Advances in the Management of Patients With Urothelial Carcinomas of the Bladder

Amishi Shah, MD
Emily Lemke, DNP, AGPCNP-BC, AOCNP®
The University of Texas MD Anderson Cancer Center

2017 JADPRO Live at APSHO

Learning Objectives

1. Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management
2. Recognize pivotal clinical trials for the treatment of urothelial carcinoma of the bladder (UCB)
3. Identify the signs and symptoms of serious or life-threatening adverse effects of immunotherapeutic agents
4. Develop education pearls to educate patients on the recognition of immune-related toxicities
5. Summarize the role of immunotherapeutic agents to patients with UCB according to established guidelines

Financial Disclosure

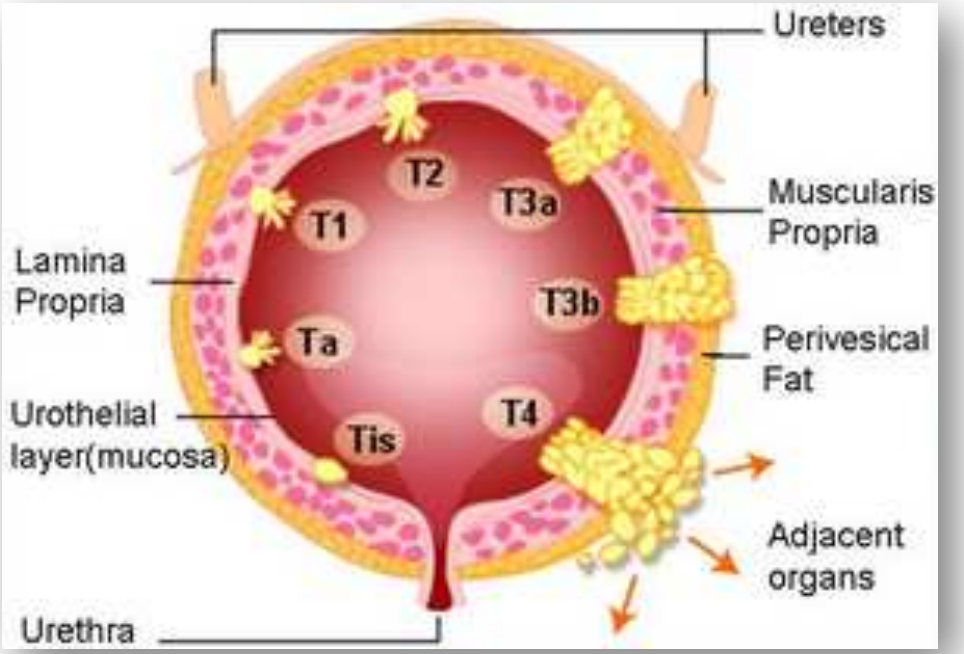
- Dr. Shah has received research support from Bristol-Myers Squibb.
- Ms. Lemke has nothing to disclose.

Bladder Cancer Facts

- Sixth most common malignancy in the United States
- Signs/symptoms: hematuria, dysuria, frequency, and urgency
- Risk factors: **smoking**, advancing age, chemical exposures

American Cancer Society, 2016.

Bladder Cancer Staging (TNM)

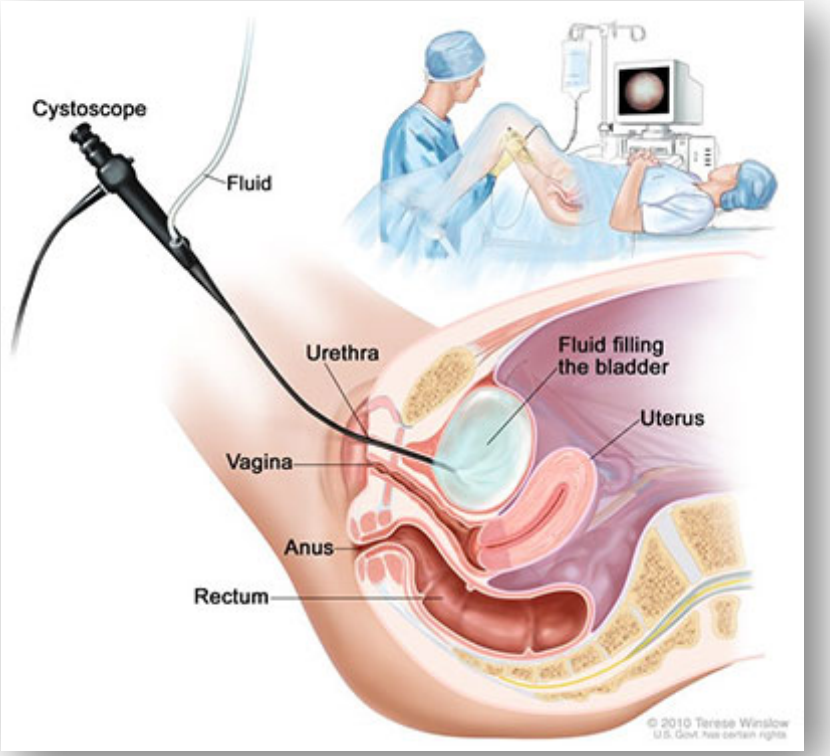


TNM = tumor, node, metastasis.

National Comprehensive Cancer Network, 2017.

Staging Workup

- CT chest, abdomen, pelvis with urogram
- Cystoscopy
- Brain MRI
  - Symptoms
  - Small cell
- Bone scan
  - Symptoms
  - Alkaline phosphatase



CT = computed tomography; MRI = magnetic resonance imaging.

National Comprehensive Cancer Network, 2017; Urology Care Foundation, What Is Cystoscopy?, https://www.urologyhealth.org/urologic-conditions/cystoscopy.

Ta and T1 Disease

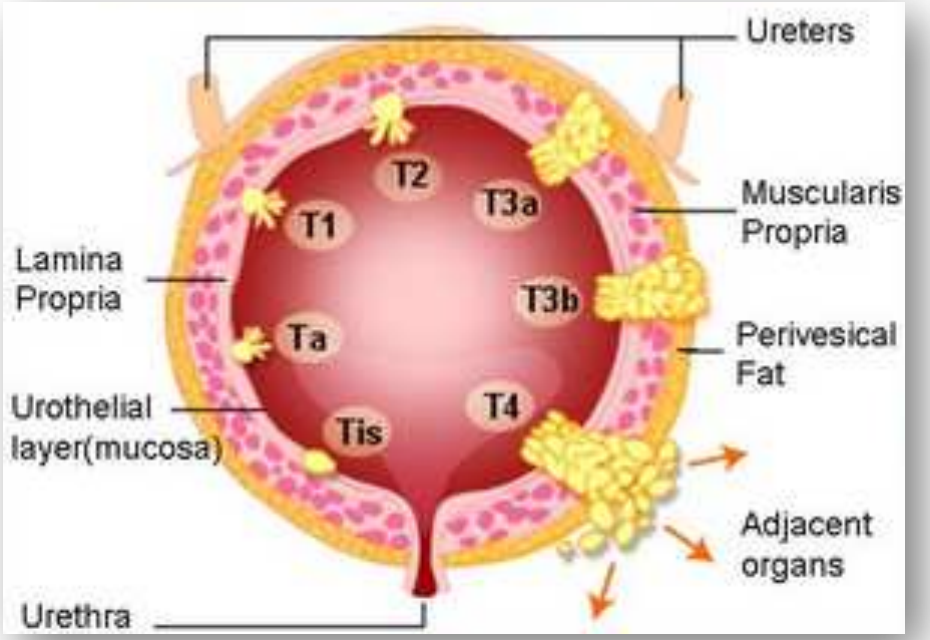
- TURBT followed by intravesicular therapy
  - Low risk: intravesicular chemotherapy X 1 (mitomycin, epirubicin, or gemcitabine)
  - Intermediate risk: intravesicular chemotherapy for 1 year
  - High risk: intravesicular immunotherapy (BCG)
- Up-front cystectomy
  - High-risk features: multiple or large tumors, variant histology, concomitant carcinoma in situ in bladder or prostatic urethra, LVI

BCG = bacillus Calmette-Guérin; LVI = lymphovascular invasion; TURBT = transurethral resection of bladder tumor.

