27th Annual Fall Cancer Conference
Translating Personalized Medicine into Cancer Care

West Virginia University

October 6, 2017

WVU Cancer Institute

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Wexner Medical Center

Management of Bladder Cancer: The New Era

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October 06, 2017

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Creating a Cancer-free World.
One Person, One Discovery at a Time.

Conflict of Interest Disclosure

- Genentech-Roche: Advisory Board
- Research grant funding received by my institution from Acerta Pharma, Genentech, Merck and Novartis

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Objectives

- After reading and reviewing this material, the participants should be able to understand:
  - Epidemiology, risk factors and clinical presentations of bladder cancer
  - Natural history of bladder cancer
  - The overall management of different stages of disease
  - The potential role for some of targeted therapies
  - The role of immuno-oncology in bladder cancer

Case

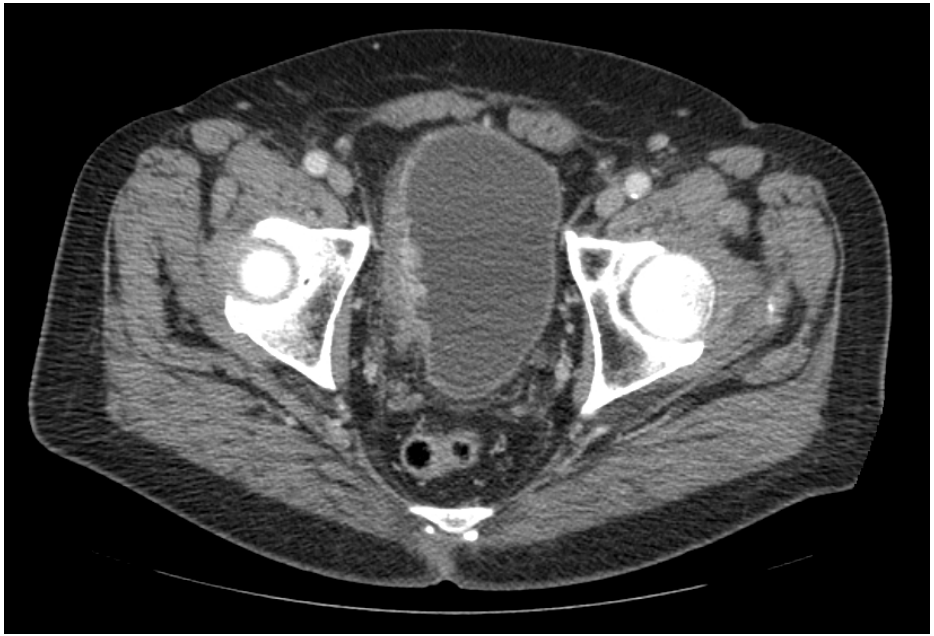
- A 65 yo Caucasian male, who is a former smoker (50 pack year) presents with the “cc” of red blood in the urine.
- Urine sediment confirmed gross hematuria and blood clots in urine.

Case

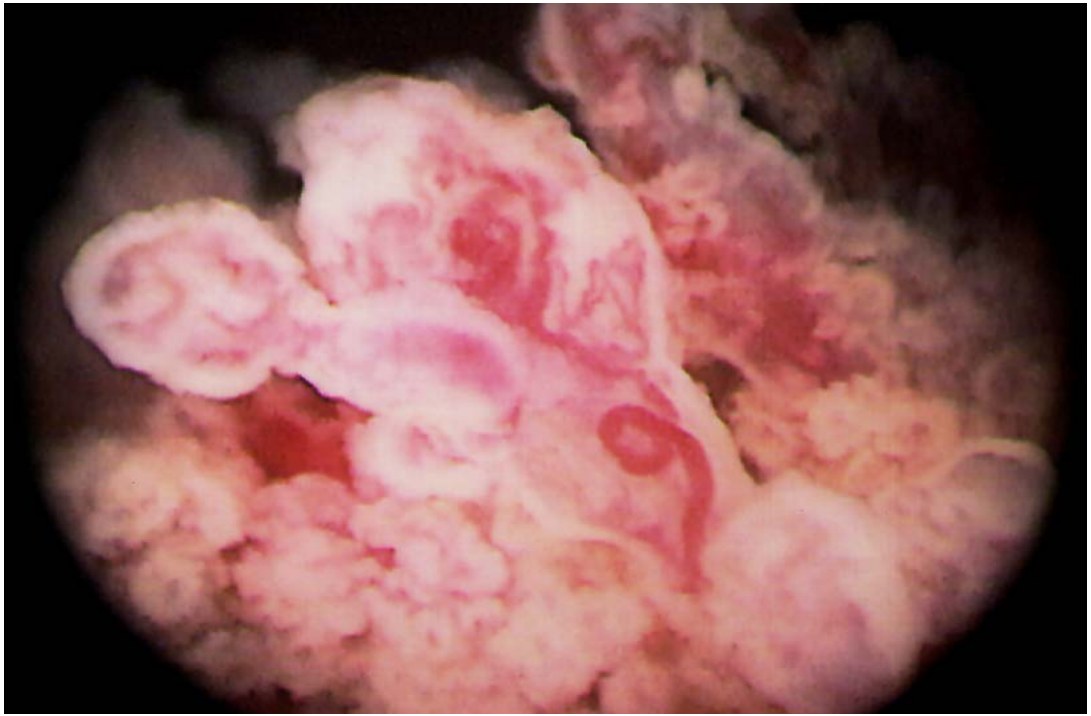
- In hematuric patients over age 50, especially with a history of heavy smoking or analgesic abuse, the risk of malignancies are appreciable (5-20%).

- Next steps:
  - CT-Urogram
  - Urology referral

CT-Urogram Findings



Cystoscopy Findings



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Bladder Cancer

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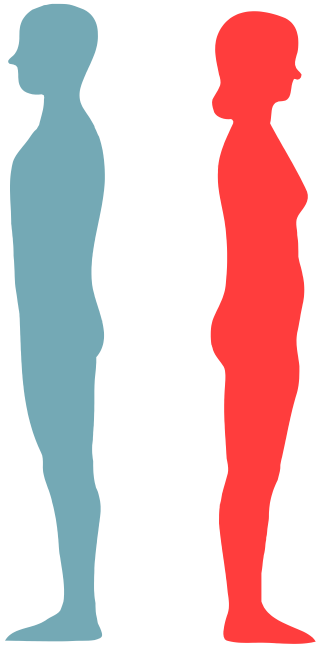
2017 Estimated New Cancer Cases*

Men	Women
836,15	852,630



Men	Women
Prostate	Breast
Lung & bronchus	Lung & bronchus
Colon & rectum	Colon & rectum
Urinary bladder	Uterine corpus
Melanoma of the skin	Thyroid
Kidney & renal pelvis	Melanoma of the skin
Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
Leukemia	Leukemia
Oral cavity & pharynx	Pancreas
Liver and intrahepatic bile duct	Kidney & renal pelvis

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2017

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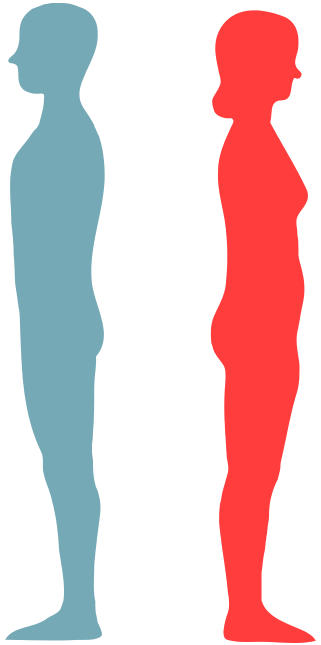
2017 Estimated Cancer Deaths

Men	Women
318,42	282,500



Men	Women
Lung & bronchus	Lung & bronchus
Colon & rectum	Breast
Prostate	Colon & rectum
Pancreas	Pancreas
Liver & intrahepatic bile duct	Ovary
Leukemia	Uterine corpus
Esophagus	Leukemia
Urinary bladder	Liver & intrahepatic bile ducts
Non-Hodgkin Lymphoma	Non-Hodgkin lymphoma
Brain and other nervous system	Brain & other nervous system

Source: American Cancer Society, 2017

Epidemiology

- Bladder cancer in the United States:
  - Estimated 79,030 new cases and 16,870 cancer related deaths in 2017
  - Whites > Blacks (2:1)
  - M>F (4:1)
  - A disease of the elderly (6^{th}-7^{th} decades)
  - Rising incidence (20% over the last 20-yr), up to this year.

Epidemiology

- In U.S., the second most prevalent cancer in men ≥60
- Bladder cancer has significant financial impact on healthcare
  - Requires intensive, life-long cystoscopic, radiologic, and cytologic surveillance
  - Most expensive malignancy in the U.S.*

* Botteman MF, et al. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics* 2003;21(18):1315-30

Bladder Cancer Pathology: Histologic Subtypes in the U.S.

- 90-95% Transitional Cell Carcinoma
- 3% Squamous Cell Carcinoma
- 2% Adenocarcinoma
- 1% Small Cell Carcinoma
- 1% Others

Risk Factors

- Chemical exposure
  - **Tobacco** (rich in aromatic amines and acrolein)
  - Industrial contact to chemicals, plastics, coal, tar, asphalt, aromatic amines, aniline dyes, nitrites, and nitrates
  - Ifosfamide and Cyclophosphamide (long-term use)
  - Analgesic abuse, particularly phenacetin
  - Drinking water: Chlorination, arsenic, low fluid intake (<1.3 L/day)

Risk Factors

- Gene abnormalities
  - Proto-oncogenes: Ras
  - Tumor suppressor genes: p53, pRB, p16, p21, p27
  - Cell cycle regulatory proteins: cyclin D1
  - Tumor-specific growth factor pathways (e.g. FGFR3) and angiogenesis
  - Chromatin regulatory genes
  - Detoxifying of carcinogens: N-acetyltransferase (NAT) genes. NAT2 alterations results in “slow acetylator state”.

