Case Studies in Immunotherapy for the Treatment of Urothelial Cancer

November 5, 2021

5:30 – 6:30 p.m. ET

sitc Society for Immunotherapy of Cancer

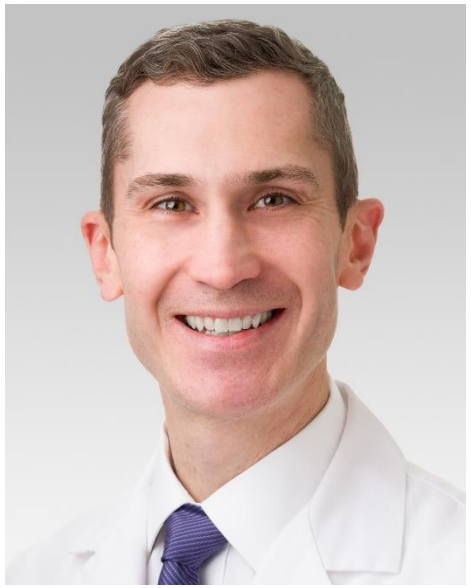
Cancer Immunotherapy GUIDELINES

AMGEN MERCK

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar faculty

Matthew Campbell, MD – *The University of Texas MD Anderson Cancer Center*



Joshua J. Meeks, MD, PhD – *Northwestern University*

Jonathan E. Rosenberg, MD – *Memorial Sloan Kettering Cancer Center*

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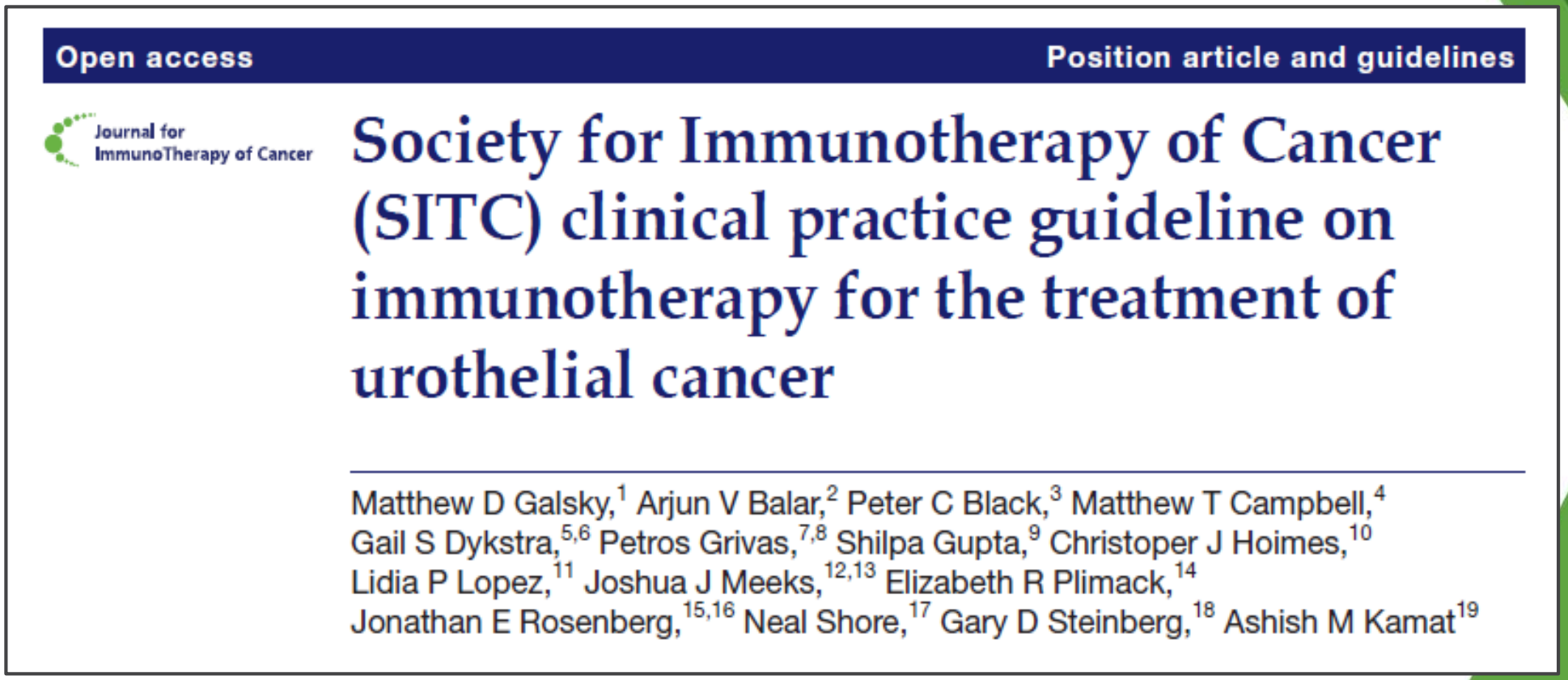
Learning objectives