Kamat AM, et al. *Lancet* 2016;388:2796-310.

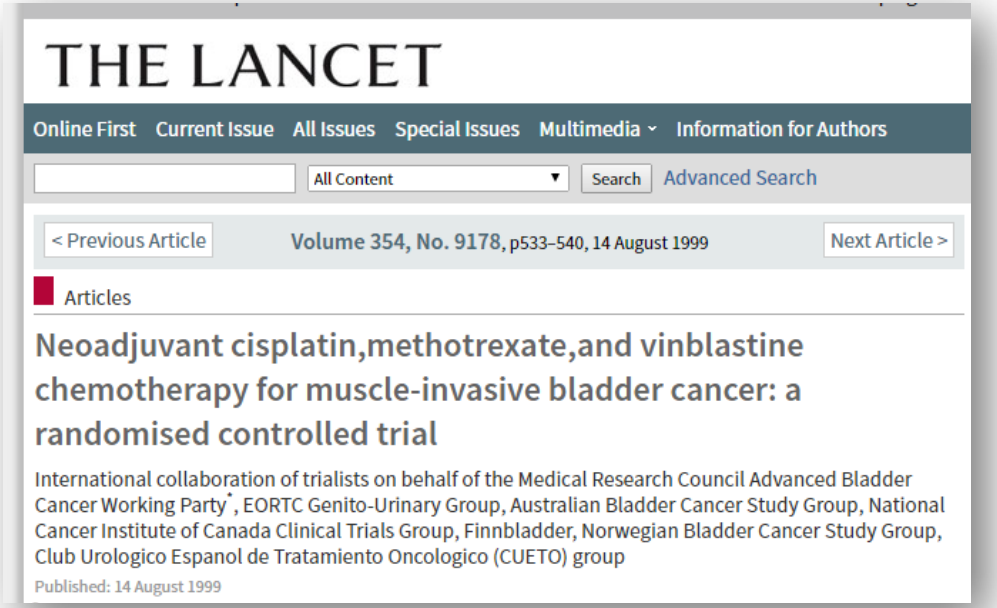
Muscle-Invasive Disease

- T2-T4aN0M0
- Standard of care: neoadjuvant chemotherapy followed by surgical consolidation
  - ddMVAC
  - Gemcitabine/cisplatin



ddMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin.

Neoadjuvant Chemotherapy



THE LANCET

Online First Current Issue All Issues Special Issues Multimedia Information for Authors

All Content Search Advanced Search

< Previous Article Volume 354, No. 9178, p533–540, 14 August 1999 Next Article >

Articles

Neoadjuvant cisplatin,methotrexate,and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial

International collaboration of trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party*, EORTC Genito-Urinary Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, Club Urologico Espanol de Tratamiento Oncologico (CUETO) group

Published: 14 August 1999

- Initial report showed increased pathologic complete responses
- At 8-year follow-up report
  - 16% reduction in the risk of death
  - Overall 10-year absolute survival increased by 6%

Lancet 1999;354:533-40.

Survival Advantage With NAC

- Confirmed survival benefit of neoadjuvant therapy for T2-T4a disease (46 → 77 months)
- pCR rate improved (38%)

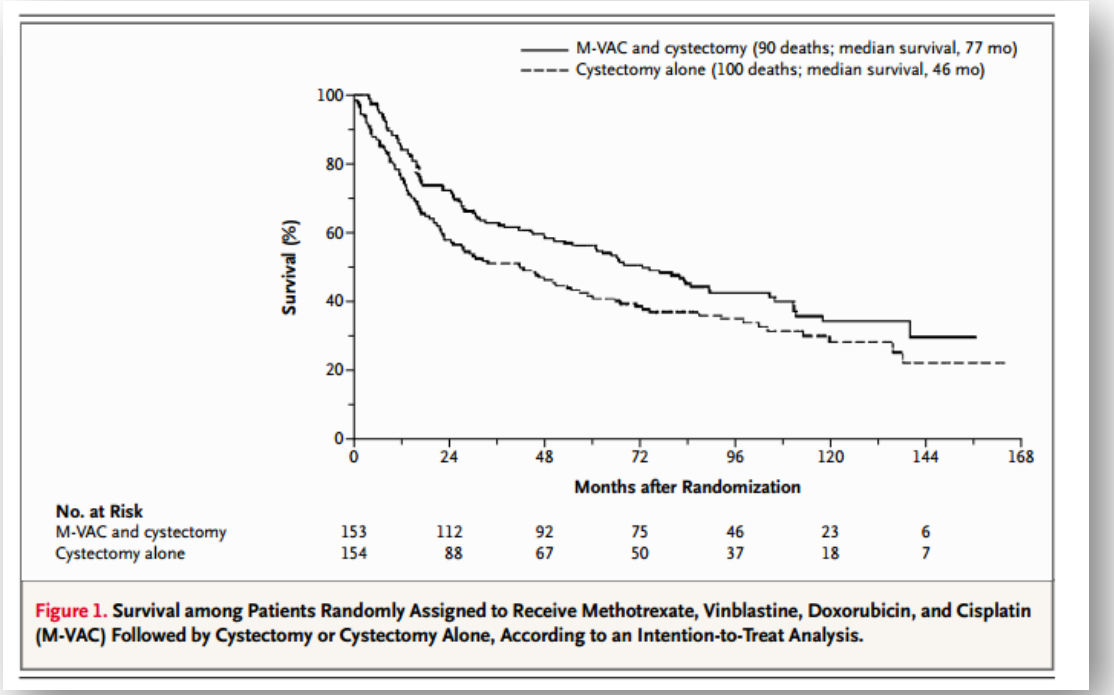


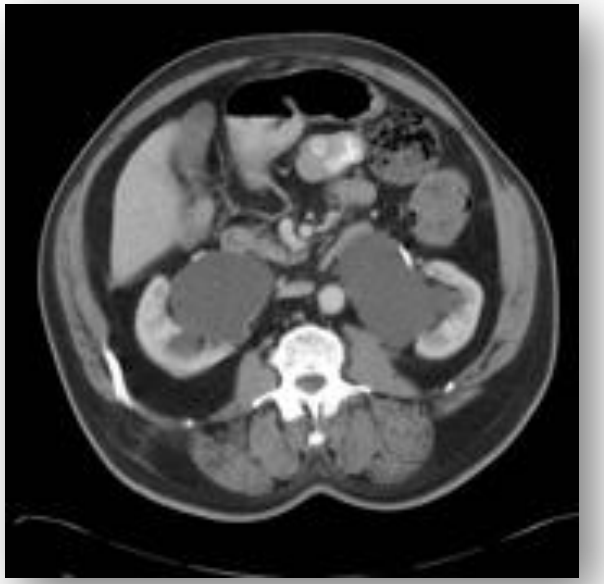
Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

NAC = neoadjuvant chemotherapy; pCR = pathologic complete response.

Grossman HB, et al. *N Engl J Med* 2003;349:859-66.

Muscle-Invasive Disease (cont.)

- MD Anderson standard
- Risk factors
  - Variant histology
  - Hydronephrosis
  - Positive LVI
  - Positive EUA



EUA = exam under anesthesia.