Risk Factors

- Chronic irritation
  - Indwelling catheters, calculi (SCC)
  - Schistosoma haematobium (SCC, TCC)
  - Irradiation (SCC)

SCC: Squamous Cell Carcinoma
TCC: Transitional Cell Carcinoma

Signs and Symptoms

- Hematuria
  - Gross or microscopic
- Irritative symptoms
  - Frequency
  - Dysuria
  - Urgency
- Bladder outlet obstruction
- Ureteral colic

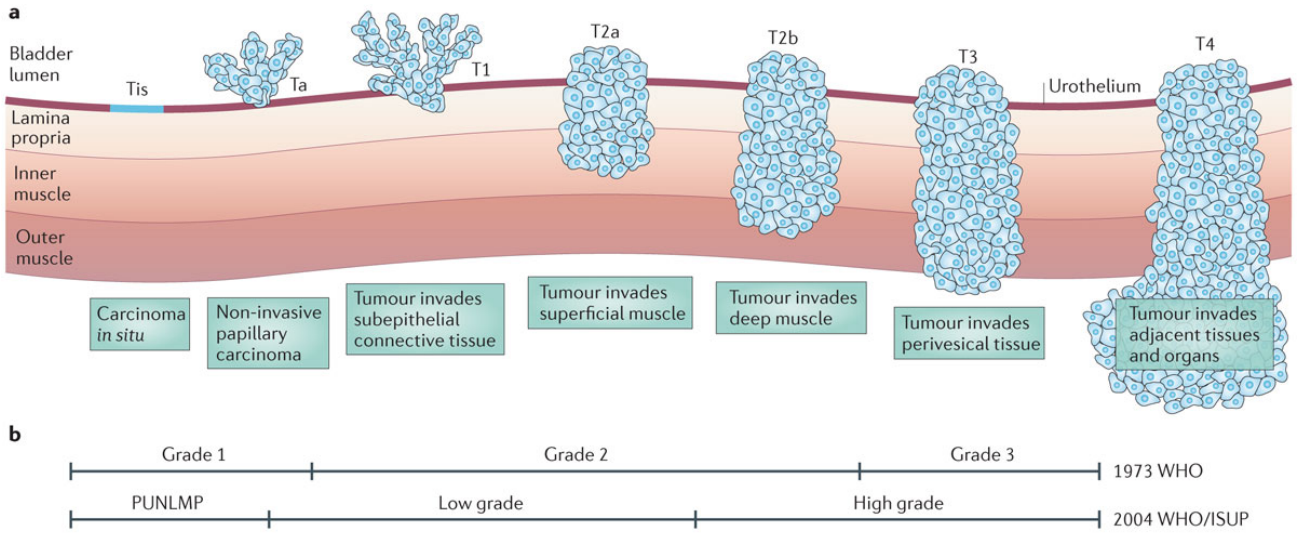
Physical Findings

- Early stage disease
  - Majority have almost no findings on routine exam
  - Palpable abdominal mass
  - Prostate induration
  - Bladder fixation to the pelvic or abdominal wall
- Advanced stage disease
  - Related to metastatic site

Diagnostic Testing

- Urine Cytology (Sensitivity 34% [12-64% based on the Grade], specificity 96%)
- Urine-based Markers (e.g. UroVysion FISH): (Sensitivity 50-80%, specificity 70-90%)
- Intravenous Urography (IVP)
- Cystoscopy
  - TURBT (TransUrethral Resection of Bladder Tumor)
  - Ureteroscopy
  - Retrograde pylography
- Radiographic Imaging (MRI or CT scan, MR-Urogram, CT-Urogram)
  - Bone Scan (if elevated Alk Phos or bone pain)

TNM Staging & Grading of Bladder Cancer



Nature Reviews | Cancer

Knowles MA & Hurst CD; Nat Rev Cancer 2015

TNM Staging, cont.

- Nodal disease
  - N0 No lymph node metastasis
  - N1 Single regional LN metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral LN)
  - N2 Multiple regional LN metastasis in the true pelvis
  - N3 LN metastasis to the common iliac LNs

- Metastatic disease
  - M0 No distant mets
  - M1 Distant mets
    - M1a Distant metastasis limited to the lymph nodes beyond the common iliacs
    - M1b Non-lumph node distant metastasis

American Joint Committee on Cancer (AJCC); 8th ed., 2017

TNM Staging, cont.

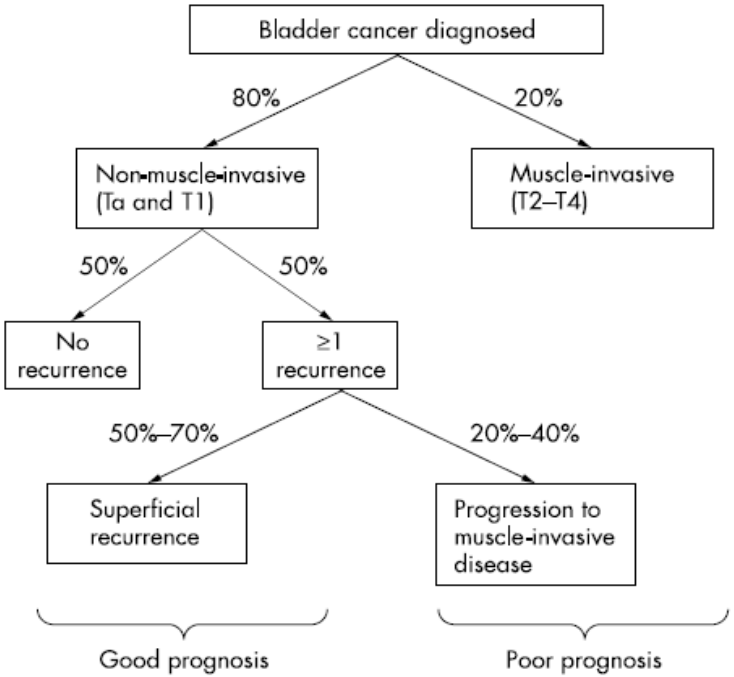
- **0**
  - **0a**: Ta
  - **0is**: Tis
- **I**: T1
- **II**: T2a, T2b
- **III**
  - **IIIA**: T3a, T3b (perivesical tumor), T4a (prostate, uterus or vagina), **OR** T1-4a, N1
  - **IIIB**: T1-4a, N2, N3
- **IV**
  - **IVA**: T4b (pelvic wall, abdominal wall) **OR** M1a (Lymph node only distant metastasis)
  - **IVB**: M1b (non-LN distant metastasis)

American Joint Committee on Cancer (AJCC); 8th ed., 2017

Stages at Presentation

- 75% Superficial cancer
- 20% Muscle-invasive cancer
- 5% Metastatic disease

Natural History of Bladder Cancer



Colquhoun AJ, et al. Postgrad Med J. 2002

Bladder Cancer Stage: Prognosis

Location	Stage	T - N - M			Survival (5 yrs)
Superficial	0a 0is	Ta Tis	N0	M0	> 80 %
Lamina	I	T1	N0	M0	60-80 %
Early Muscle	II	T2a	N0	M0	30-60 %
Deep Muscle	II	T2b	N0	M0	20-40 %
Perivesical Fat	III	T3	N0	M0	15-25 %
Lymph Nodes	IV	Any T	N1-3	M0	5-20 %
Metastatic	IV	Any T	Any N	M1	< 2 %

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AJCC Cancer Staging, 1998

Case, cont.

- He had a cystoscopy and TURBT, and pathology revealed non-muscle-invasive, high grade urothelial carcinoma (T1).

- He had complete resection of 2 tumors.

Superficial Bladder Cancer

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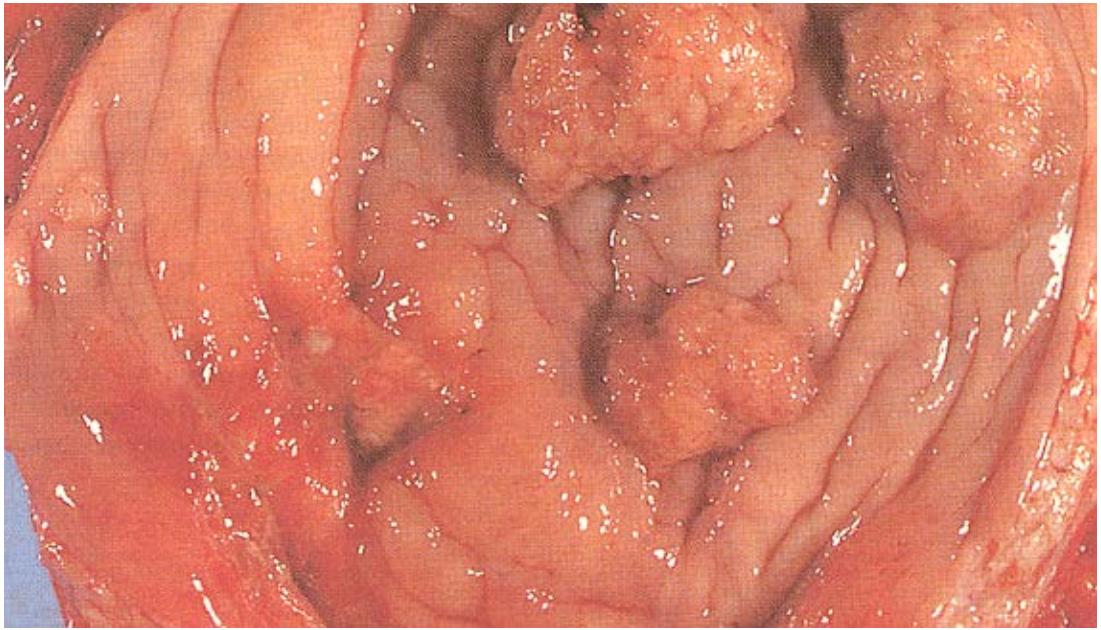
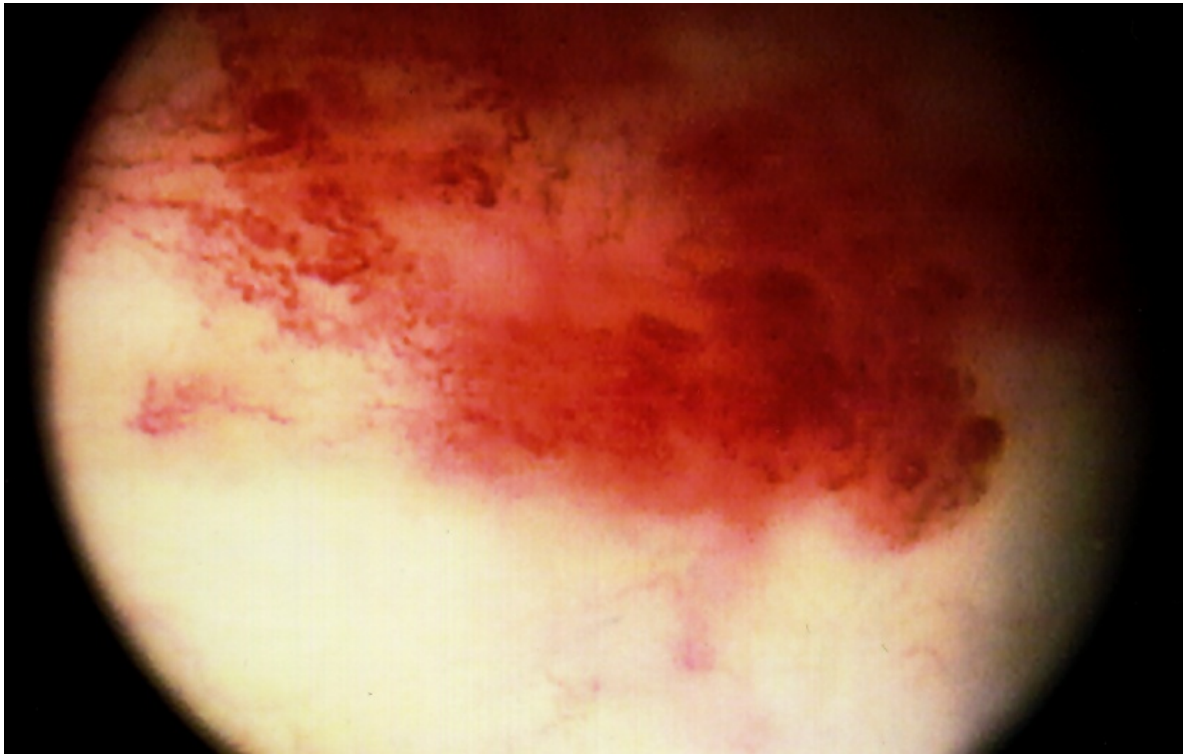
Papillary Transitional Cell Carcinoma



