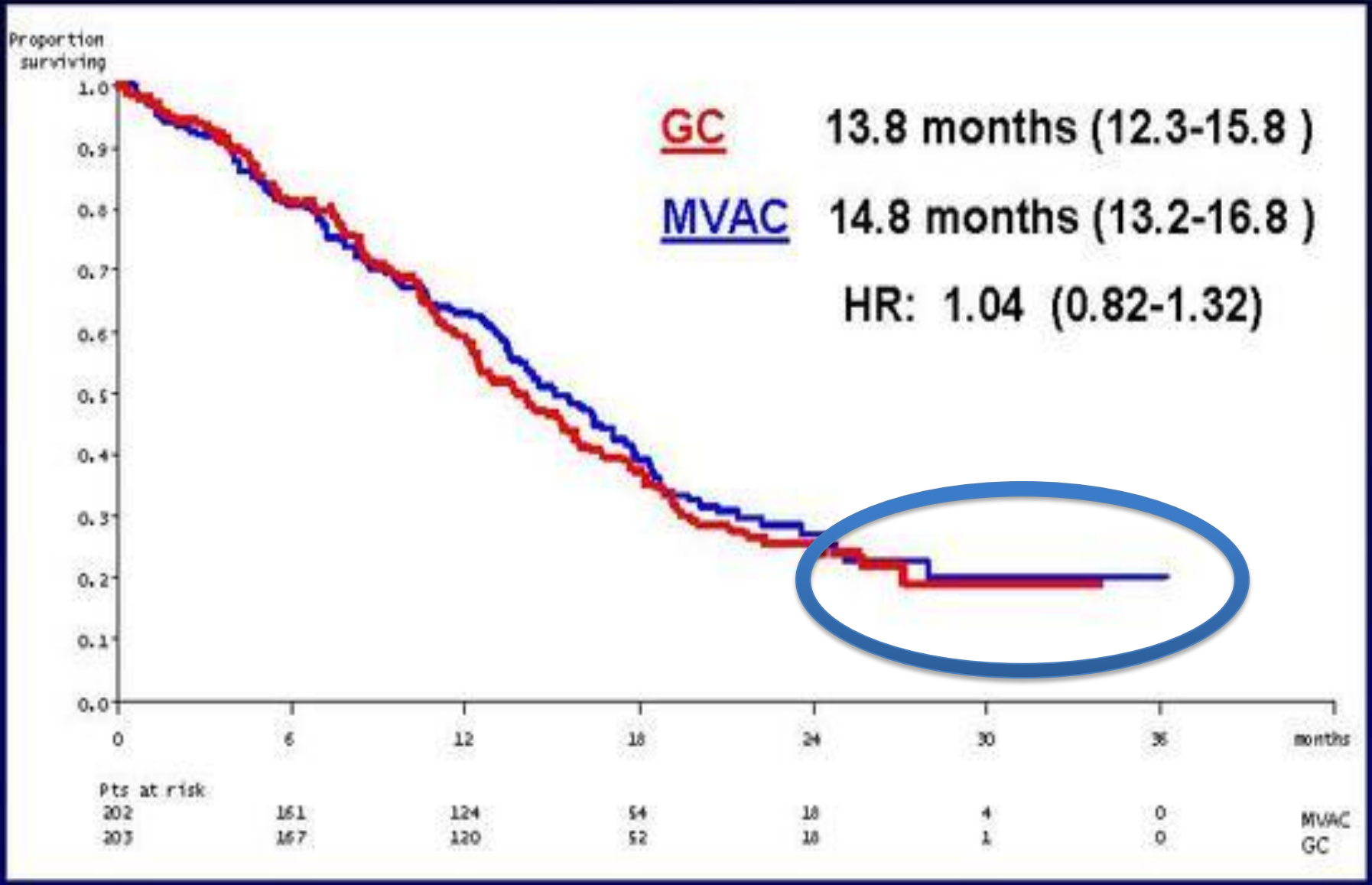
GC vs MVAC

- Primary endpoint: overall survival
- Non-inferiority study

	GC	MVAC
Complete response	12%	12%
Partial response	37%	34%
Overall response	50%	46%