Standard-of-Care Cisplatin-Based Regimens

- ddMVAC: dose-dense scheduling
  - Every 2-week dosing
  - Reduced time to surgery
  - 38% of patients achieve pCR
- Gemcitabine cisplatin
  - Every 3-week dosing with day 8 gemcitabine
  - 21%–26% of patients achieve pCR

Grossman HB, et al. *N Engl J Med* 2003;349:859-66; Moore MJ, et al. *J Clin Oncol* 1999;17:2876-81; Kaufman D, et al. *J Clin Oncol* 2000;18:1921-7; Yuh BE, et al. *J Urol* 2013;189:1682-6.

Other Regimens

- Cisplatin ineligible
  - Gemcitabine/paclitaxel/doxorubicin (GTA)
- Small cell histology
  - Etoposide/cisplatin (EP)
  - Alternating doublet ifosfamide/doxorubicin and etoposide/cisplatin (IA/EP)
- Cisplatin/gemcitabine/ifosfamide (CGI)
  - Dosed every 2 weeks
  - Cisplatin dose: 50 mg/m^2
- Ifosfamide/doxorubicin/gemcitabine (IA-Gem)
  - Dosed every 3 weeks
  - Inpatient administration

Siefker-Radtke AO, et al. *J Clin Oncol* 2009;27:2592-7; Pagliaro LC, et al. J Clin Oncol. 2011;29(7 suppl):246; Siefker-Radtke AO, et al. *Cancer* 2013;119:540-7.

Monitoring

- Kidney function: Cockcroft-Gault CrCl
- Electrolytes
- Hearing
- Neuropathy
- ECHO
- Cytopenias

CrCl = creatinine clearance; ECHO = echocardiography.

Supportive Care During Chemo

- Toxicity checks in between cycles
  - IVF if borderline CrCl
  - Electrolyte repletion
    - Potassium
    - Magnesium
  - Nausea/vomiting
  - PRBC infusions
- Pegfilgrastim given if neoadjuvant therapy

IVF = intravenous fluids; PRBC = packed red blood cells.

Bladder Case Study #1

- 49-year-old male, never-smoker
- Presenting signs and symptoms: gross hematuria
- Up-front imaging: CT CAP revealed asymmetrical left lateral urinary bladder wall thickening; no hydronephrosis, no suspicious lymph nodes

CAP = chest/abdomen/pelvis.

Bladder Case Study #1

- TURBT
  - Papillary urothelial carcinoma with focal micropapillary features, high grade, invasive into the muscularis propria
  - Suspicious for LVI
  - EUA: negative

EUA = examination under anesthesia; LVI = lymphovascular invasion.

Bladder Case Study #1

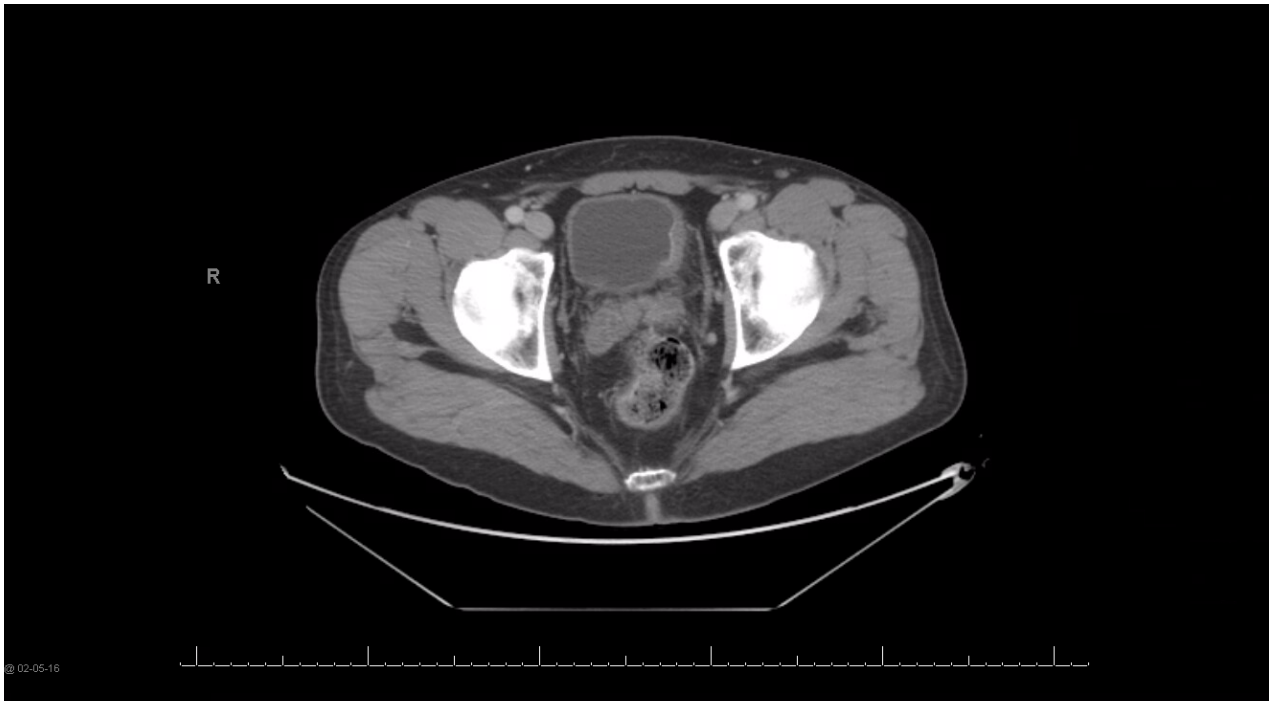
- Comorbidities: none
- CrCl: 110 mL/min
- EF: 62%
- Should he get neoadjuvant chemotherapy?
- What regimen would you choose?

EF = ejection fraction.

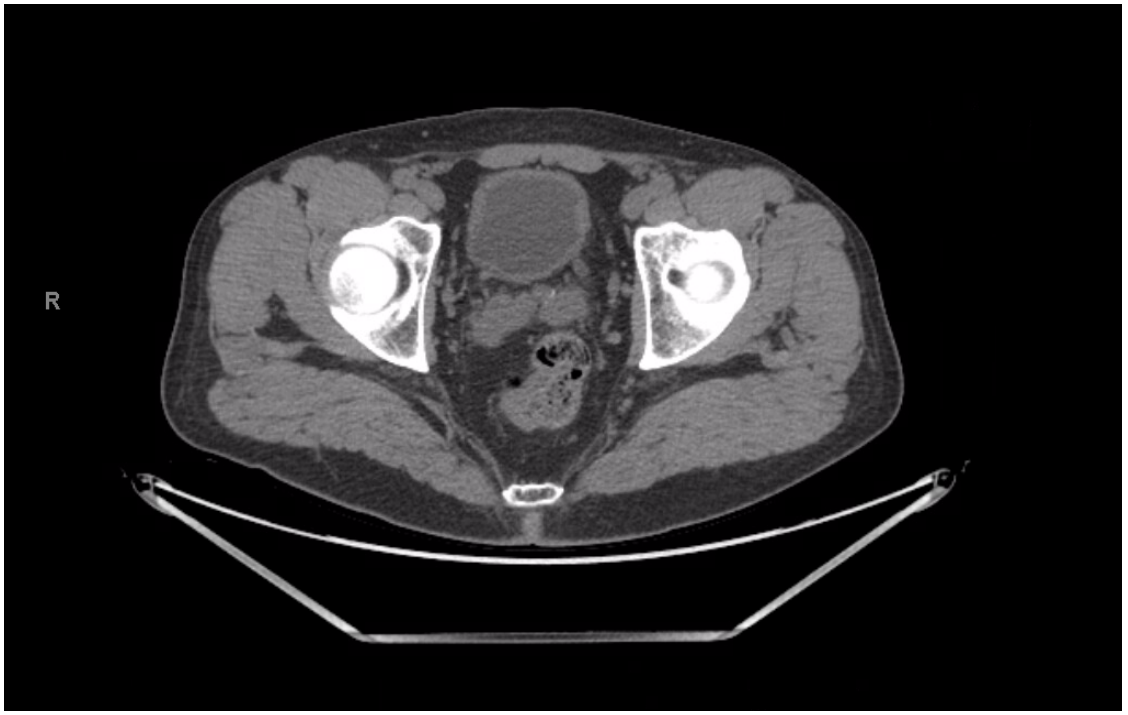
Bladder Case Study #1

- Should he get neoadjuvant chemotherapy? YES!
  - Why? Muscle-invasive disease, variant histology, suspicious LVI
- What chemo should he get? ddMVAC
  - Why? High chance of pCR, quicker time to surgery