Courtesy of Kamal Pohar, MD

Bladder Carcinoma In Situ



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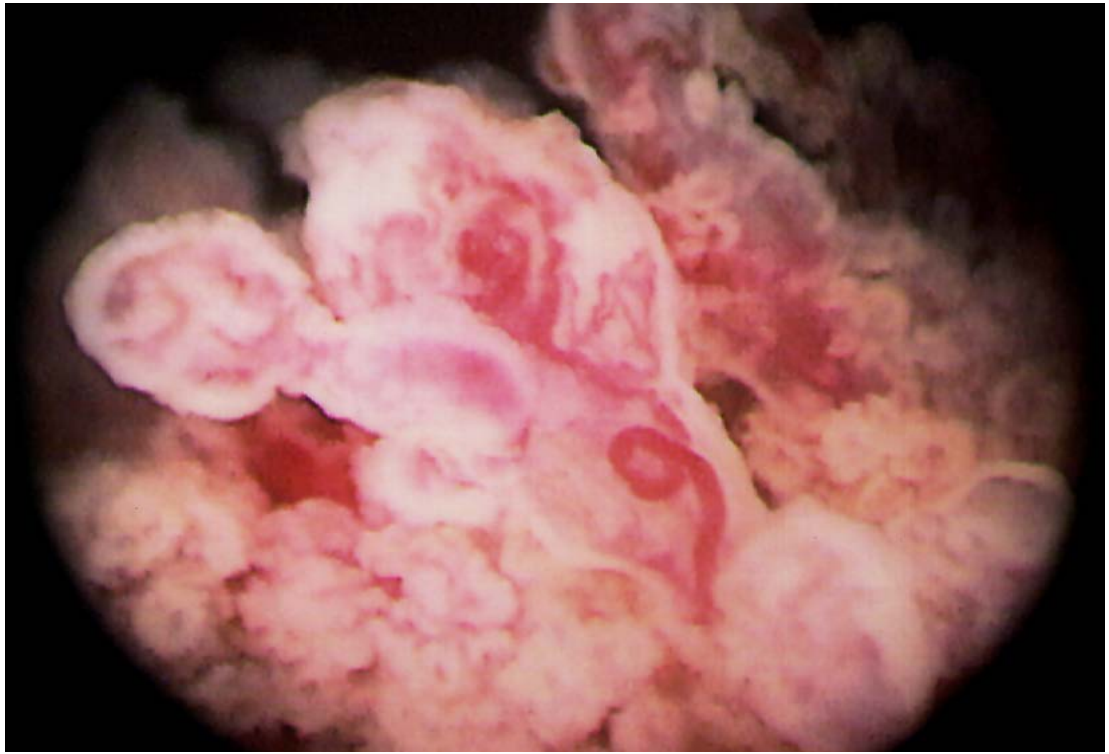
Papillary Bladder Cancer and CIS



Courtesy of Kamal Pohar, MD

Natural History of Superficial Bladder Cancer

	Recurrence Rates (%)	
	1 Yr	3 Yr
Grade 1	30	50
Grade 2	38	59
Grade 3	70	80
Ta	-	48
T1	-	70

National Bladder Cancer Group - *Heney et al. JU 130: 1083, 1983*

Natural History of Superficial Bladder Cancer

	Progression Rates (%)*
Grade 1	2
Grade 2	11
Grade 3	45
Ta	4
T1	30

*Defined as muscle invasion (≥ pT_2) or clinical metastases

National Bladder Cancer Group - *Heney et al. JU 130: 1083, 1983*

Therapy of Superficial Bladder Cancer

- Eradicate existing disease
- Prevent recurrence (Polychronotropism)
- Prevent progression: Avoid the development of muscle-invasive disease

Therapy of Superficial Bladder Cancer

- Resection
  - TURBT (gold-standard)
  - Photodynamic Therapy
  - Laser Resection

- Intravesical therapy
  - BCG* (High-risk patients [Grade 2 or 3, T1 or Tis])
  - Cytokines (High-risk patients)
  - Chemotherapy (High grade, mod-high volume, recurrent tumors)

* *Morales et al JU 116: 180, 1976*

Radical Cystectomy for Superficial Bladder Cancer

- Not possible to remove the cancer by TURBT (cancer is too extensive)
- Risk of cancer progression to muscle invasion is high (early cystectomy)
- Failure of intravesical BCG and/or chemotherapy but disease remains superficial

Post-treatment Follow-up for Superficial Disease

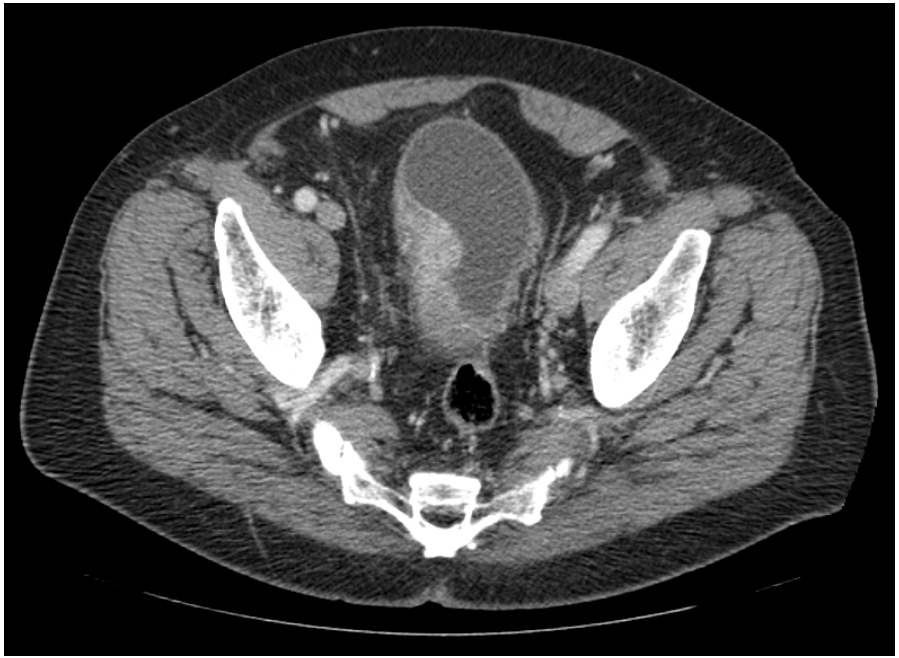
- Cystoscopy, urine cytology and as needed repeat TURBT; every 3-6 months for the first five years, and then annually.
- Repeat intravesical therapy if indicated.
- Imaging of the upper tracts; every one to two years.
- Consider cystectomy for recurrent / persistent disease.

Case, cont.

- Our patient had few Ta, T1 and Tis disease recurrences over the next 5 years, requiring multiple cystoscopies, TURBTs and intravesical instillations.

- Last TURBT revealed progression to muscle-invasive (T2) transitional cell carcinoma of the bladder.

CT-Urogram Findings



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Muscle-Invasive Bladder Cancer

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Surgical treatment outcome

- In the U.S., the “Gold Standard Treatment” of muscle-invasive disease is radical cystectomy with bilateral pelvic lymph node dissection.
- Bladder-preserving combined- (tri-) modality therapy (maximal TURBT, followed by concurrent chemotherapy and radiation therapy) is an option for selected patients.
- After surgery, 40-50% of these patients develop metastases within 2-5 years and most die of their disease.

How to improve this outcome?

- Bladder cancer is a radio- and chemo-sensitive disease.
- Cisplatin-based chemotherapies have 40-75% RRs with 12-20% CRs.
- Multimodality treatment with neoadjuvant/adjuvant chemotherapy and/or radiation therapy can potentially improve outcome.

Randomized Neoadjuvant Trials

Study	Neoadjuvant Arm	Standard Arm	Patients (N)	Survival
Cisplatin chemotherapy				
Australia/UK[17]	Cis/RT	RT	255	No difference
Canada/NCI[18]	Cis/RT or preop RT+cystectomy	RT or preop RT+cystectomy	99	No difference
Spain (CUETO)[19]	Cis/cystectomy	Cystectomy	121	No difference
Combination chemotherapy				
EORTC/MRC[11]	CMV/RT or cystectomy	RT or cystectomy	976	5.5% difference in favor of CMV
SWOG Intergroup[20]	M-VAC/cystectomy	Cystectomy	298	Benefit with M-VAC ($P = 0.06$)
Italy (GUONE)[15]	M-VAC/cystectomy	Cystectomy	206	No difference
Italy (GISTV)[21]	M-VEC/cystectomy	Cystectomy	171	No difference
Genoa[22]	Cis/5-FU/RT/cystectomy	Cystectomy	104	No difference
Nordic I[24]	ADM/Cis/RT/cystectomy	RT/cystectomy	311	No difference, 15% benefit with ADM + Cis in T3–T4a
Nordic II[16]	MTX/Cis/cystectomy	Cystectomy	317	No difference
Abol-Enein *et al.*[23]	CarboMV/cystectomy	Cystectomy	194	Benefit with CarboMV

Meta-analysis for Neoadjuvant Studies

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

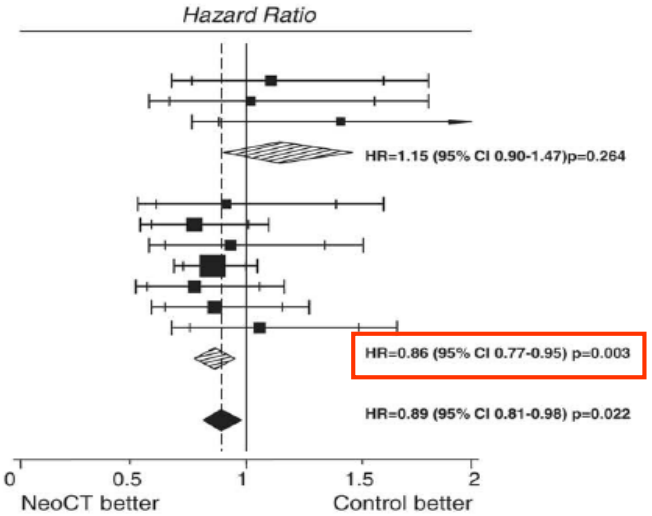
Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

***Eur Urol* 48:202, 2005**

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

- 11 randomized trials, 3005 pts

	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45



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Adjuvant Chemotherapy Trials

Study	Chemotherapy	Chemotherapy	No Chemotherapy	Results
Logothetis *et al.* (1988)[81]	CISCA	62	71	Benefit, but not randomized
Skinner *et al.* (1991)[75]	CAP	47	44	Benefit, few patients received therapy
Stockle *et al.* (1992)[76]	M-VAC/M-VEC	26	23	Benefit, few patients, no treatment at relapse
Studer *et al.* (1994)[77]	DDP	40	37	No benefit, DDP alone inadequate
Bono *et al.* (1997)[78]	CM	48	35	No benefit for N0M0
Freiha *et al.* (1996)[79]	CMV	25	25	Benefit in relapse-free survival only
Otto *et al.* (2001)[80]	M-VEC	55	53	No benefit