GC versus MVAC

Overall survival



Prognostic Model

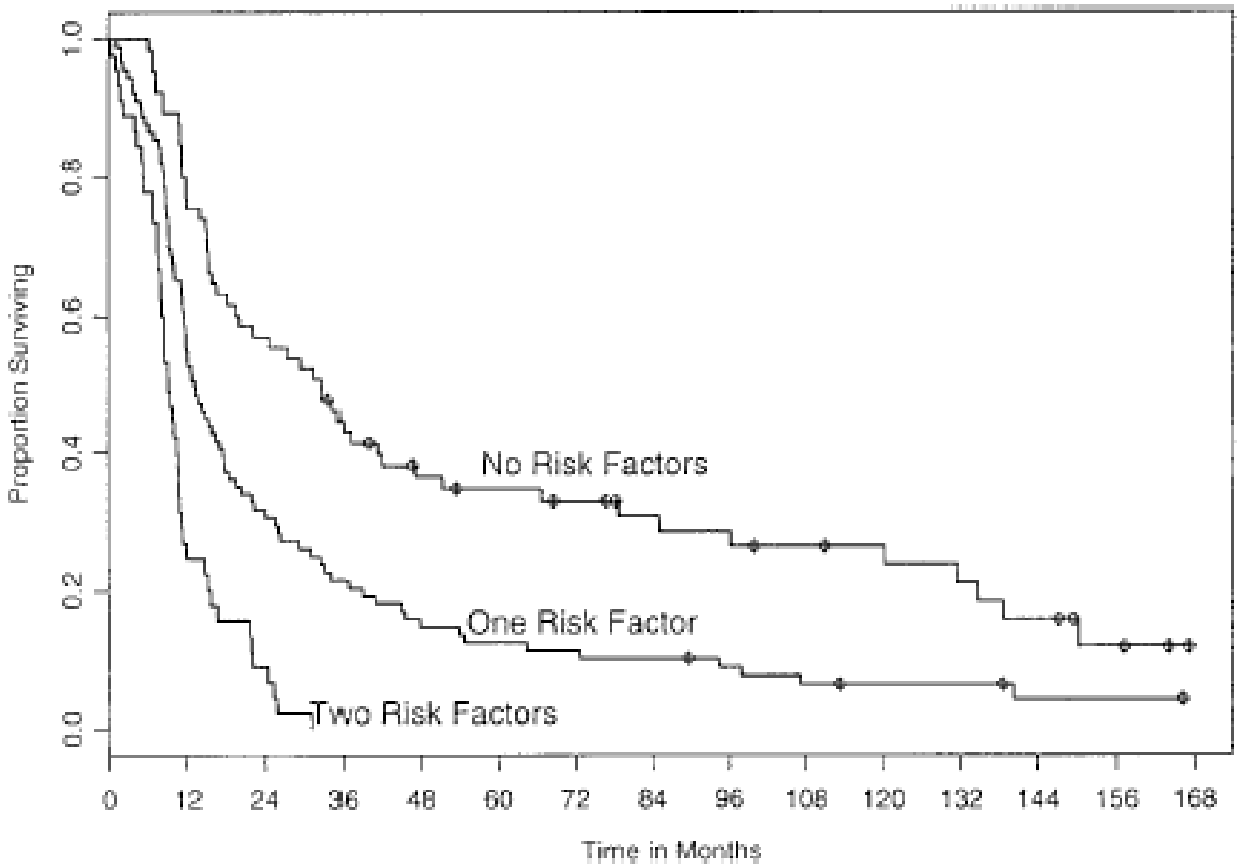


Fig 2. Survival for all patients grouped according to number of risk factors present at baseline. Poor risk factors include KPS < 80% and presence of visceral metastasis.

Grade 3/4 toxicity with GC

Toxicity	Frequency
Anemia	27%
Thrombocytopenia	57%
N/V	22%
Allopecia	11%
Diarrhea	3%
Toxic Deaths	1%

The Bad

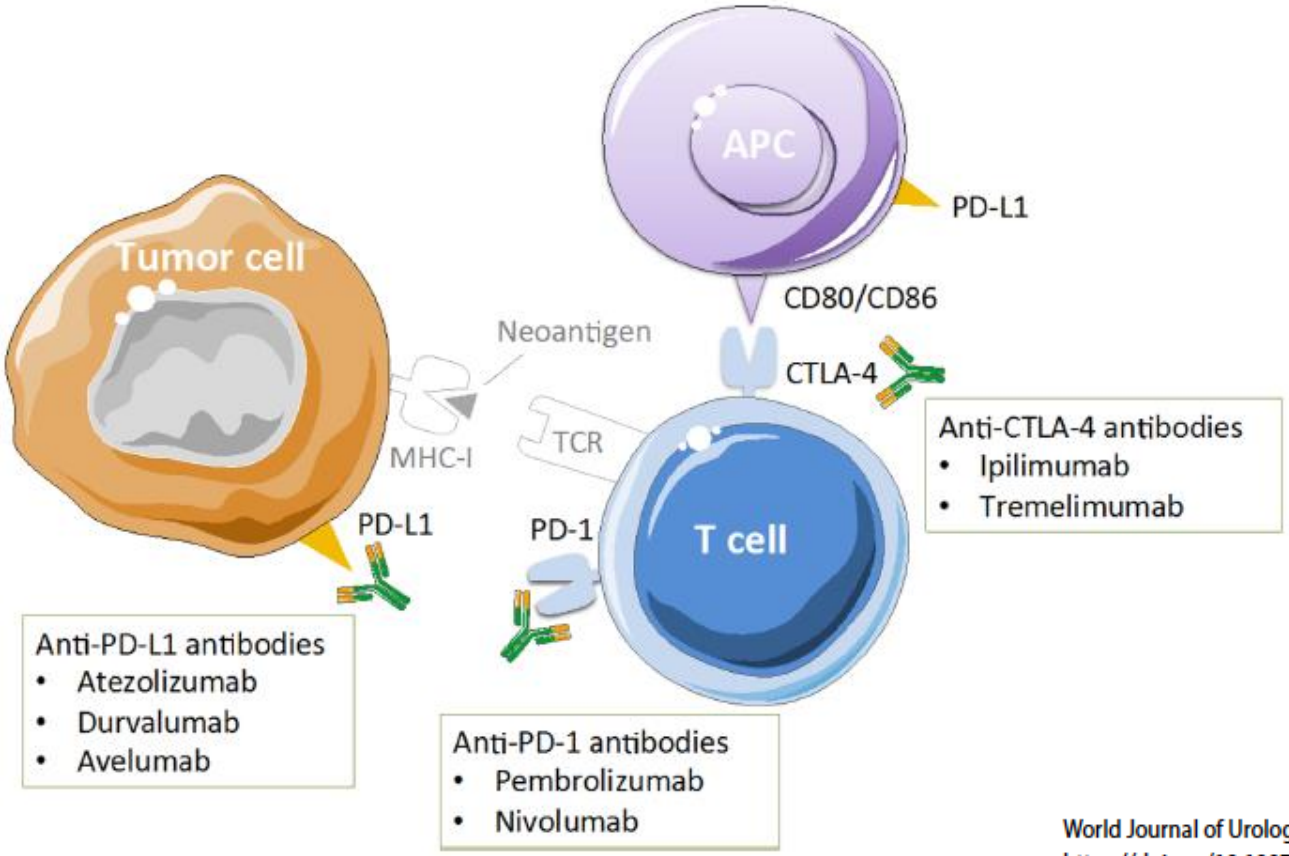
Arterial or venous thromboembolic complications: >15%