Bladder Case Study #1



Bladder Case Study #1



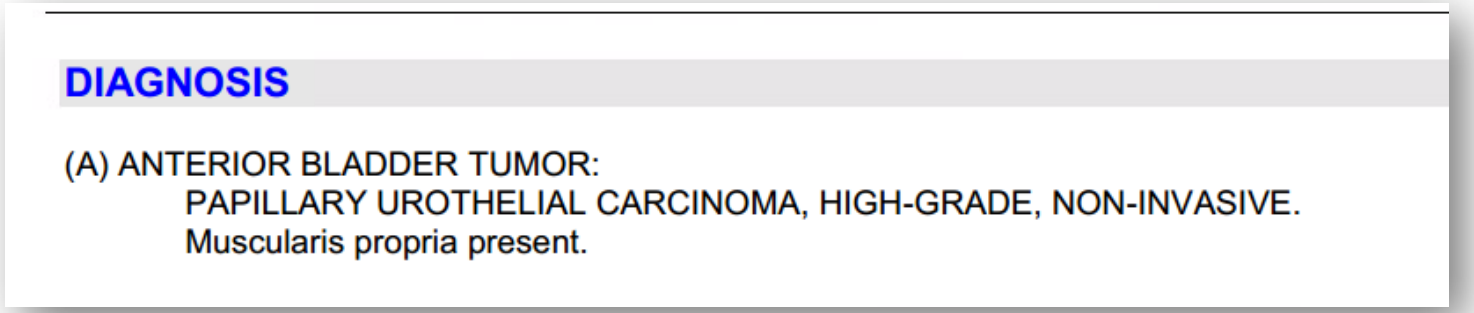
Bladder Case Study #1: Final Path

Specimen: Bladder, prostate, seminal vesicles and pelvic lymph node dissection
Procedure: Radical cystoprostatectomy
Tumor size
- **Greatest dimension:** N/A (A scar is grossly identified measuring 4.2 cm)
- **Additional dimensions:** N/A

Tumor type: Urothelial carcinoma in situ
Histologic type: Urothelial carcinoma
Histologic grade: High-grade
Microscopic tumor extension: Flat carcinoma in situ
Margins: Uninvolved by tumor
Lymph-vascular invasion: Not identified
Associated epithelial lesions: N/A
Pathologic staging (pTNM)
- **Primary tumor (pT):** ypTis
- **Regional lymph nodes (pN):** ypN0
  - **Number of lymph nodes examined:** 41
  - **Number of lymph nodes involved (any size):** 0
- **Distant metastasis (pM):** pMx

Bladder Case Study #2

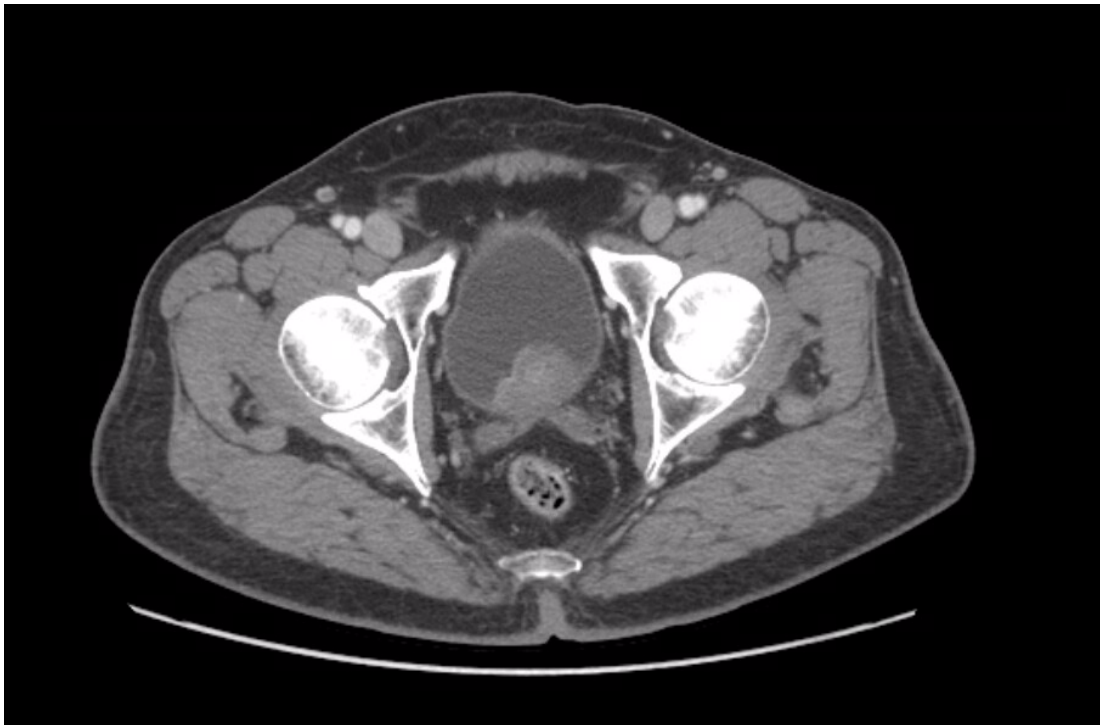
- 73-year-old male presents with painless hematuria
- TURBT pathology



DIAGNOSIS

(A) ANTERIOR BLADDER TUMOR:
PAPILLARY UROTHELIAL CARCINOMA, HIGH-GRADE, NON-INVASIVE.
Muscularis propria present.

Bladder Case Study #2

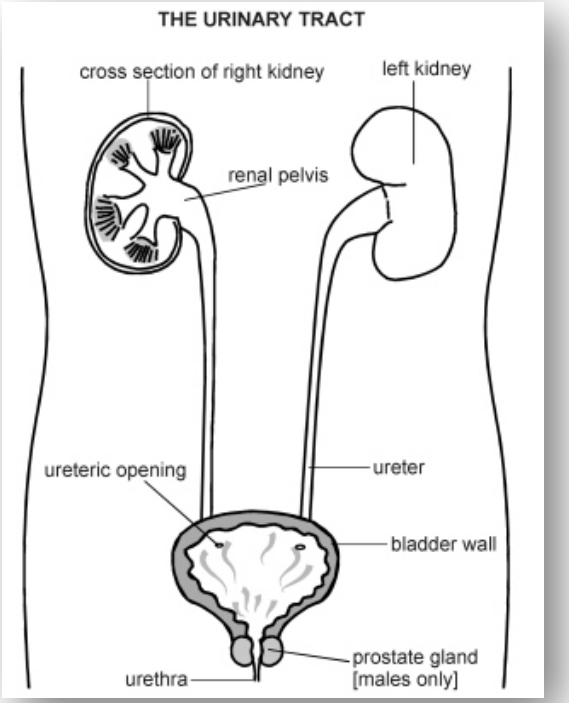


Bladder Case Study #2

- Does this patient need neoadjuvant chemotherapy? NO!
- Why?
  - No muscle-invasive disease
  - No high-risk features
- Management
  - Urology: TURBT followed by intravesicular therapy

Upper Tract Urothelial Carcinoma

- 5% of all urothelial carcinoma
- Hereditary predisposition: Lynch syndrome
  - MSI testing
- No clearly defined role for neoadjuvant or adjuvant therapy
- Extrapolate from bladder cancer data
  - **High grade and sessile polyps:** neoadjuvant therapy



MSI = microsatellite instability.