Sternberg *Urology* 2007

Meta-analysis for Adjuvant Studies

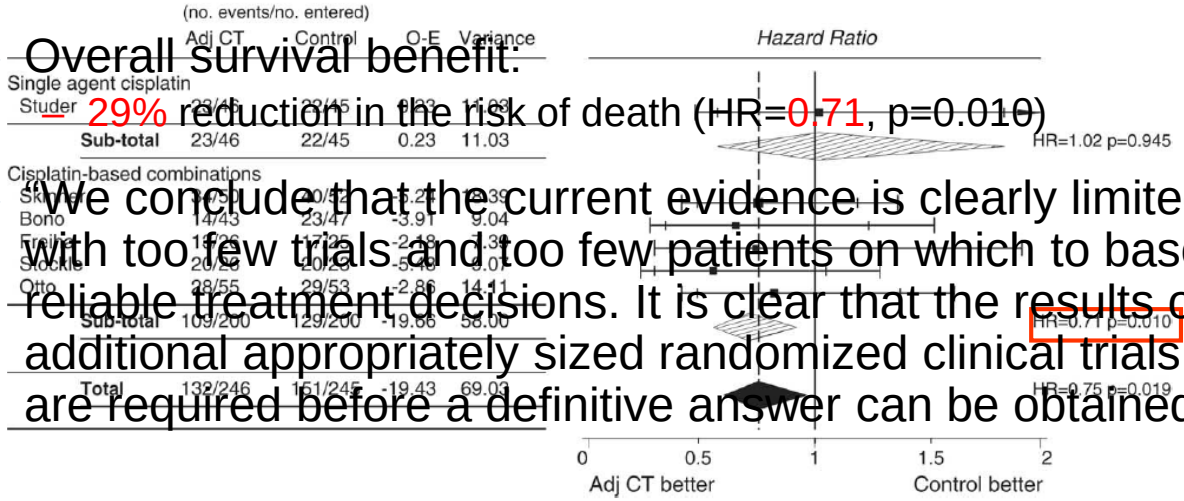
Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data

***Eur Urol* 48:189, 2005**

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

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

- 6 randomized trials, 491 pts



- ~~Overall survival benefit:~~
  - ~~29% reduction in the risk of death (HR=0.71, p=0.010)~~
- ~~"We conclude that the current evidence is clearly limited with too few trials and too few patients on which to base reliable treatment decisions. It is clear that the results of additional appropriately sized randomized clinical trials are required before a definitive answer can be obtained".~~

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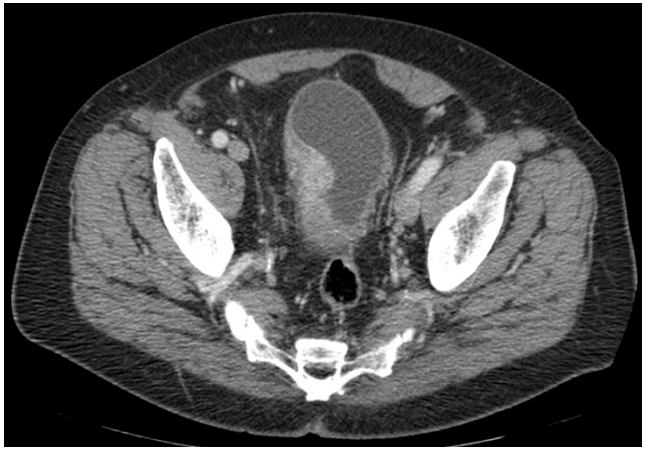
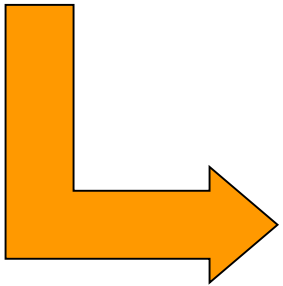
Case, cont.

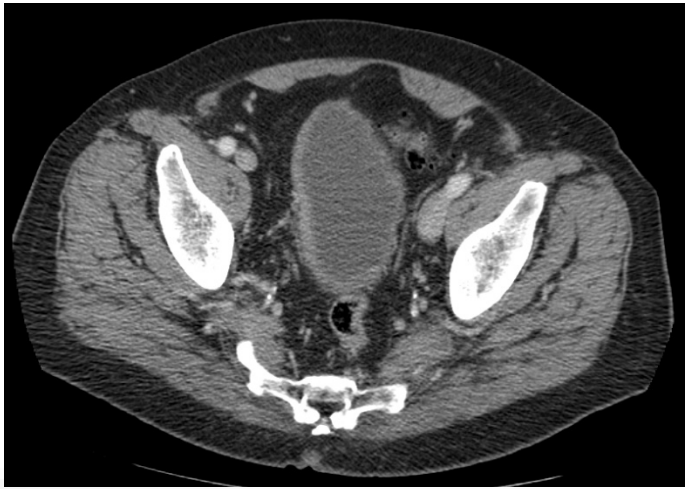
- He received 4 cycles of neoadjuvant cisplatin and gemcitabine.

- Overall, he tolerated chemotherapy well with expected and manageable side effects.





After neoadjuvant chemotherapy



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Case, cont.

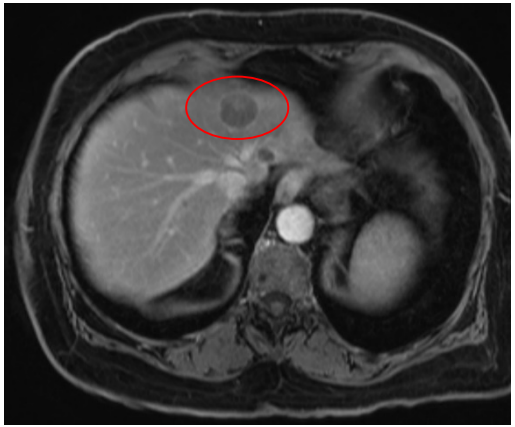
- Then, he underwent a radical cystoprostatectomy, bilateral pelvic lymph node dissection and ileal conduit urinary diversion.
- His final path was favorable, ypT1N0, 35 LNs, and negative surgical margins.
- He recovered well from surgery and started surveillance.

Post Radical Cystectomy Surveillance

- Serial exam and labs
- Chest and abd/pelvis imaging
- Upper tract surveillance (CT-Urogram, urine cytology)

Case, cont.

- Three years later, he was found to have new retroperitoneal LNs and liver lesions.
- Liver biopsy positive for TCC



Metastatic Bladder Cancer

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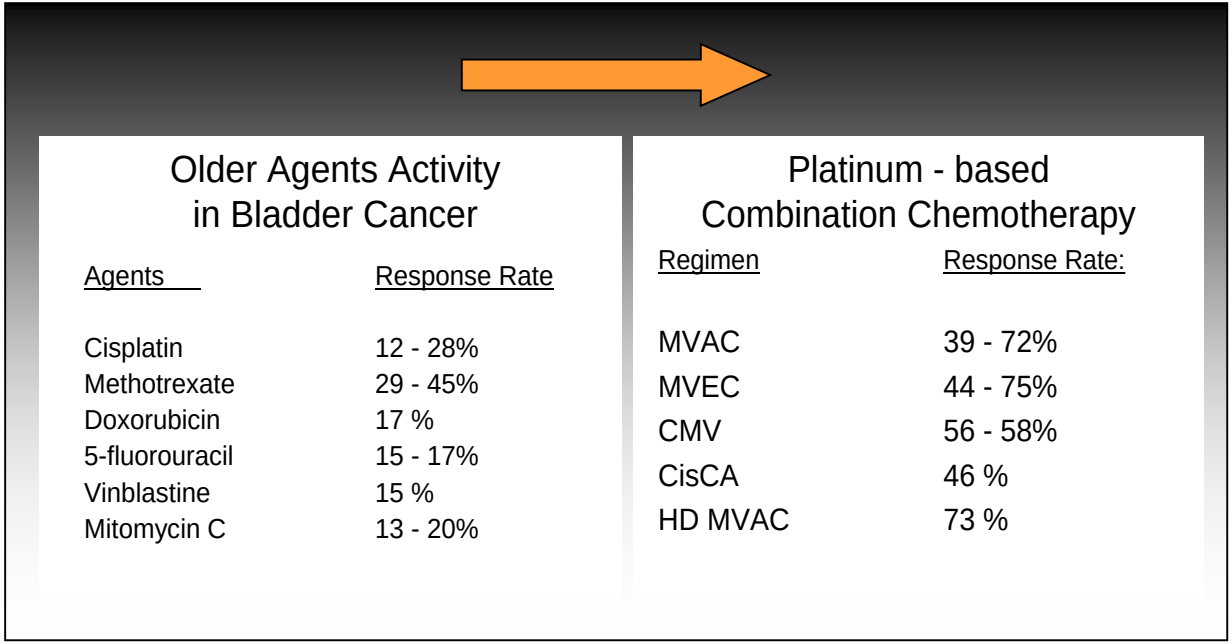
Introduction

- Metastatic sites: regional and distant lymph nodes, lungs, bones, liver, brain, skin and elsewhere.
- Median survival with Best Supportive Care: 4-6 months
- Median survival with cisplatin-based combination chemotherapy: 13-15 months, 60% 1-yr and 20% 3-yr survival

Introduction

- TCC is a chemosensitive solid tumor
  - Phase II clinical trials: RR 70-80%
  - Phase III clinical trials: RR 50%
- Short duration of response: 4-6 mo

Pre-1990s Chemotherapy



Older Agents Activity in Bladder Cancer

Agents	Response Rate
Cisplatin	12 - 28%
Methotrexate	29 - 45%
Doxorubicin	17 %
5-fluorouracil	15 - 17%
Vinblastine	15 %
Mitomycin C	13 - 20%

Platinum - based Combination Chemotherapy

Regimen	Response Rate:
MVAC	39 - 72%
MVEC	44 - 75%
CMV	56 - 58%
CisCA	46 %
HD MVAC	73 %

Late 1980s → Mid1990s

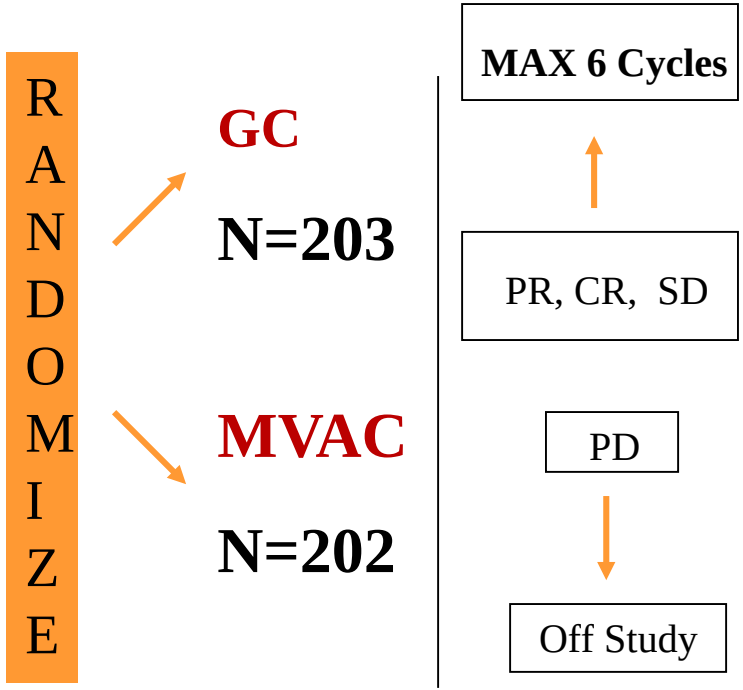
Goals: Identify new agents & combinations
lower toxicity, better efficacy