- Plan immunotherapy treatment regimens for challenging patient populations
- Identify management strategies for uncommon and/or atypically responsive toxicities
- Select appropriate treatment strategies for patients with relapsed and/or unresponsive urothelial cancer
- Articulate the potential risks and benefits for proceeding with any other possible interventions specific to urothelial cancer in the context of an immunotherapy treatment plan

Webinar outline

- Development of the guideline
- NMIBC, BCG and Pembrolizumab
- Unresectable bladder cancer
- Fatal toxicities
- Aggressive disease presentation
- Immune irritability
- Key takeaways

Development of the Guideline



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of urothelial cancer

Matthew D Galsky,[1] Arjun V Balar,[2] Peter C Black,[3] Matthew T Campbell,[4] Gail S Dykstra,[5,6] Petros Grivas,[7,8] Shilpa Gupta,[9] Christoper J Hoimes,[10] Lidia P Lopez,[11] Joshua J Meeks,[12,13] Elizabeth R Plimack,[14] Jonathan E Rosenberg,[15,16] Neal Shore,[17] Gary D Steinberg,[18] Ashish M Kamat[19]

Development of the Guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 15 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

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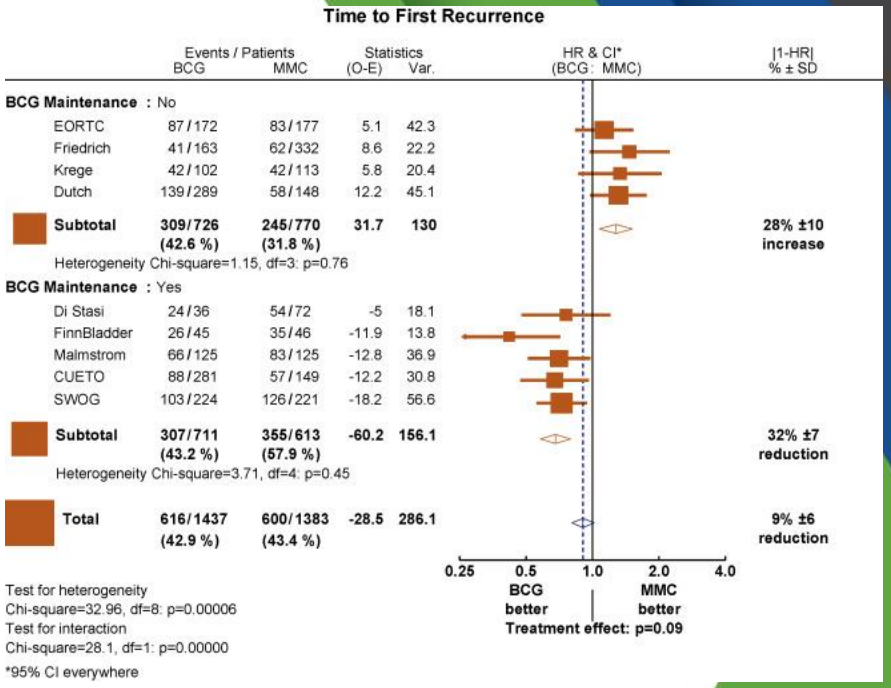
Case 1 – NMIBC, BCG and Pembrolizumab