Campbell MT, et al. *Urol* Oncol 2017;35:492-8; Patient, Urinary Tract (diagram), https://patient.info/diagram/urinary-tract-diagram.

Benefits for UTUC Neoadjuvant Chemotherapy

- Increased nephrons prior to nephroureterectomy
- Similar to bladder
  - Eradication of micrometastatic disease
  - Downsizing for surgical consolidation
  - Reducing risk of recurrence
  - Better tolerability prior to surgery rather than post-op

UTUC = upper tract urothelial carcinoma.

Siefker-Radtke AO, et al. *J Clin Oncol* 2017;35:816-7.

Metastatic Urothelial Cancer

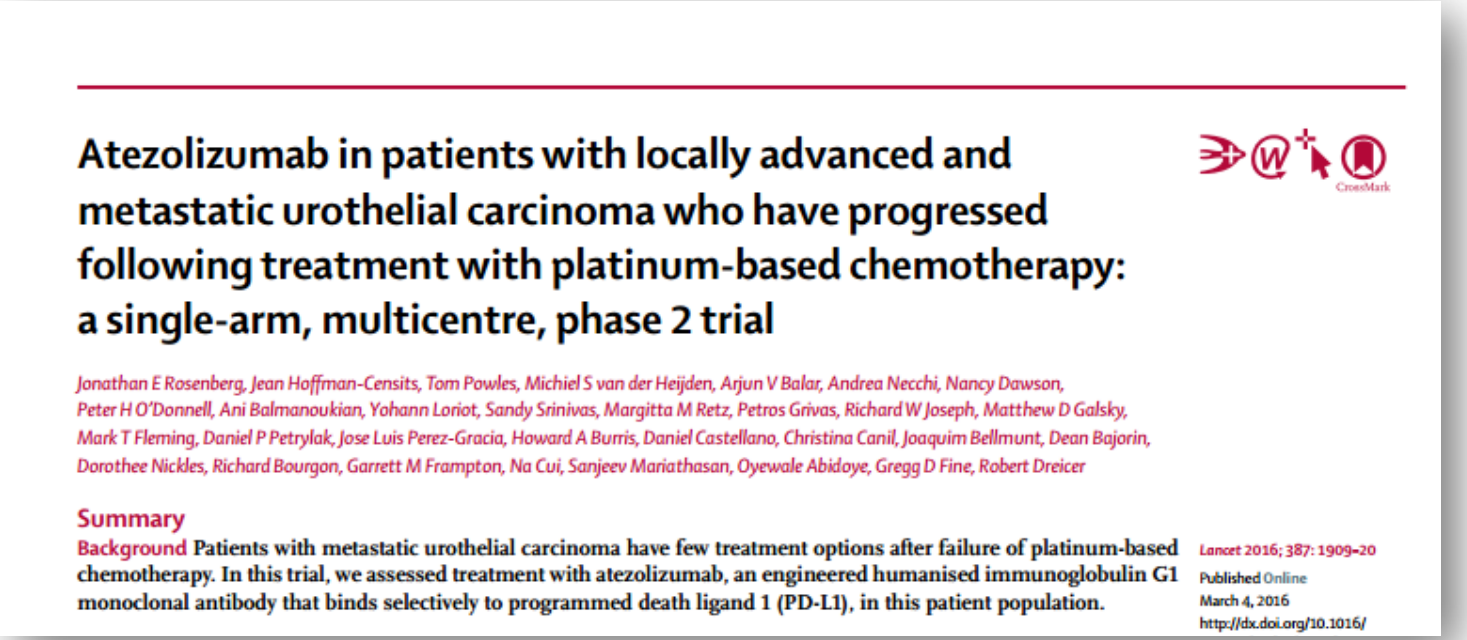
- First line: cisplatin-based chemotherapy
- Second line: immunotherapy
  - Also indicated first line if cisplatin-ineligible (CrCl < 60 mL/min)

National Comprehensive Cancer Network, 2017.

Immunotherapy: Five New Therapies or One New Treatment?

- Atezolizumab
- Nivolumab
- Avelumab
- Durvalumab
- Pembrolizumab

Atezolizumab



Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer

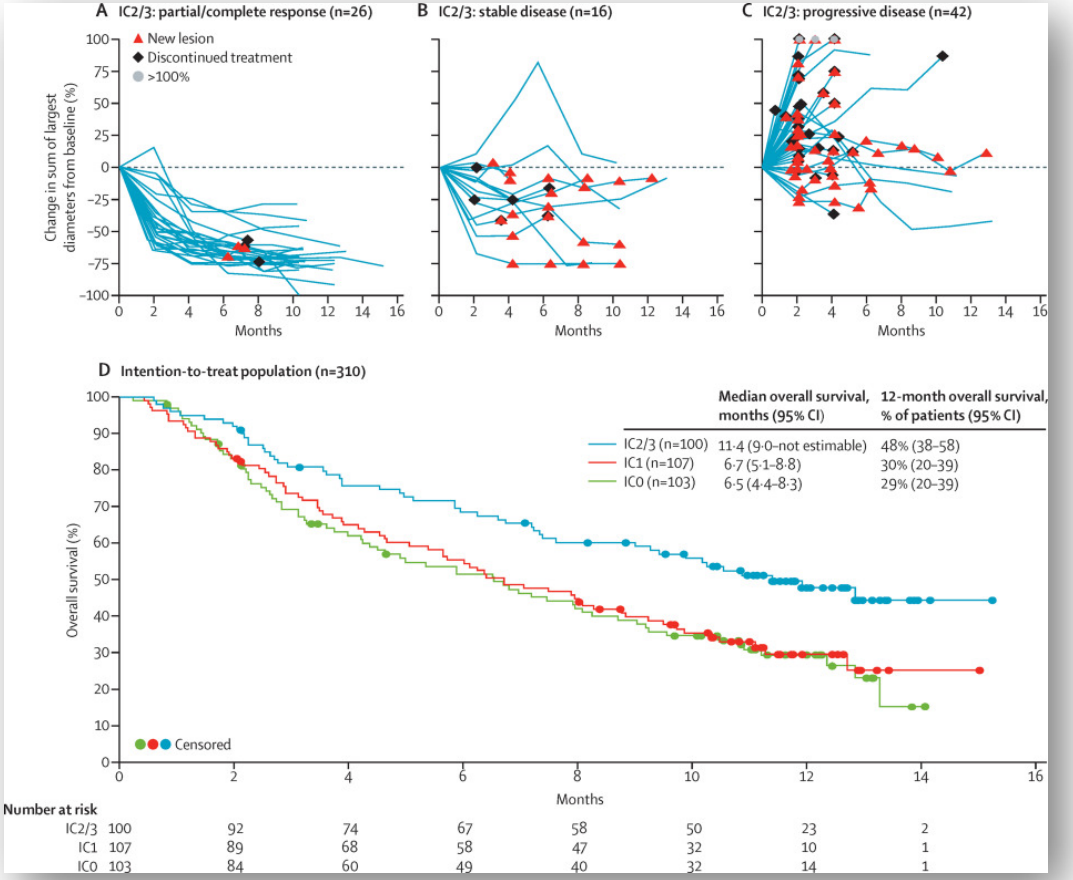
Summary

Background Patients with metastatic urothelial carcinoma have few treatment options after failure of platinum-based chemotherapy. In this trial, we assessed treatment with atezolizumab, an engineered humanised immunoglobulin G1 monoclonal antibody that binds selectively to programmed death ligand 1 (PD-L1), in this patient population.