Agent	Response Rate
Paclitaxel	10-56%
Gemcitabine	23-28%
Carboplatin	13-15%
Docetaxel	13-31%
Ifosfamide	20-31%

Advanced Bladder Cancer: Gemcitabine Plus Cisplatin vs. MVAC

Stratification

- Stage
- Visceral mets
- PS
- Prior radiotherapy
- Investigator site
- Disease measurability
- Alkaline Phosphatase



MVAC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin

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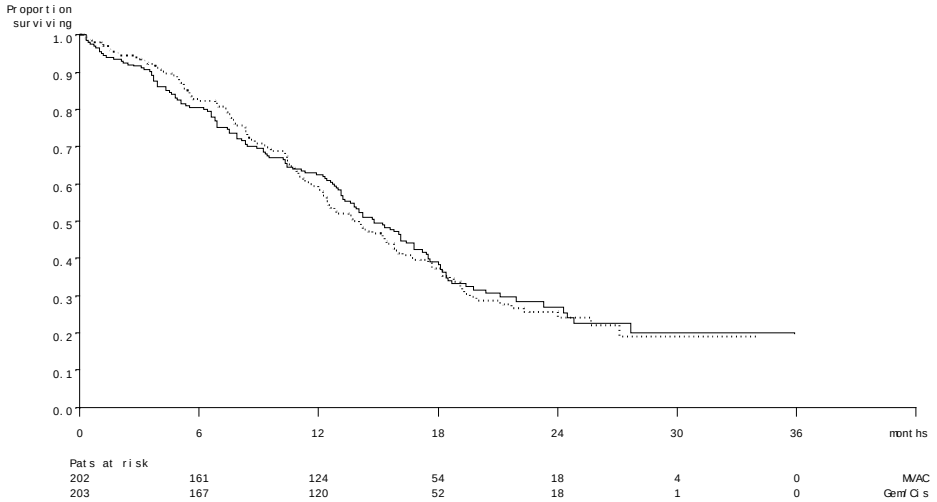
GC vs. MVAC: Response and Survival

	GC (203)	MVAC (202)
RR	49.4%	45.7%
CR	12.2%	11.9%
PR	37.2%	33.8%
MS	13.8	14.8
	(12.3-15.8)	(13.2-16.8)



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Von der Maase, JCO 2000

GC vs. MVAC: G3/4 Toxicities

	GC	MVAC
▪ Neutropenia (Grade 3/4)	71%	82%
Neutropenic sepsis	1%	12%
Febrile neutropenia	1.5%	13.4%
▪ Thrombocytopenia	57%	21%
▪ Mucositis	1%	22%
▪ Alopecia	11%	55%
▪ Nausea/vomiting	22%	21%
▪ Drug-toxicity death rate	1%	3%

Von der Maase, JCO 2000

Carboplatin vs. Cisplatin

- Single agent: Carbo appears to be less active (Marcuello *Eur J Cancer* 1990, Trump *J Urol* 1990)
- Combinations: Carbo appears inferior, with shorter TTP and MS (12.8 vs.9.8 mos, Dogliotti *Eur Urol* 2007)

Regimen	CR (%)		OR (%)	
	Cis	Carbo	Cis	Carbo
MVAC vs. Carbo, MTX, Vlb (Bellmunt 1997)	17	0	52	39
MVEC vs. MVE-Carbo (Petrioli 1996) (p=0.04)	25	11	71	41
GC vs. G-Carbo (Dogliotti 2007)	15	2	49	40

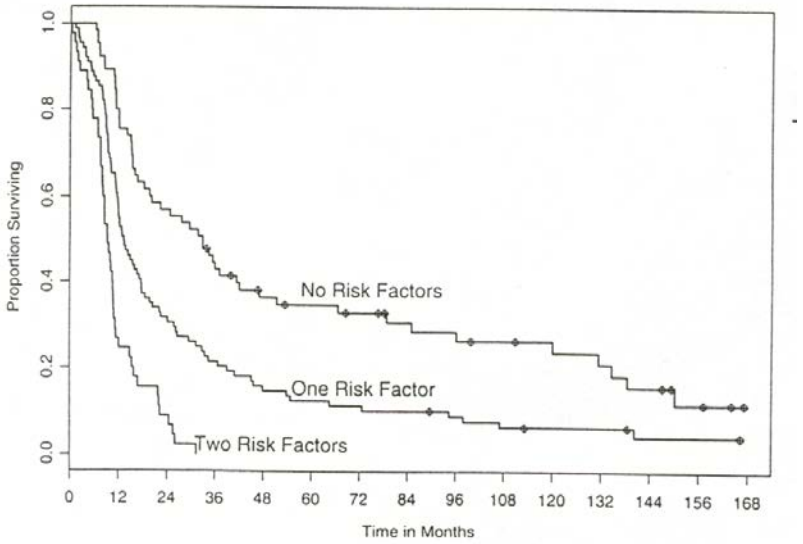
Prognostic Factors & Survival
Univariate and Multivariate Analysis (n=203) Bajorin, *JCO* 1999

Prognostic Factors:

1) Visceral Mets
   (bone, liver, lung)
2) KPS (<80%)

# of PF	MS (mo)	CR (%)
0	33	35
1	13.4	11
2	9.3	0

p = 0.0001



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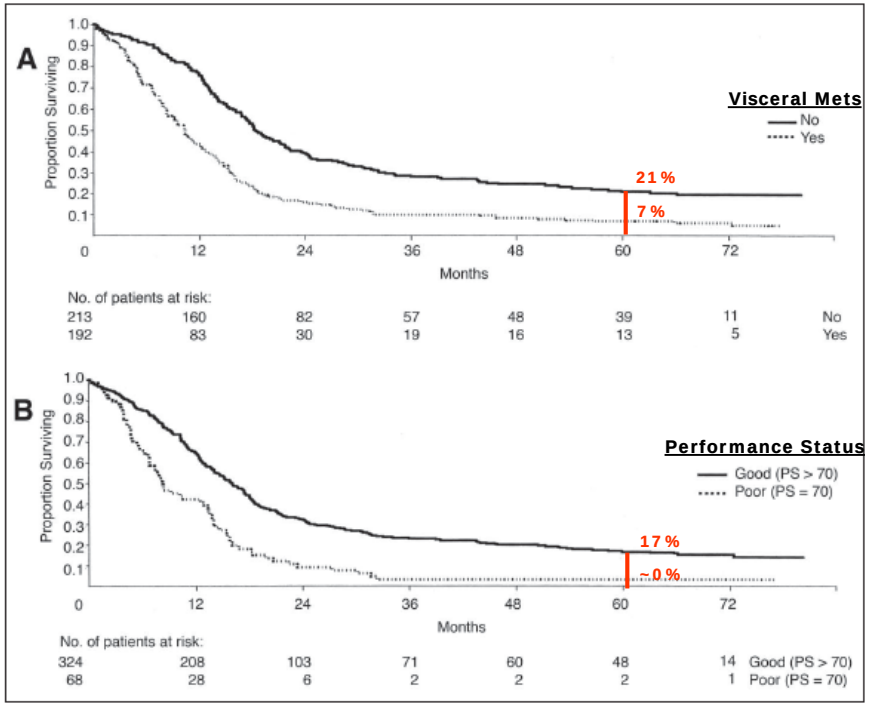
GC vs. MVAC (5-year f/u)



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von der Maase *JCO* 2005

Systemic Therapy for Bladder Cancer Pre-2016

Non-Muscle Invasive	Neoadjuvant Adjuvant	1st Line Metastatic	Next Line Metastatic
No systemic therapy			
	Gem + Cisplatin or A-MVAC (Cisplatin)		
		Gem + Cisplatin A-MVAC (Cisplatin) or Gem + Carbo	
			• Paclitaxel/Docetaxel • Vinflunine*

Cisplatin:
ORR 50-60%
median OS 15 mo.
1 year OS 60%
Carboplatin
ORR 36%
median OS 9 mo.
1 year OS 37%

ORR: 12%
Median OS 7 mo.
1 year OS 26%*

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Courtesy of Elizabeth Plimack, MD

Precision Medicine and Targeted Therapies in Bladder Cancer

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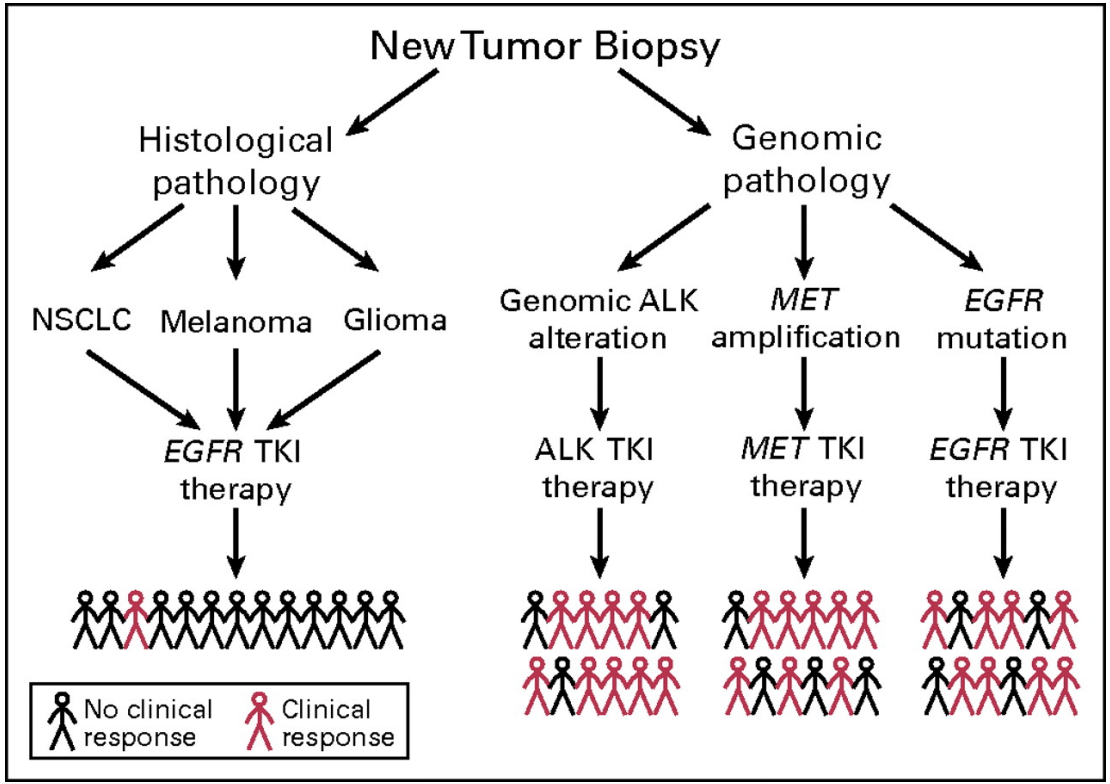
Precision Medicine