Can’t use with impaired renal function

Patient Selection

- Single most important factor for choosing systemic therapy is patient related comorbidity and performance status
- Typically elderly, most commonly smokers, frequently multiple smoking related health issues (CAD, PVD, COPD)
- Frequently impaired renal function
- Often sedentary

Immuno-oncology Checkpoint inhibition



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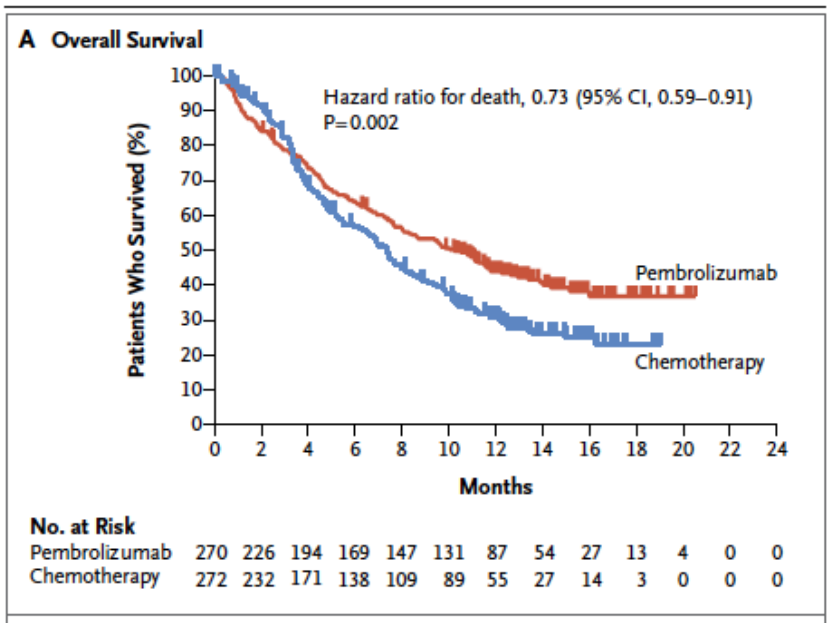
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang,

- Pembrolizumab: anti-PD-1 monoclonal antibody

The immunologic

- 1:1 randomization – control arm paclitaxel, docetaxel or vinflunine
- Objective response rate: 21.1% versus 11.4% (p=0.001)