Lancet 2016; 387: 1909–20
Published Online
March 4, 2016
http://dx.doi.org/10.1016/

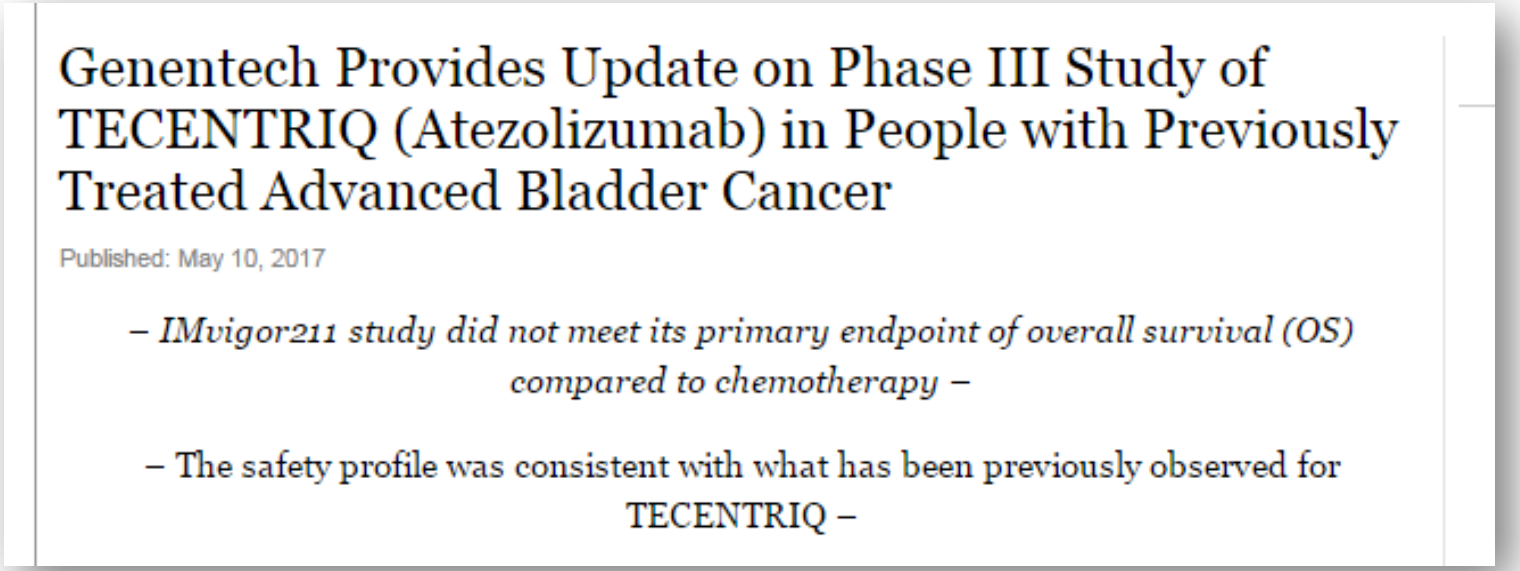
Rosenberg JE, et al. *Lancet* 2016;387:1909-20.

Atezolizumab



Rosenberg JE, et al. *Lancet* 2016;387:1909-20.

Atezolizumab



Genentech Provides Update on Phase III Study of TECENTRIQ (Atezolizumab) in People with Previously Treated Advanced Bladder Cancer

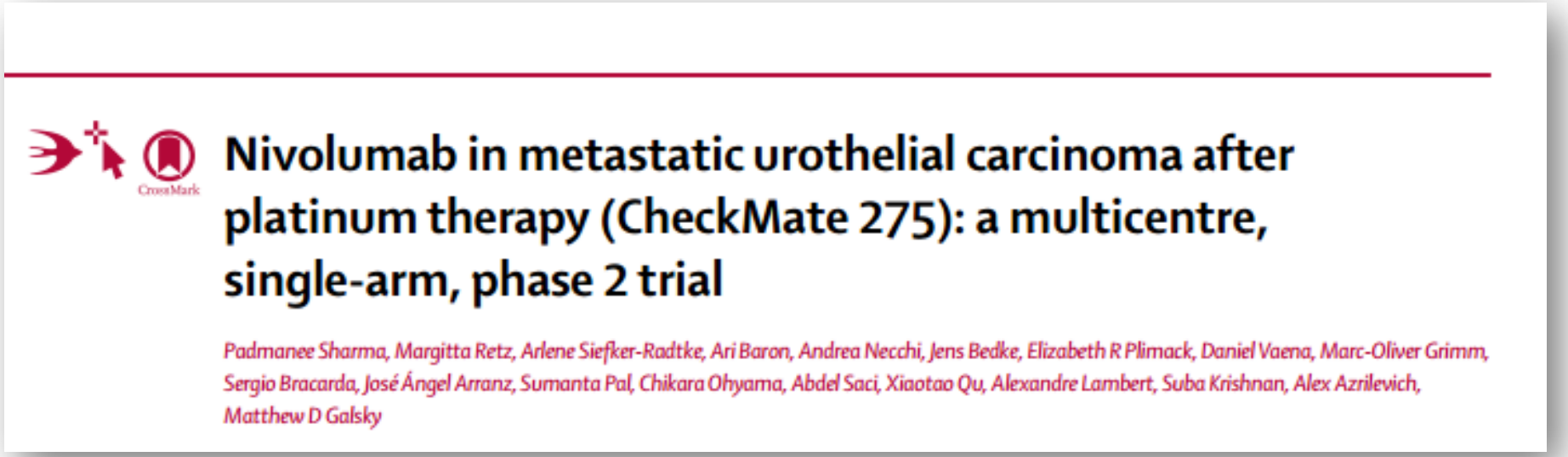
Published: May 10, 2017

– IMvigor211 study did not meet its primary endpoint of overall survival (OS) compared to chemotherapy –

– The safety profile was consistent with what has been previously observed for TECENTRIQ –

Genentech Press Release, https://www.gene.com/media/press-releases/14665/2017-05-09/genentech-provides-update-on-phase-iii-s.

Nivolumab

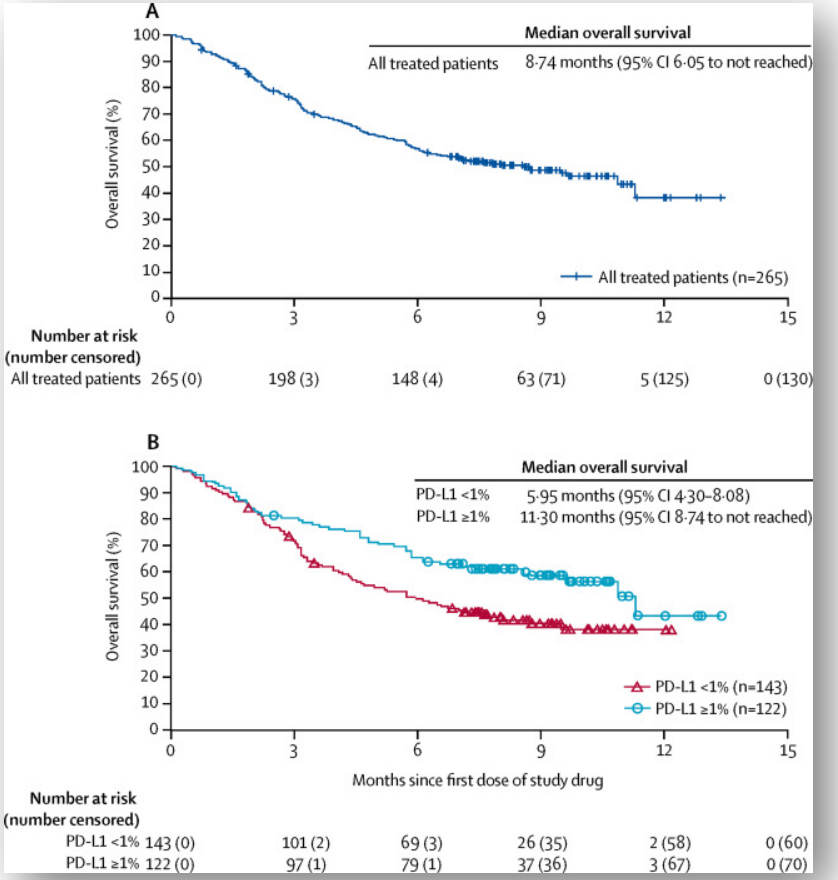


Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial

Padmanee Sharma, Margitta Retz, Arlene Siefker-Radtke, Ari Baron, Andrea Necchi, Jens Bedke, Elizabeth R Plimack, Daniel Vaena, Marc-Oliver Grimm, Sergio Bracarda, José Ángel Arranz, Sumanta Pal, Chikara Ohyama, Abdel Saci, Xiaotao Qu, Alexandre Lambert, Suba Krishnan, Alex Azrilevich, Matthew D Galsky