Past → Present

Present → Future

Precision Cancer Targeted Therapy



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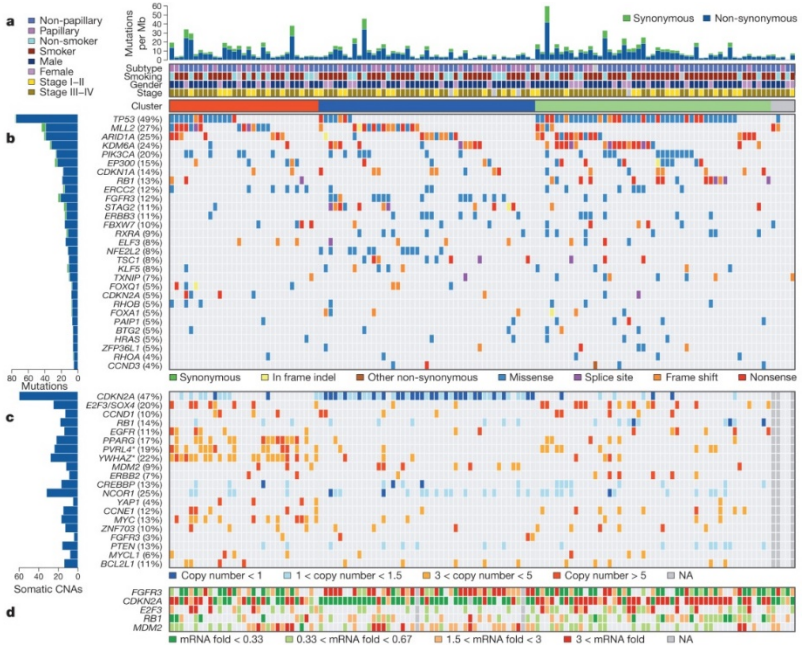
The Cancer Genome Atlas (TCGA)

- Compares the DNA in normal tissue and cancer tissue from the same patient with the goal of creating a genomic atlas of human cancer accessible to everyone

- 131 urothelial carcinomas
  - Discovered statistically significant recurrent mutations in 32 genes



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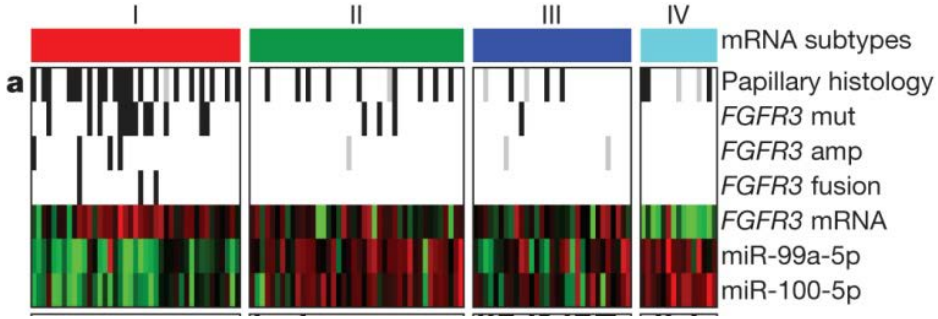
Comprehensive molecular characterization of urothelial bladder carcinoma, *Nature* 507, 315-322 (2014)

TCGA for Bladder Cancer

- Whole-genome and RNA sequencing identified multiple mechanisms of Fibroblast Growth Factor Receptor 3 (FGFR3) activation



Comprehensive molecular characterization of urothelial bladder carcinoma, *Nature* 507, 315-322 (2014)

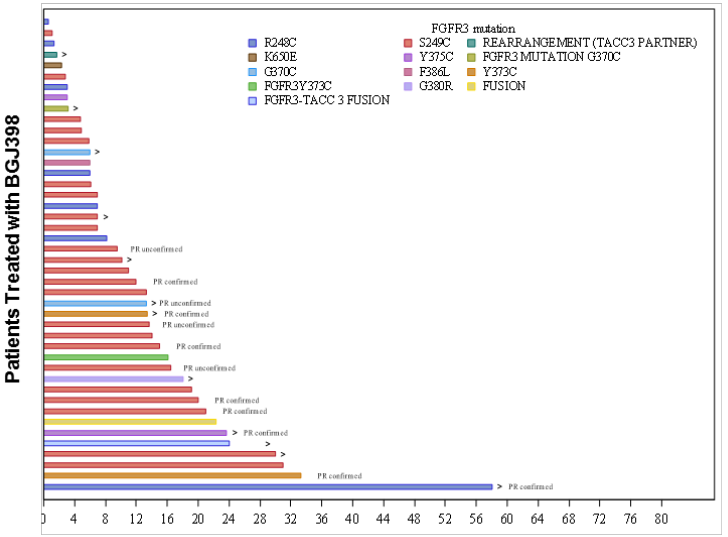
Efficacy of BGJ398, a fibroblast growth factor receptor 1-3 inhibitor, in patients with previously treated advanced/ metastatic urothelial carcinoma with FGFR3 alterations

Tumor Response With BGJ398 Treatment

BGJ398 125 mg QD 3 Weeks On/1 Week Off N = 44	n (%)
Number of Evaluable Patients[a]	37
Overall Response[b] (CR, PRc, PRu)	13 (35.1)
Disease Control[b] (CR, PRc/PRu, SD)	22 (59.4)
Best overall response[b]	
Complete response	1 (2.7)
Partial response confirmed (PRc)	8 (21.6)
Partial response unconfirmed[c] (PRu)	4 (10.8)
Stable disease	9 (24.3)
Progressive disease	10 (27.0)
Unknown	5 (13.5)

CR, complete response; PR, partial response; SD, stable disease.
[a] Patients with baseline and at least 1 post-baseline tumor assessment are included.
[b] Percentages are calculated based on evaluable patients.
[c] Unconfirmed denotes the lack of a confirmatory scan at least 4 weeks after noting PR (≥30% decrease in sum of target lesions as per investigator assessment) according to RECIST criteria. (pending confirmatory scan, n=1; subsequent scan showed progressive disease, n=2; no subsequent scan performed, patient discontinued with clinical evidence of disease progression, n=1).

Duration on Treatment by *FGFR3* Alteration[a,b]



PR, partial response; > denotes ongoing treatment
[a] Data cutoff on March 1, 2016.
[b] Patients are ordered by duration on study. Responses are based on investigator determination.
[c] Received prior therapy with a checkpoint inhibitor.

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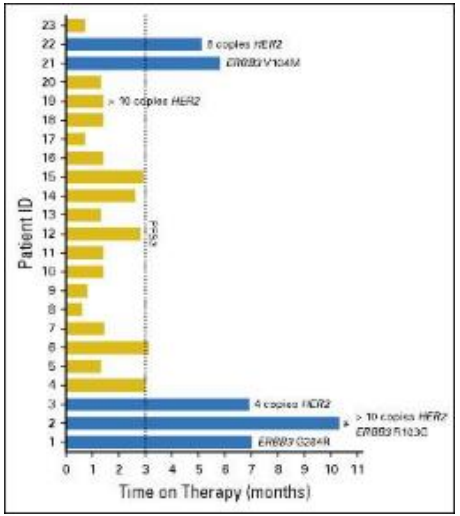
VOLUME 34 · NUMBER 18 · JUNE 20, 2016

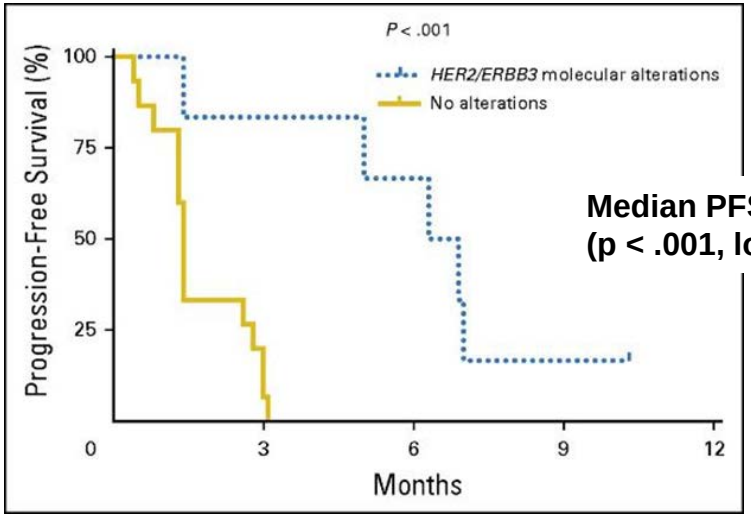
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma in Patients With *ERBB* Alterations

Noura J. Choudhury, Alexa Campanile, Tatjana Antic, Kai Lee Yap, Carrie A. Fitzpatrick, James L. Wade III, Theodore Karrison, Walter M. Stadler, Yusuke Nakamura, and Peter H. O'Donnell





Median PFS 6.6 vs. 1.4 mo
(p < .001, log-rank test)

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Novel Treatments in Bladder Cancer

- **Trastuzumab** (Hussain, 2007 JCO; Single-agent CALGB study)
- **Gefitinib** (Galsky, 2007 Invest New Drugs; Philips, 2009 Ann Oncol)
- **Afatinib** (Choudhury 2016 JCO)

- **Sorafenib** (Sridhar, 2008 ASCO GU, #340)
- **Sunitinib** (Gallagher, 2007 ASCO, #5080; Bellmunt, 2008 ASCO GU, #291)
- **Bevacizumab** (With GC: CALGB-90601 study; Hahn, 2009 ASCO, #5018)

- **FGFR3 Inhibitors** (BGJ398, Pal, 2016 ASCO)

- **Histone Deacetylase Inhibitors** (Mocetinostat, Vorinostat, AR42)

- **Immune Modulation** (Her2/neu Dendritic Cell Cancer Vaccines)
- **Checkpoint Inhibitors** (PD-1, PD-L1 and CTLA-4 inhibitors)