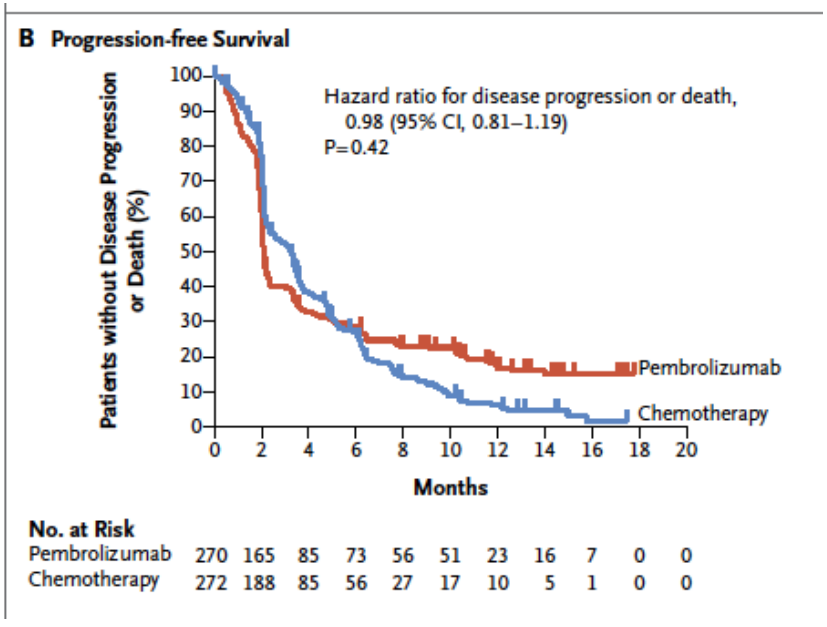
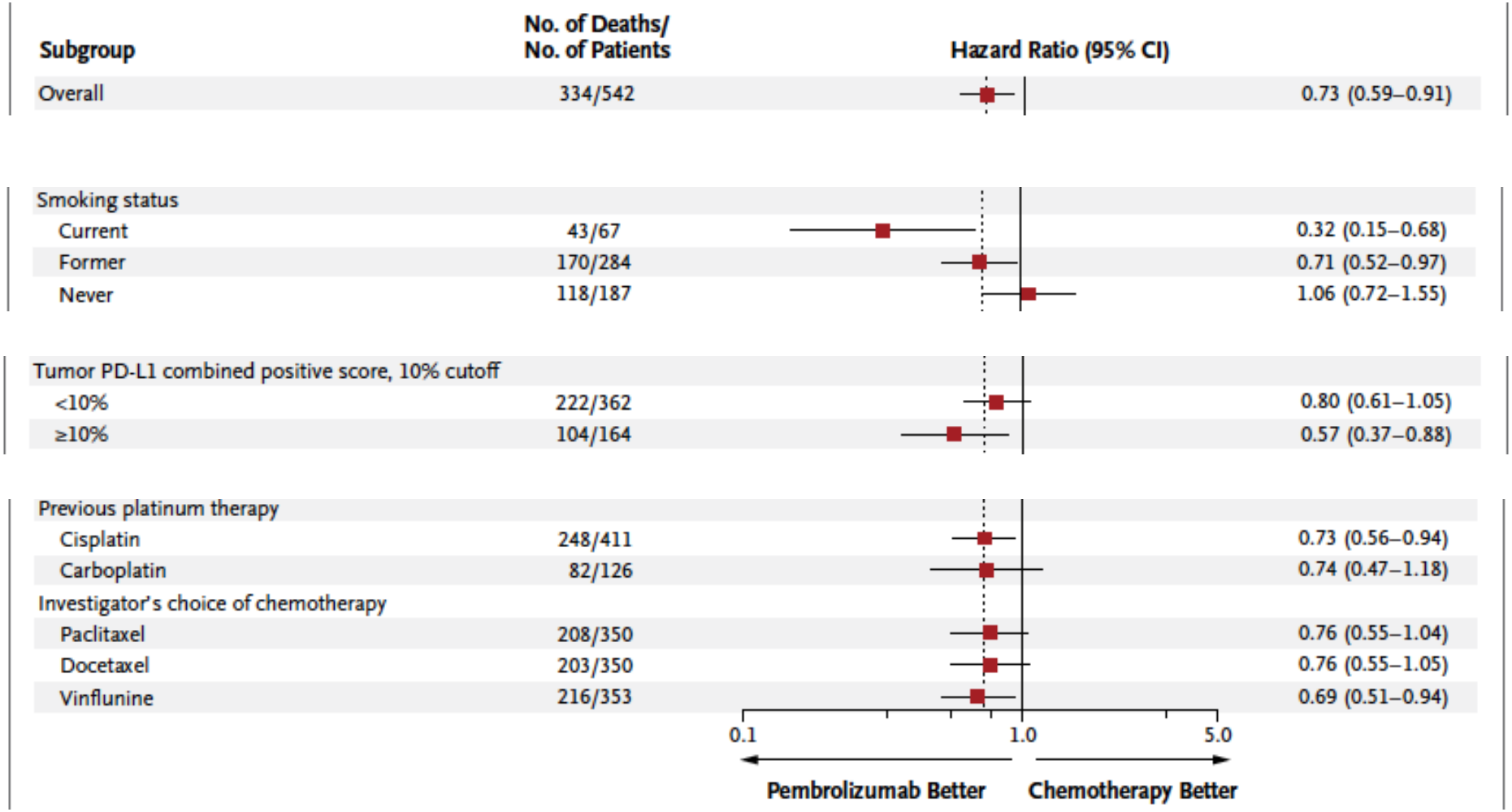


Table 2. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)

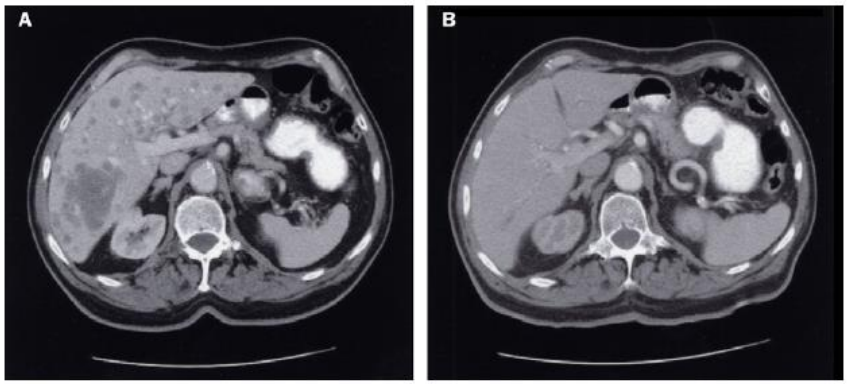

Subgroup
No. of Deaths/ No. of Patients
Hazard Ratio (95% CI)
Overall
334/542
0.73 (0.59–0.91)
Smoking status
Current
43/67
0.32 (0.15–0.68)
Former
170/284
0.71 (0.52–0.97)
Never
118/187
1.06 (0.72–1.55)
Tumor PD-L1 combined positive score, 10% cutoff
<10%
222/362
0.80 (0.61–1.05)
≥10%
104/164
0.57 (0.37–0.88)
Previous platinum therapy
Cisplatin
248/411
0.73 (0.56–0.94)
Carboplatin
82/126
0.74 (0.47–1.18)
Investigator's choice of chemotherapy
Paclitaxel
208/350
0.76 (0.55–1.04)
Docetaxel
203/350
0.76 (0.55–1.05)
Vinflunine
216/353
0.69 (0.51–0.94)
0.1
1.0
5.0
Pembrolizumab Better
Chemotherapy Better

Off-target autoimmune effects

Event of interest§		
Any event	45 (16.9)	12 (4.5)
Hypothyroidism	17 (6.4)	0
Hyperthyroidism	10 (3.8)	0
Pneumonitis	11 (4.1)	6 (2.3)
Colitis	6 (2.3)	3 (1.1)
Infusion reaction	2 (0.8)	0
Nephritis	2 (0.8)	2 (0.8)
Severe skin reaction	2 (0.8)	1 (0.4)
Thyroiditis	2 (0.8)	0
Adrenal insufficiency	1 (0.4)	1 (0.4)
Myositis	0	0

Newer Regimens

Regimen	RR (%)	MS (mo.)
MVAC	30-70	12-20
GC	50-65	12-15
GCT	85	24+ (?)
GCaT	68	15
TCa	50-60	9-10
TC	50-70	11-13
ITP	68-79	18-20
ITP-AG	?	?