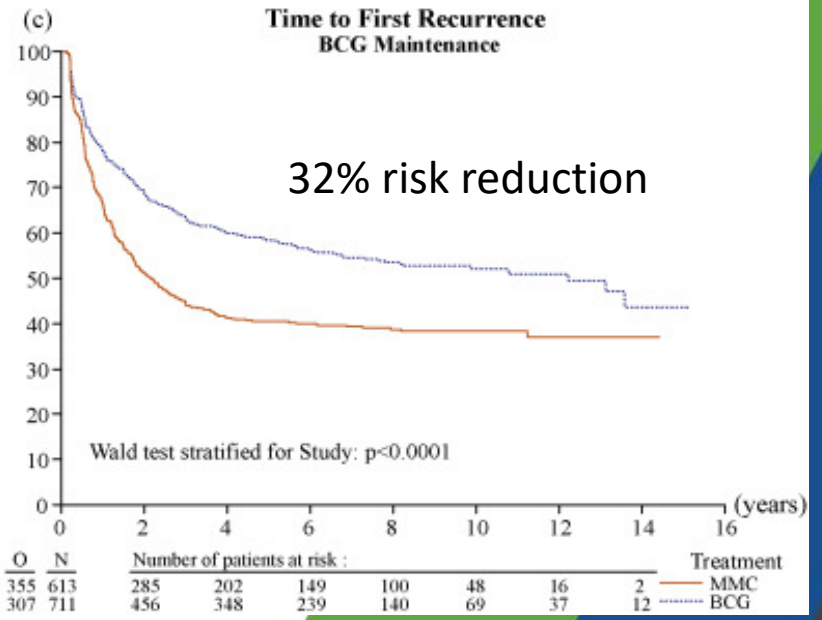
- A 63 yo male with hx of gross hematuria, found to have a 3 cm T1HG NIMBC with CIS.
- Re-TUR did now show cancer.
- How would you decide how to treat this patient's cancer?

Case 1 – NMIBC, BCG and Pembrolizumab

- He is a high-risk NMIBC (T1HG and CIS)
- He should receive 3 years of BCG
- Intermediate risk 1 year
- Most common regimen BCGX6, 3X 3, 6, 12, 18, 24, 30, 36

- BCG is superior to chemotherapy

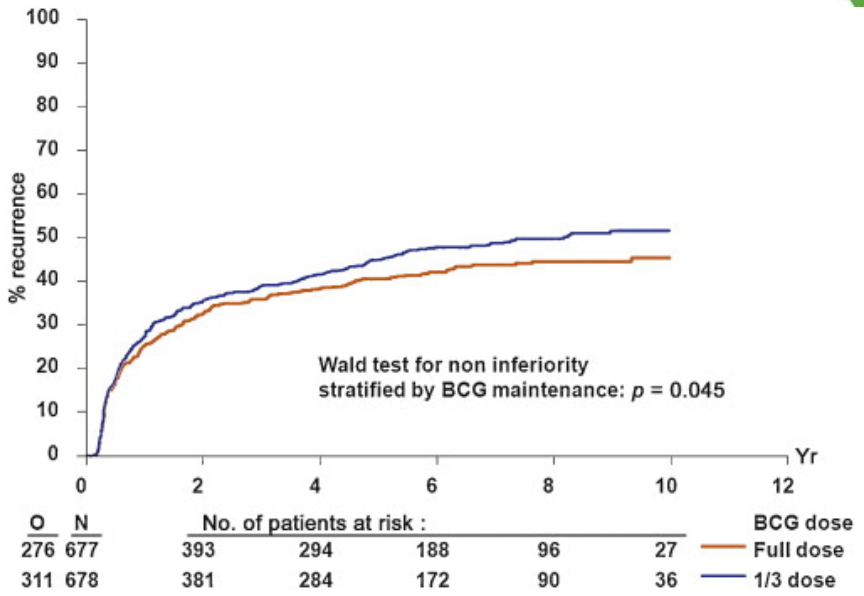




1.Malmström P-U, *et al* An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus Bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247–5

What would be options if no BCG?