Immuno-Oncology in Bladder Cancer

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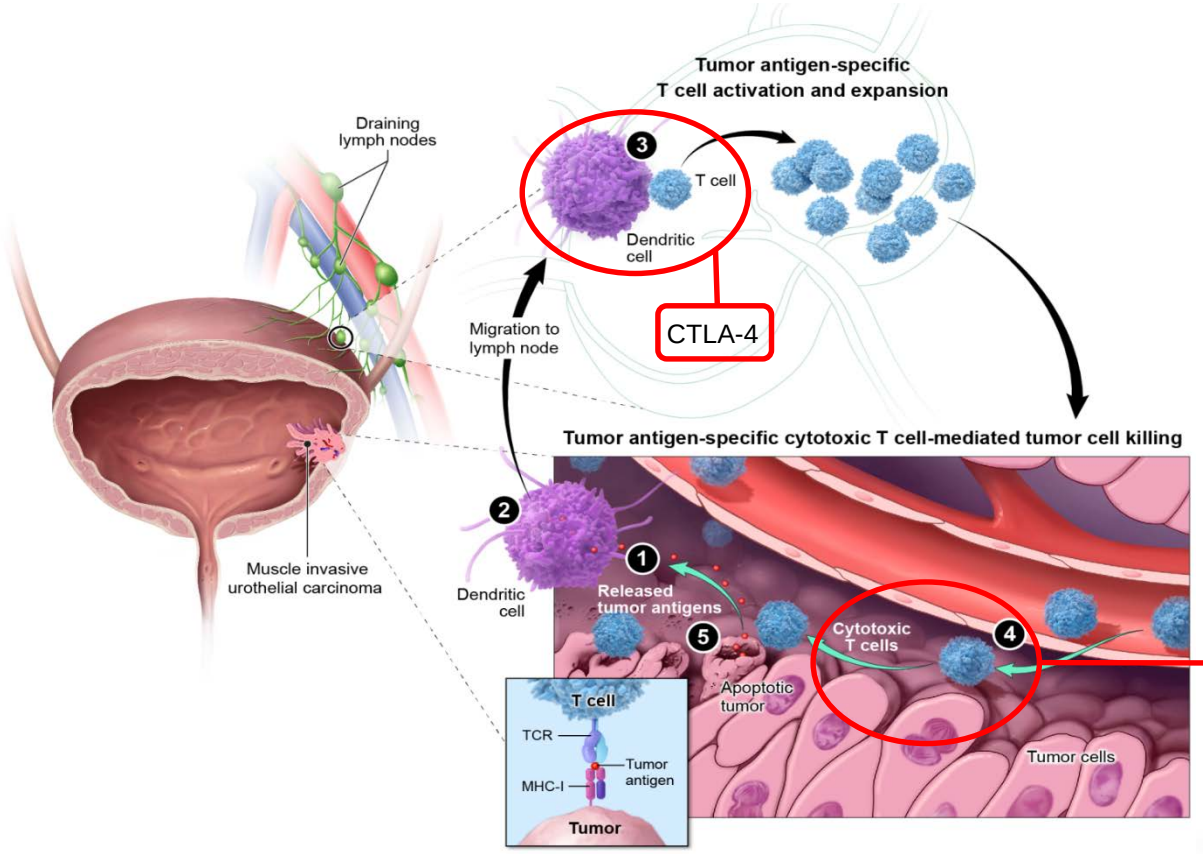
Immune Tolerance in Urothelial Carcinoma



Tumors maintain an immunosuppressive state via **PD-L1/PD-1** binding, therefore, Inhibiting:

- ❖ T-cell migration
- ❖ Proliferation
- ❖ secretion of cytotoxic mediators

PD-1: Programmed Cell Death-1
PD-L1: PD-1 Ligand

PD1-PDL1

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Kim JW, Tomita Y, Trepel J, Apolo AB. Emerging immunotherapies for bladder cancer. Curr Opin Oncol. 2015

PD-1 and PD-L1 in Bladder Cancer

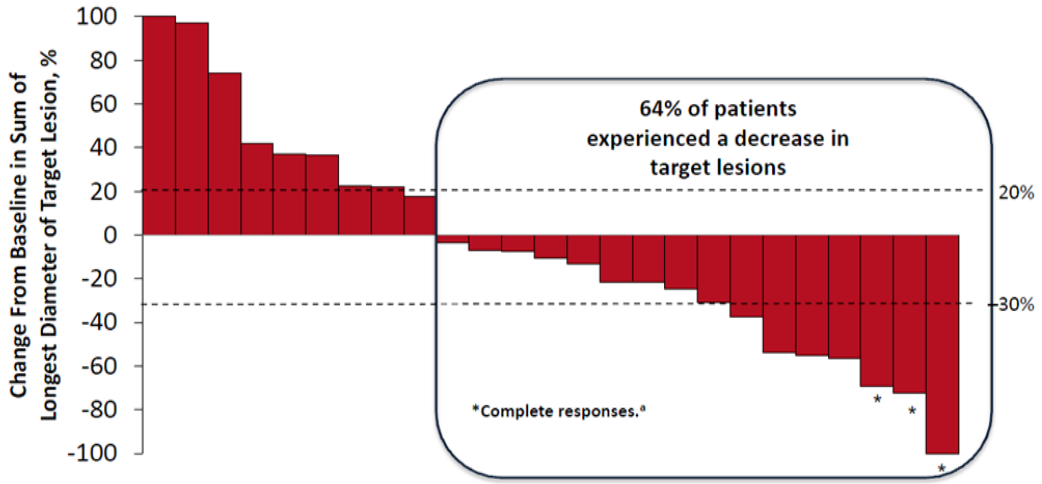
- Melanoma, lung cancer and bladder cancer are the top 3 cancers that has high mutational burden.
- PD-L1 is highly expressed in urothelial cancer of the bladder and correlates with pathological stage and overall survival

Iñigo Martincorena, Peter J. Campbell; Science 2016

PD-1 Targeting in Bladder Cancer

- Pembrolizumab: PD-1 inhibitor, 24% ORR, 12% Grade 3/4 toxicities

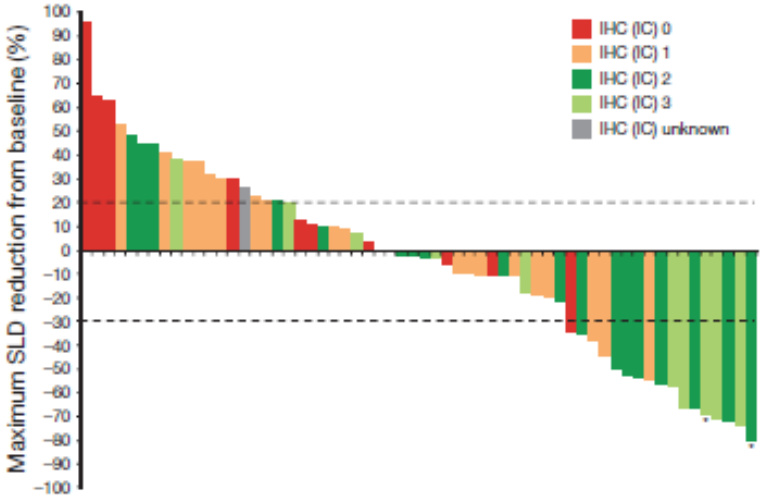
  (Plimack E, et al. ESMO 2014, abstract # LBA23)



PD-L1 Targeting in Bladder Cancer

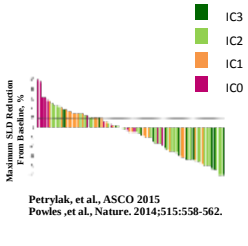
- Atezolizumab: PD-L1 inhibitor, 25% ORR, 4.4% Grade 3/4 toxicities

  (Powels T, et al. Nature 2014)



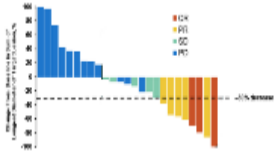
Checkpoint Inhibition in Metastatic Urothelial Carcinoma

Atezolizumab
Summary of ORR



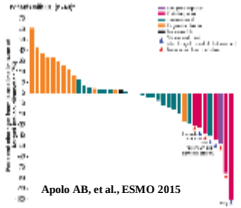
Petrylak, et al., ASCO 2015
Powles ,et al., Nature. 2014;515:558-562.

Pembrolizumab
Summary of ORR



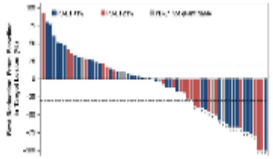
Plimack E, et al., ASCO 2015

Avelumab
Summary of ORR



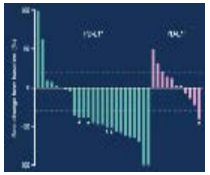
Apolo AB, et al., ESMO 2015

Nivolumab
Summary of ORR



Sharma P, et al., ASCO 2016

Durvalumab
Summary of ORR



Massard, et al., ASCO 2016

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Courtesy of Andrea Apolo, MD

Frontline Therapy for UC: Cis-Ineligible

Gem Carbo

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986

Marie De Santis, Joaquim Bellmunt, Gedske Daugaard, Ivana Skoneczna, Sandra Collette, Julie Lorent, Ronald de Wit, and Richard Sylvester

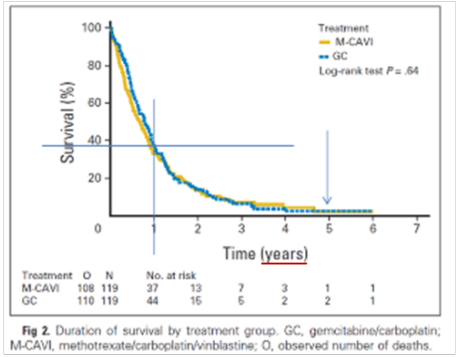


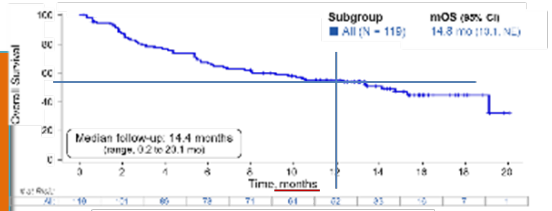
Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

Plimack E, ASCO 2016

ORR: 36%	ORR: 23%
mOS: 9.3 mo.	mOS: 15.9 mo.
1-year OS: 37%	1-year OS: 57%
5-year OS: ~ 0	5-year OS: ?

Atezolizumab

Cisplatin ineligibility criteria[1]	N = 119
Renal impairment GFR < 60 mL/min but > 30	70%
Hearing loss, 25 dB[e]	14%
Peripheral neuropathy, ≥ Grade 2	6%
ECOG PS2	20%
Renal impairment **and** ECOG PS2	7%