GCT

In Renal Insufficiency?

Regimen	N	RR (%)	OS (mo.)
MVNCa	23	57	10
Paclitaxel	6	66	NR
Paclitaxel	13	45	9
Docetaxel	11	30	11
Carbo/Gem	16	44	NR
Carbo/Gem	17	56	NR
Carbo/Paclitaxel	34	21	8.7

Table 3 Ongoing immunotherapeutic trials in advanced urothelial carcinoma

NCT number	Trial design	Clinical setting: phase (*n*)	Interventions	Primary endpoint	Secondary endpoints
Metastatic UTC					
Monotherapy					
02807636	Atezolizumab monotherapy and in combination with platinum-based chemotherapy	III ($n=1200$)	Atezolizumab | carboplatin | gemcitabine | cisplatin	PFS|OS | AEs	
02527434	Tremelimumab	II ($n=64$)	Tremelimumab monotherapy | biological: MEDI4736 monotherapy | biological: MEDI4736 + tremelimumab combination therapy	ORR | DoR | DCR | PFS | OS | BOR	
Combination therapy					
02925533	B-701 in combination with pembrolizumab	IB	B-701 | pembrolizumab	Safety of B-701 in combination	Efficacy of B-701 in combination
02989 584		I/II ($n=30$)	Atezolizumab | gemcitabine | cisplatin	Safety (DLT)	
03288545		I ($n=85$)	Enfortumab vedotin | pembrolizumab | atezolizumab	Incidence of DLT	AEs
03123055		I ($n=48$)	B-701 | pembrolizumab	FGFR3 expression safety and tolerability	Safety and tolerability
02437370		1 ($n=38$)	Pembrolizumab | docetaxel | gemcitabine hydrochloride	Safety and tolerability of MK-3475 (pembrolizumab) in combination	Efficacy, programmed death (PD)-ligand (L)1 expression in archived tumour specimens—correlation with patient outcomes
02043665		I ($n=90$)	Biological: CVA21	Response rate	
02619253		I/Ib ($n=42$)	Pembrolizumab | vorinostat	Recommended phase II dose	Serious AEs | ORR | PFS
03093922		II ($n=31$)	Atezolizumab | gemcitabine | cisplatin	ORR	
03324282		II ($n=90$)	Avelumab | GC	Efficacy and safety	Specific immunological toxicity | DoR | PFS | OS | GC + avelumab efficacy according to expression of PD-L1 at the tumour site | GC + avelumab efficacy according to immune infiltrate populations at the tumour level and/or the tumour surroundings
Maintenance therapy					
02500121	Pembrolizumab as maintenance therapy after initial chemotherapy	II ($n=200$)	Placebo | pembrolizumab	6-month PFS	Six-month PFS rates among the subsets of subjects with PD-L1 positive and PD-L1 negative tumours | OS
02603432	Study of avelumab in patients with locally advanced or metastatic urothelial cancer (JAVELIN Bladder 100)	3 (668)	Avelumab	OS	PFS | ORR | DoR

Neo-adjuvant chemotherapy

- Chemotherapy prior to definitive treatment to ↓ risk of recurrence

Chemo-sensitivity of UC

- In advanced disease with cisplatin-based poly-chemotherapy:
  - 60-70% overall response rate
  - 30% CR in Phase II studies

Overall survival – combination chemotherapy

Meta-analysis of 9 studies, 2492 subjects; node negative

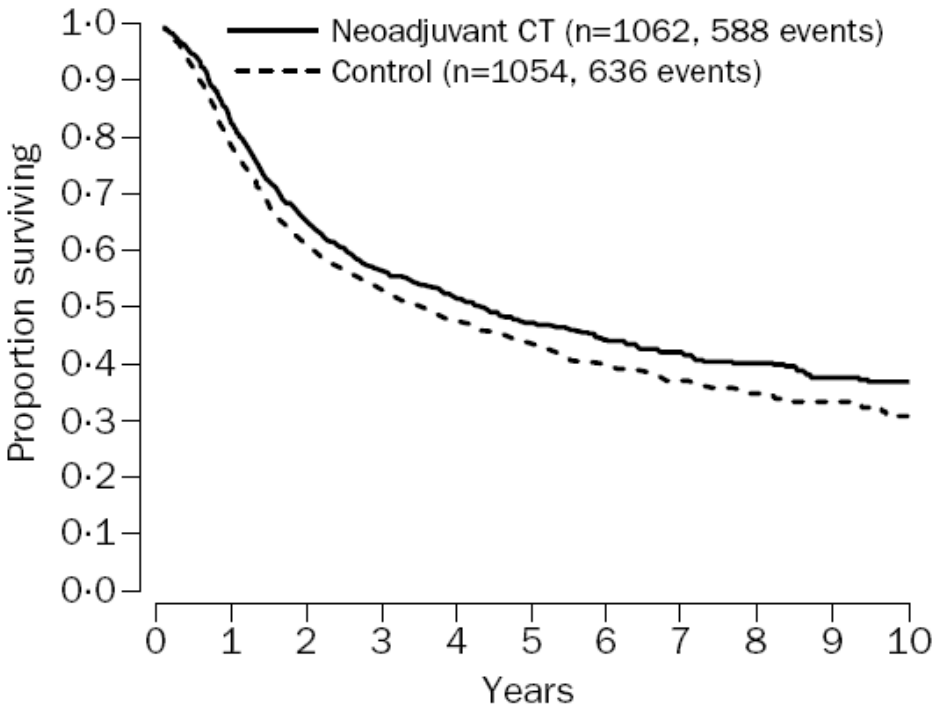


Figure 2: **Survival in combination chemotherapy (CT) trials**

HR 0.87

P = 0.016

ABC Meta-analysis Collaboration. Lancet 2003; 361: 1927.