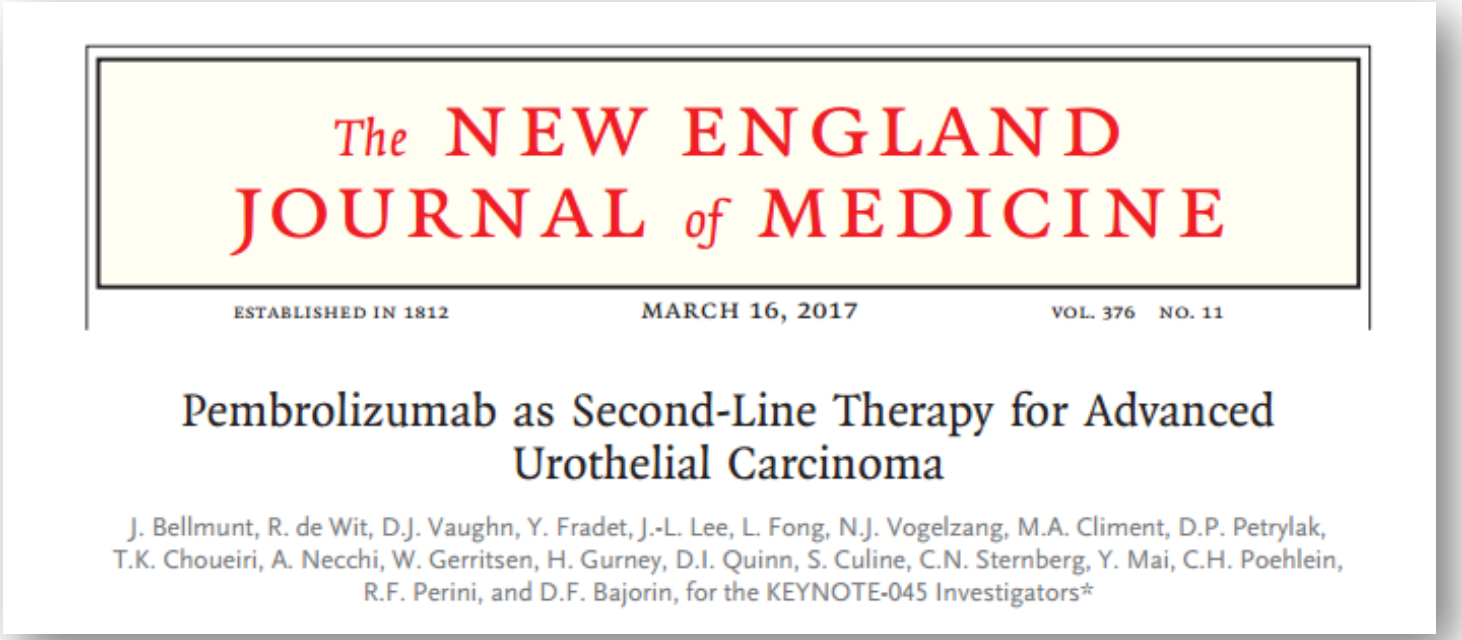
Sharma P, et al. *Lancet Oncol* 2017;18:312-22.

Nivolumab



Sharma P, et al. *Lancet Oncol* 2017;18:312-22.

Pembrolizumab



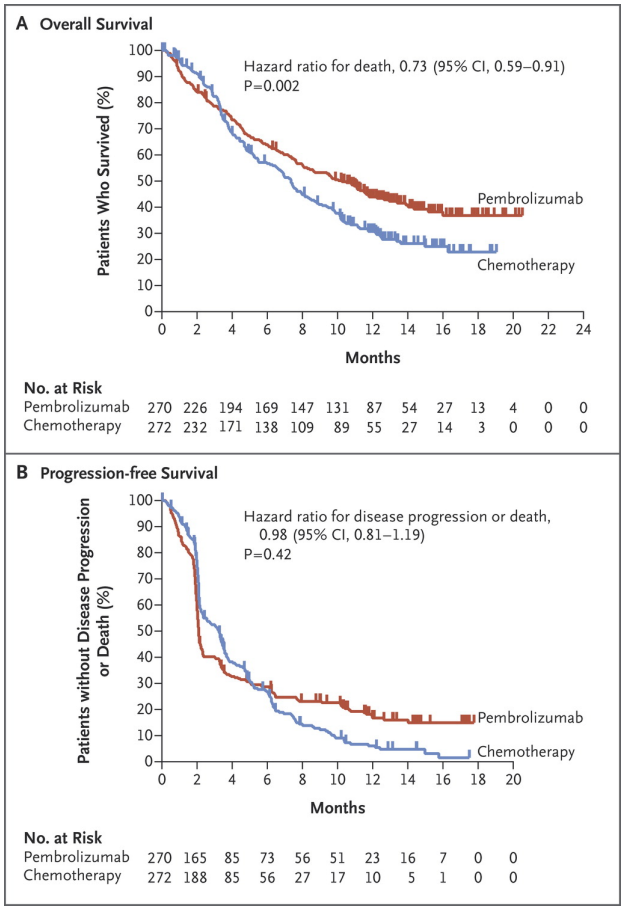
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2017 VOL. 376 NO. 11

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, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

Pembrolizumab



Bellmunt J, et al. *N Engl J Med* 2017;376:1015-26.

Pembrolizumab

- Indications: platinum-refractory metastatic urothelial carcinoma, or platinum-ineligible metastatic urothelial carcinoma
- Dosing: 200 mg every 3 weeks

Areas of Exploration

- PD-L1 expression
- PD-1 vs. PD-L1 blockade
- Combination with CTLA-4 blockade
- Combination with cytoxic chemotherapy
- Sequencing of treatment
- Duration of treatment
- Role in curative intent setting

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

Immuno-Oncology Toxicity Management

Baseline labs

- Hematology: CBC with differential
- Electrolytes: Na, K, Cl, CO2, BUN, Cr, Ca, Mg, Phos
- Liver: ALT, AST, total bilirubin, alk phos, LDH
- Endocrine: cortisol, ACTH, TSH, free T4, total T3, glucose, PH, FSH, testosterone (male), estradiol (female)
- Gastrointestinal: amylase, lipase
- Inflammatory: ESR, CRP, ANA
- TB: T-spot tuberculosis

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; CO2 = bicarbonate; Cr = creatinine; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; IO = immuno-oncology; K = potassium; LDH = lactate dehydrogenase; LH = luteinizing hormone; Mg = magnesium; Na = sodium; Phos = phosphorus; TB = tuberculosis; TSH = thyroid-stimulating hormone.