	All Patients (N = 119)
ORR[a] (95% CI)	23% (16, 32)
CR	9%
PR	14%

Balar et al. Lancet 2017

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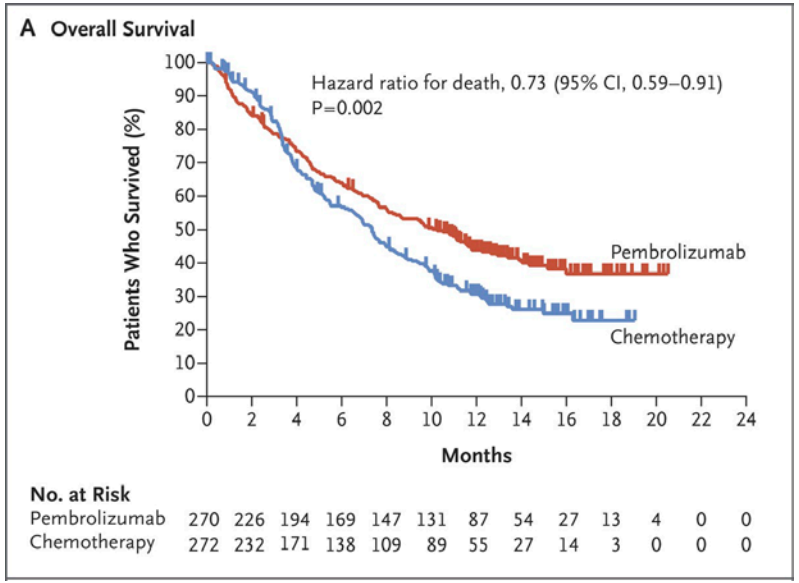
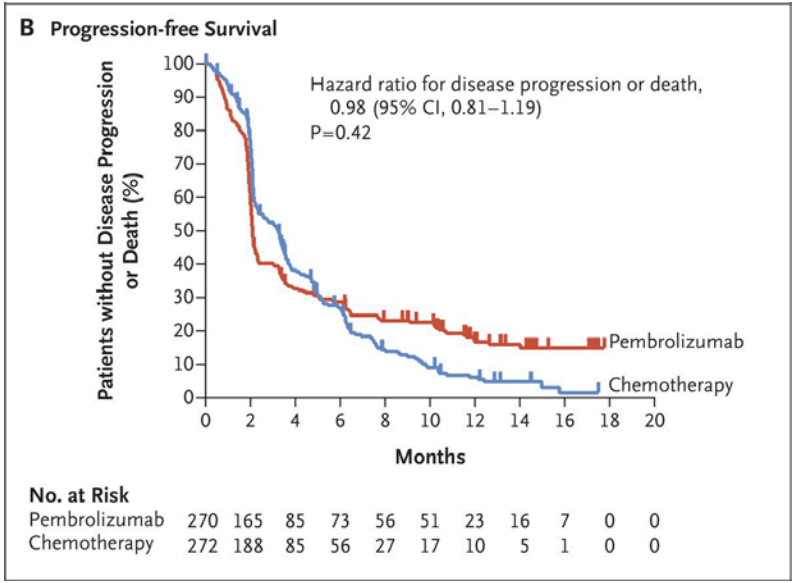
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma





The NEW ENGLAND JOURNAL of MEDICINE

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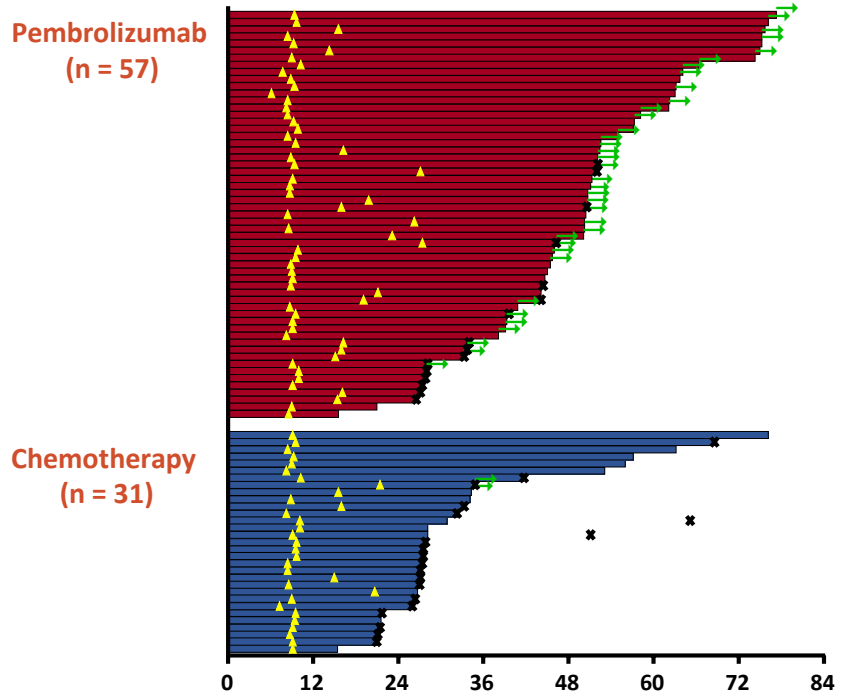
Bellmunt J, et al. *NEJM* 2017

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma



- Median (range) time to response: 2.1 mo (1.4-6.3)
- **Median (range) duration of response: NR (1.6+ to 15.6+ mo)**
- **Patients with response ≥12 mo: 68% (KM estimate)**

- Median (range) time to response: 2.1 mo (1.7-4.9)
- Median (range) duration of response: 4.3 mo (1.4+ to 15.4+)
- Patients with response ≥12 mo: 35% (KM estimate)

First response
PD or death
Treatment ongoing

Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: Sep 7, 2016.

Only responders in each treatment arm are shown.
Bar length equals duration of response.

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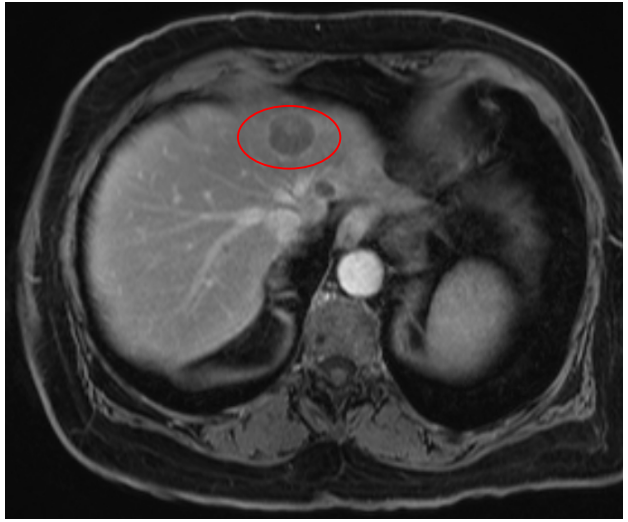
FDA Approved Immune Checkpoint Inhibitors in Metastatic Bladder Cancer

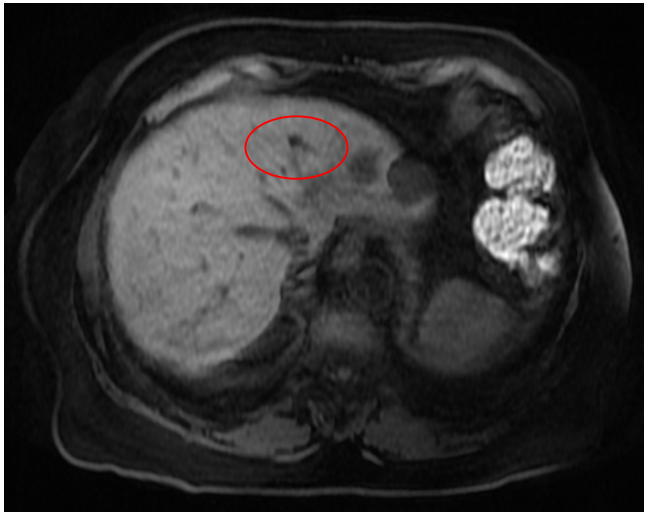
- First-line cisplatin-ineligible
  - Atezolizumab (Balar AV, et al. *Lancet* 2017)
  - Pembrolizumab (Balar AV, et al. *ASCO Annual Meeting* 2017)

- Second-line and beyond
  - Pembrolizumab (Bellmunt J, et al. *NEJM* 2017)
  - Atezolizumab (Powles T, et al. *Nature* 2014. Rosenberg JE, et al. *Lancet* 2016)
  - Nivolumab (Sharma P, et al. *Lancet Oncology* 2017)
  - Avelumab (Apolo AB, et al. *JCO* 2017)
  - Durvalumab (Powles T, et al. *JAMA Oncology* 2017)

Case, cont.

- He was not a candidate for cisplatin-based therapy, because of CKD and borderline performance status.
- He was started on atezolizumab 15 months ago.
- So far, tolerating treatment well, having excellent response and no toxicities.





After immunotherapy (now 15 months)

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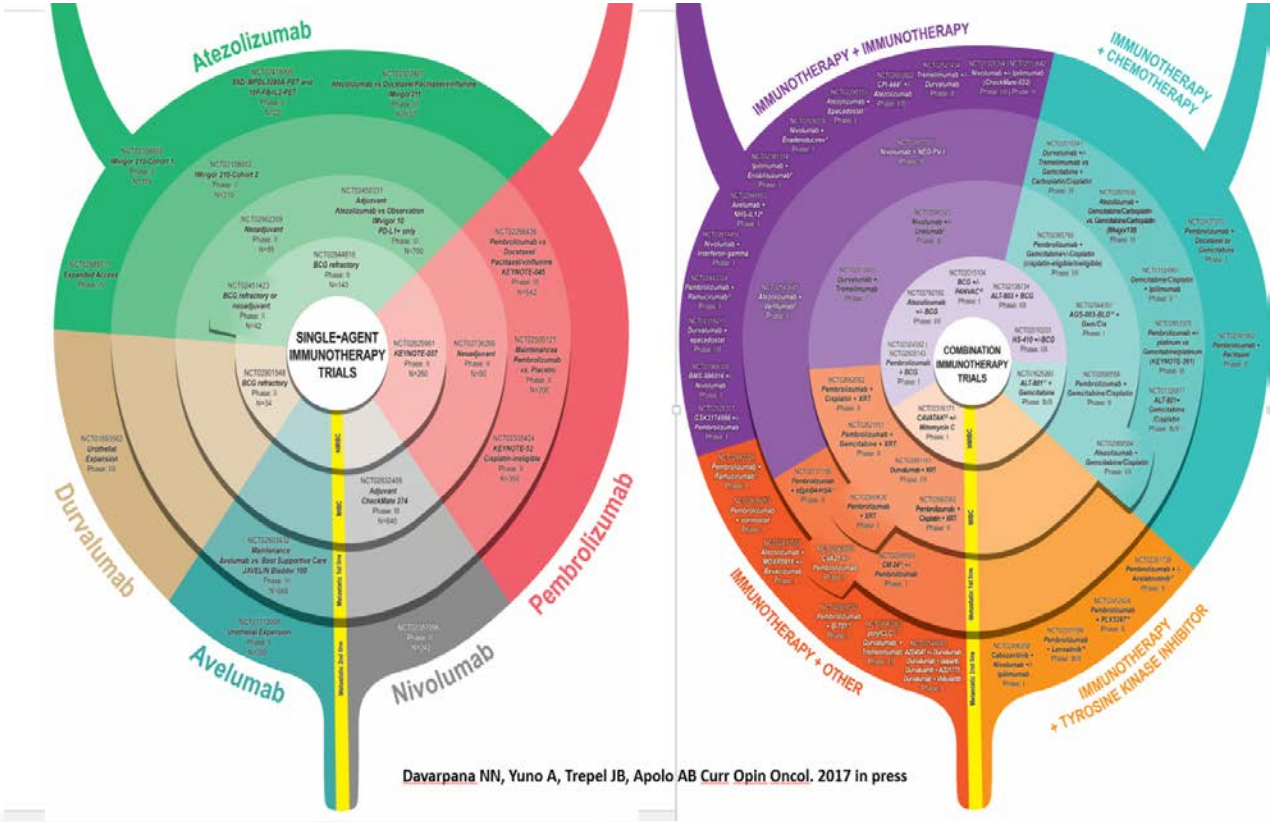
Immuno-Oncology Clinical Trials in Bladder Cancer



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Thank You

27th Annual Fall Cancer Conference
Translating Personalized Medicine into Cancer Care

WVU Cancer Institute

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