Endpoints – Combination Chemotherapy

Endpoint	Absolute Benefit (95% CI)	*P*
OS	5% (1-9%)	0.016
DFS	7% (4-11%)	0.0001
Loco-regional DFS	5% (1-9%)	0.012
Metastases-free Survival	7% (3-11%)	0.001

ABC Meta-analysis Collaboration. Lancet 2003; 361: 1927.

Adjuvant chemotherapy

- Chemotherapy post definitive treatment to ↓ risk of recurrence
- Eliminate micro-metastases
  - Low volume
  - Less genetic heterogeneity/resistance

Table 1. Summary of selected clinical trials of adjuvant chemotherapy for MIBC

Study (year of publication)	Patients randomized (*N*)	Eligibility TNM stage	Chemotherapy	Years to accrue	Recurrence observation vs. chemotherapy	Overall survival observation vs. chemotherapy
Skinner et al. (1991)	102	pT3-4 or N+	Cisplatin-based combinations	8 (1980–1988)	3-years DFS 46% vs. 70%	Median OS 2.4 vs. 4.3 years; $p = 0.006$
Studer et al. (1994)	91	Multifocal recurrent pT1 or T2-T4a	Single-agent cisplatin	5 (1984–1989)	–	5-years OS 54% vs. 57% $P = 0.65$
Freiha et al. (1996)	55	pT3b-4, N0 or N+	CMV	7 (1986–1993)	No recurrence 25% vs. 48% Median PFS 12 vs. 37 mon; $p = 0.01$	Median OS 36 vs. 63 mon; $p = 0.32$
Lehmann et al. (2006)	49	pT3-4a and/or N+	MVAC or MVEC	6 (1994–2000)	PFS 13.0% vs. 43.7%; $p = 0.002$, HR 2.84	Median OS 20. 4 vs. 35.1 mon 10-years OS 17.4% vs. 26.9%; $p = 0.069$, HR 1.75
Paz-Ares et al. (2010)	142	pT3-4 and/or pN+	PGC	7 (2000–2007)	3-years recurrence rate 44% vs. 73%; $p < 0.0001$, HR 0.36	Median OS 26 mon vs. not reached 5-years OS 31% vs. 60%; $p < 0.0009$, HR 0.44
Stadler et al. (2011)	114	p53+ and T1 and T2, pN-	MVAC	9 (1997–2006)	5-years recurrence rate 20% (both arms); $p = 0.62$, HR 0.78	5-years OS 85% (both arms)
Cognetti et al. (2012)	194	pT2G3, N0-2; pT3-4, N0-2; or pN1-2, any T	GC	6 (2001–2007)	DFS 42.3% vs. 37.2%; $p = 0.70$, HR 1.08	5-years OS 48.5% (both arms); $p = 0.24$, HR 1.29
Stenberg et al. (2015)	284	pT3-4 and/or pN+	GC, MVAC or DD-MVAC	6 (2002–2008)	PFS 31.8% vs. 47.6%; $p = < 0.0001$, HR 0.54	Median OS 6.7 vs. 4.6 years 5-years OS 53.6% vs. 47.7%; $p = 0.13$, HR 0.78

MIBC muscle-invasive bladder cancer, *TNM stage* tumor/node/metastasis stage, *OS* overall survival, *vs.* versus, *DFS* disease-free survival, *MVAC* methotrexate, vinblastine, doxorubicin and cisplatin, *MVEC* methotrexate, vinblastine, epirubicin and cisplatin, *CMV* cisplatin, methotrexate and vinblastine, *PFS* progression-free survival, *mon* months, *HR* hazard ratio, *PGC* paclitaxel, gemcitabine and cisplatin, *GC* gemcitabine and cisplatin,*DD-MVAC* dose-dense MVAC