IO Toxicity Management

- Endocrinopathies: cortisol, ACTH, FSH, LH, testosterone, estradiol, MRI brain
- Diarrhea/Colitis: stool studies including *C. diff*, lactoferrin, calprotectin, CT A/P, colonoscopy + biopsy
- Pneumonitis: sputum culture, respiratory panel PCR, cardiac panel, EKG, 2-D ECHO, 6-minute walk test, complete PFTs, chest x-ray, chest CT
- Myositis: aldolase, CPK (in addition to baseline labs)

A/P = abdomen/pelvis; CPK = creatine phosphokinase; EKG = electrocardiogram; IO = immuno-oncology; PCR = polymerase chain reaction; PFTs = pulmonary function tests.

Management

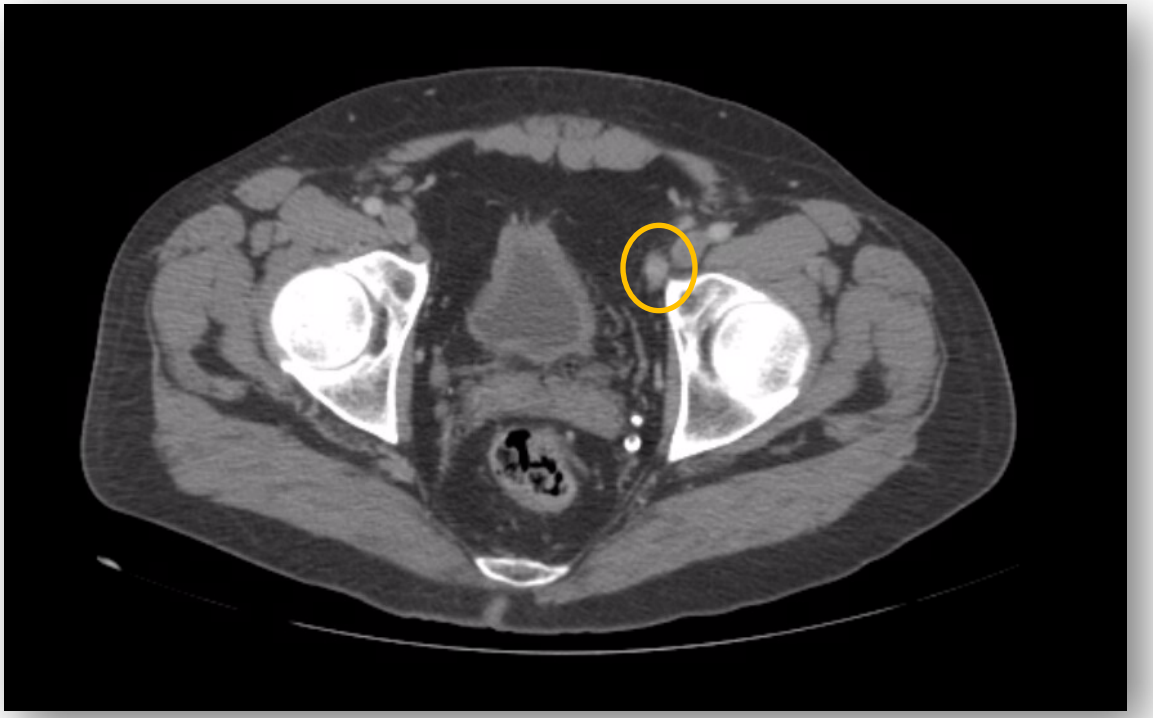
- **Early detection is key**
- Corticosteroids: 1 mg/kg twice per day
- Colitis considerations
  - Colonoscopy for biopsy: lymphocytic infiltrate
  - Mesalamine
  - Infliximab

IO Case Study

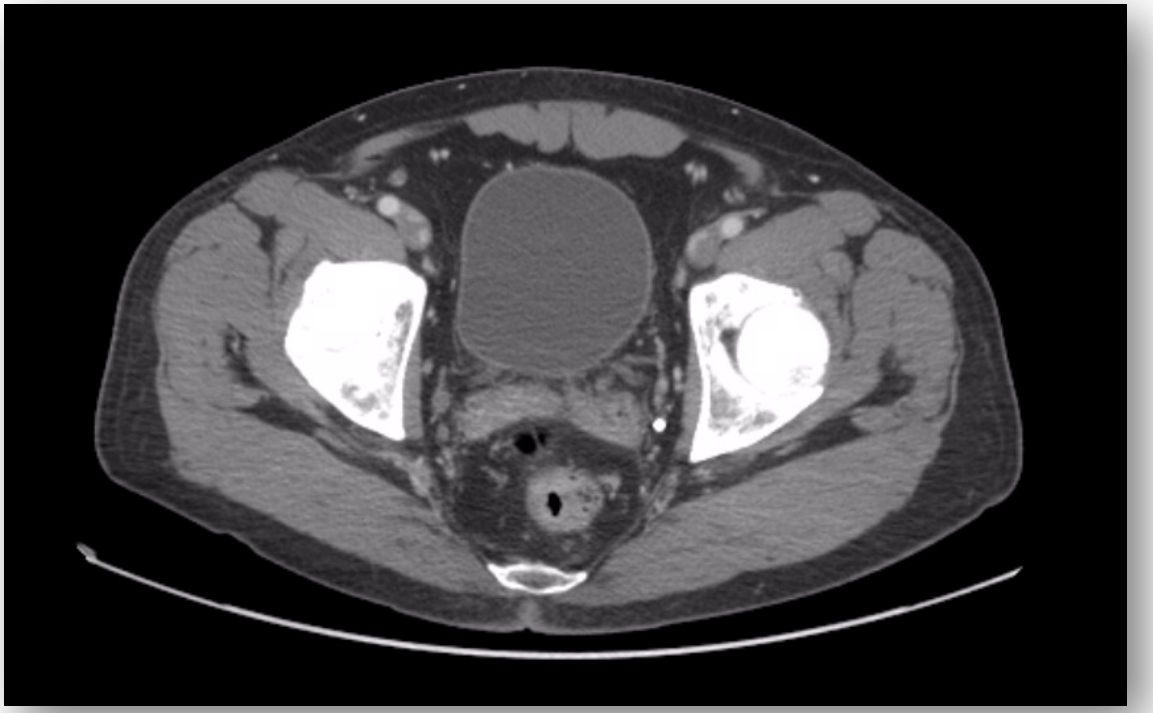
- 54-year-old with metastatic urothelial carcinoma to regional LN, biopsy proven
- Prior treatment
  - IA Gem x 4 cycles → enlarged pelvic LN
  - ddMVAC x 6 cycles → persistent enlarged LN
  - GTA x 2 → persistent enlarged LN

LN = lymph node.

IO Case Study



IO Case Study



IO Case Study

- Now: continues on nivolumab
- Unknown: when to stop
- Unknown: role for consolidative surgery

Future Directions

- Expansion of approvals for immunotherapy
- Further molecular characterization

Urothelial Molecular Characterization

- Basal
  - Aggressive biology, highest proliferation markers
  - Poorer outcomes, often metastatic at presentation
  - Chemo-sensitive
- Luminal
  - More common in micropapillary
  - *FGFR3* mutations common
  - Initially superficial and progress to muscle invasive
- P53-like
  - Low proliferation, stromal enrichment
  - Chemo-resistant
  - Bone-trophic
  - Better outcomes

FGFR3 = fibroblast growth factor receptor 3.

McConkey DJ, et al. *Hematol Oncol Clin North Am.* 2015;29(2):377-94.

Urothelial Molecular Characterization

- Testing to consider in metastatic setting
  - Panel molecular testing
  - *FGFR* mutation testing
  - MTAP
  - MSI

MTAP = methylthioadenosine phosphorylase.

Questions?

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

SMARTIE

This has been a SMARTIE presentation.

SMARTIE participants, you can now go to smartie2017.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.