Nadal, Apolo Curr Treatment Options in Oncology, 2018

Immediate versus Delayed Chemotherapy for MIBC

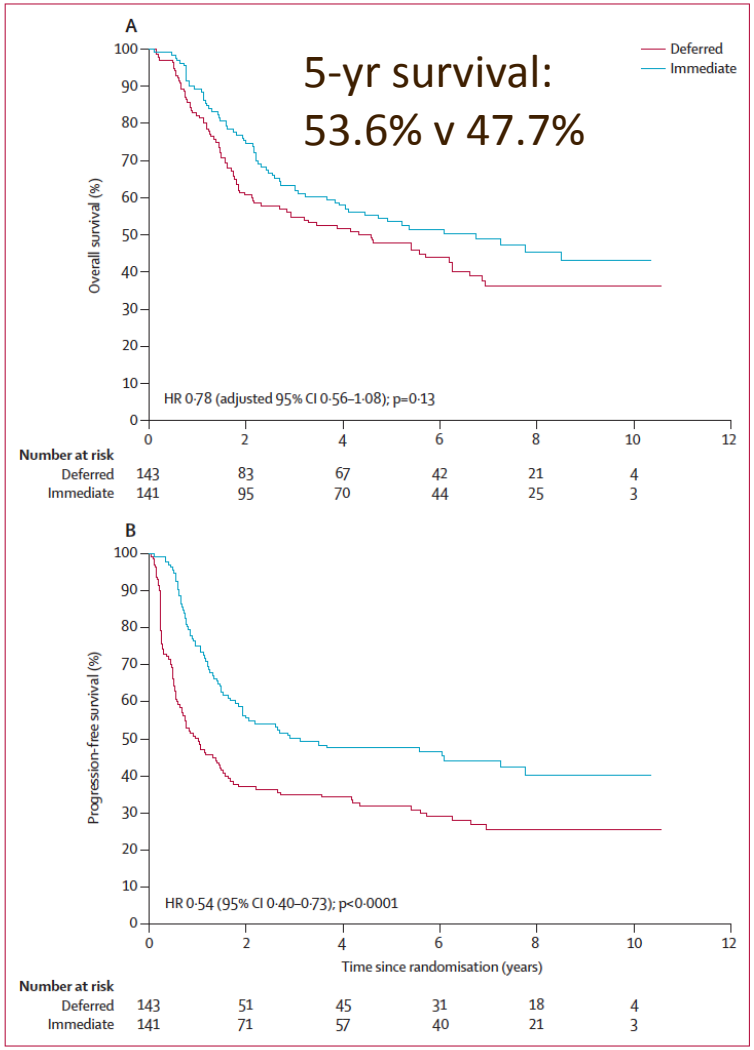


Figure 2: Kaplan-Meier survival curves
(A) Overall survival. (B) Progression-free survival. HR=hazard ratio.

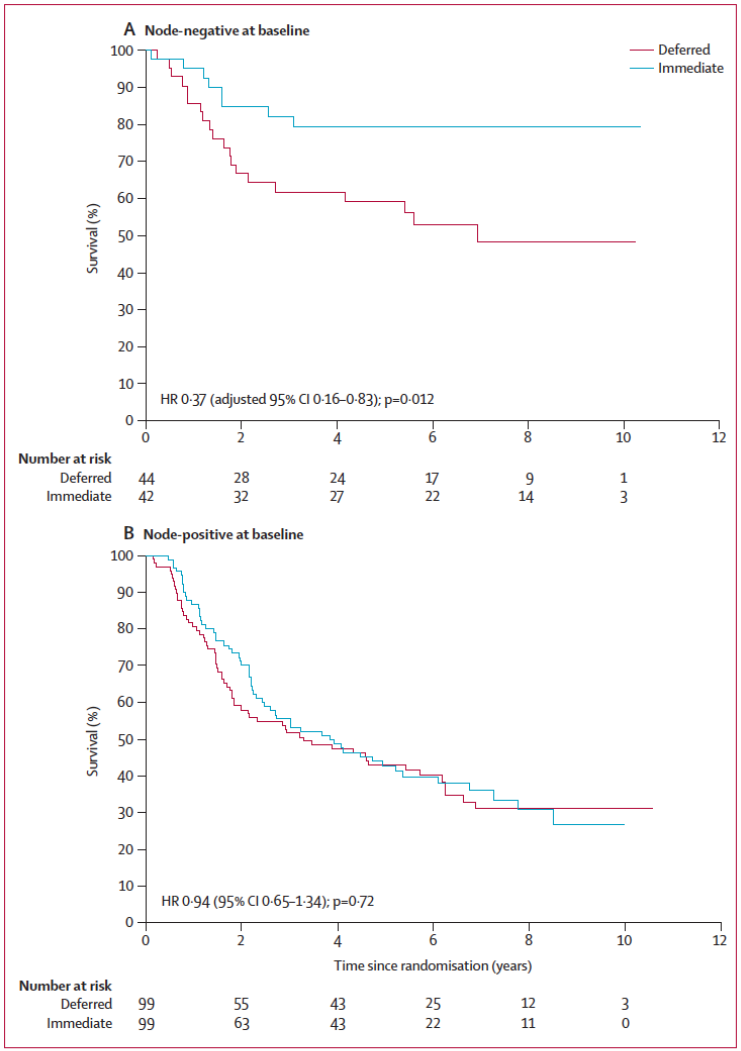


Figure 4: Kaplan-Meier overall survival curves in patients who were node negative at baseline
Overall survival in patients who had no lymph node involvement at baseline (A) and those with lymph node involvement at baseline (B). HR=hazard ratio.

Toxicity of adjuvant therapy

- PMH retrospective study:
  - 35 patients with high risk disease
  - CMV or MVAC x 4
- 9 episodes of febrile neutropenia
- 2/35 treatment related deaths (6%)
- 17% incidence of venous or arterial thrombo-embolic phenomena

Michael et al. Br J Urol 1998; 82: 366.

Active adjuvant trials – checkpoint inhibitors

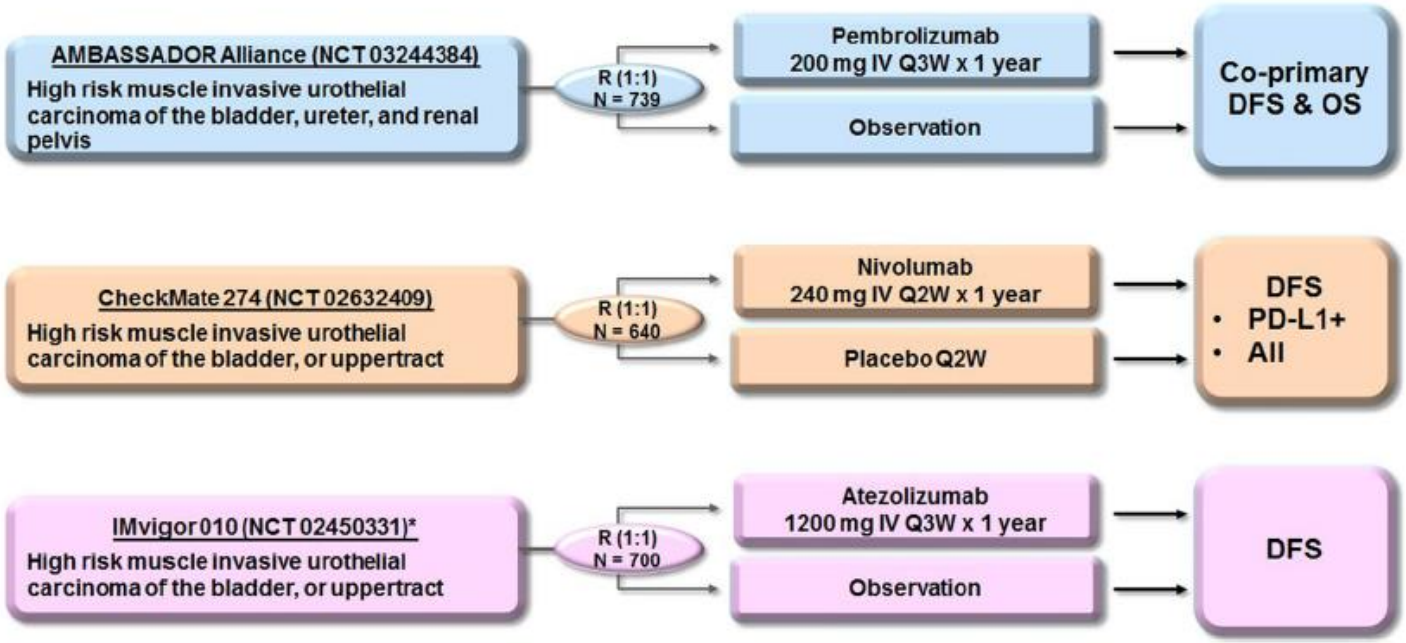


Fig. 1. Summary of ongoing phase III trials using adjuvant immune checkpoint inhibitors in muscle-invasive bladder cancer. *IMvigor 010 initially aimed to enroll only patients with PD-L1 positive tumors; however, this trial was amended to allow enrollment of all comers. IV intravenous, Q every, W week.

The NEW ENGLAND JOURNAL of MEDICINE

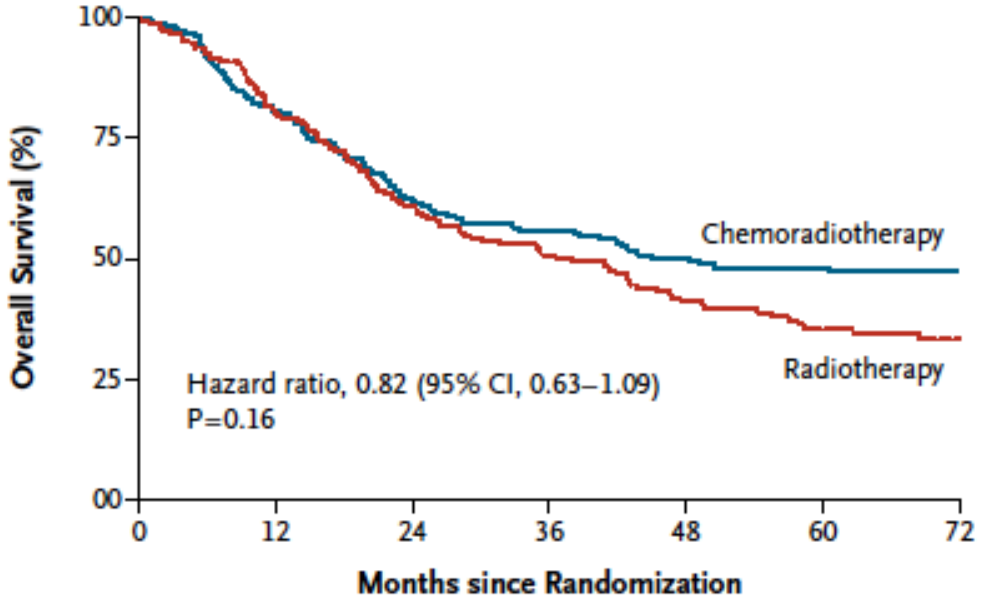
ORIGINAL ARTICLE

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

Nicholas D. James, M.B., B.S., Ph.D., Syed A. Hussain, M.B., B.S., M.D., Emma Hall, Ph.D., Peter Jenkins, M.B., B.S., Ph.D., Jean Tremlett, M.Sc., Christine Rawlings, M.Sc., Malcolm Crundwell, M.D., B.Chir., Bruce Sizer, M.B., B.S., Thiagarajan Sreenivasan, M.B., B.S., Carey Hendron, M.Sc., Rebecca Lewis, B.Sc., Rachel Waters, M.Sc., and Robert A. Huddart, M.B., B.S., Ph.D., for the BC2001 Investigators*

N Engl J Med 2012;366:1477-88.

C Overall Survival



No. at Risk (no. of events)							
Chemoradiotherapy	182 (35)	144 (33)	111 (11)	94 (9)	75 (3)	62 (1)	39
Radiotherapy alone	178 (35)	141 (34)	104 (17)	85 (15)	60 (7)	41 (2)	20

Take Home Messages

- MIBC is chemosensitive
- Cisplatin historically has been most active drug
- These patients are often difficult to give chemotherapy to safely due to comorbidities, age
- Neoadjuvant chemotherapy provides a modest benefit in node-negative disease
- Adjuvant therapy probably provides a similar benefit
- Chemoradiotherapy can be an option for those who wish to retain bladder
- Checkpoint inhibitors are active – lots of studies ongoing