A. Reduce Maintenance
B. Stop at 12 months
C. Give dual agent chemotherapy
D. Consider Trial
E. Refer
F. All of the above



3 years of maintenance was superior to 1 year of maintenance by percentage of disease-free patients at 5 years for patients receiving full-dose BCG (HR 1.61; 95% CI 1.13 to 2.30; p=0.0087)

What are the anticipated side-effects of BCG?

A. Urinary frequency
B. Urinary urgency
C. Flue-like symptoms
D. Myalgias
E. All of the above

Our patient has severe urgency, all are acceptable management options except

A. Dose reduction (1/2 or 1/3 dose)
B. Skip doses
C. Steroids
D. Anti-TB medications
E. Antibiotics (non-TB)
F. All of the above

Case 1- continued

- Our patient receives 9 doses and has a + cytology with some erythema in the bladder
- Cystoscopy demonstrates a blue light positive area, that is CIS on biopsy.
- Is he BCG unresponsive? How is this defined?

What are his options?

- Radical cystectomy
- Salvage intravesical chemotherapy
- Keytruda
- Clinical trial

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

What:

To evaluate pembro in BCG-unresponsive w CIS

How:

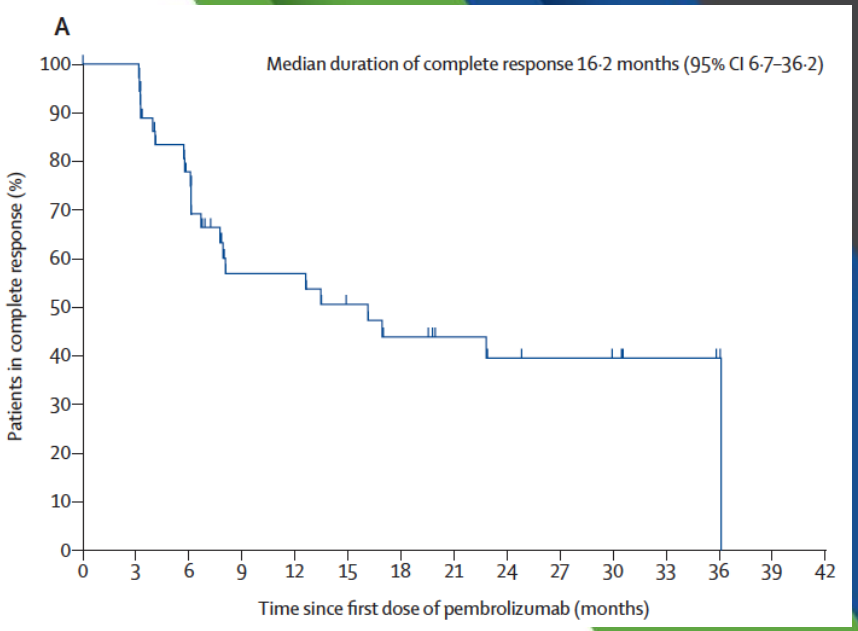
- 96 cohort A= CIS +/- papillary

Findings:

- 39 (41%) CR at 3 mo
- Median duration of was 16 mo, 46% (18) CR at 12 (19% of 96)
- 17% progression, 83% PFS at 12 mo
- 9% MIBC, metastatic cancer or death
- Median duration on pembro: 4 mo, 7 doses
- 66% had adverse events, 13% G3-4, 11 SAE
- 11/25 responders had RC- most low stage (pT0 or pTis)
- 29/57 non-responders had an RC, 3 w pT2, pT3, N0-1

Pembro q 3 wks is an option for CIS

Need clear plans for use and followup



Note: showing only 3 m responders (durability)

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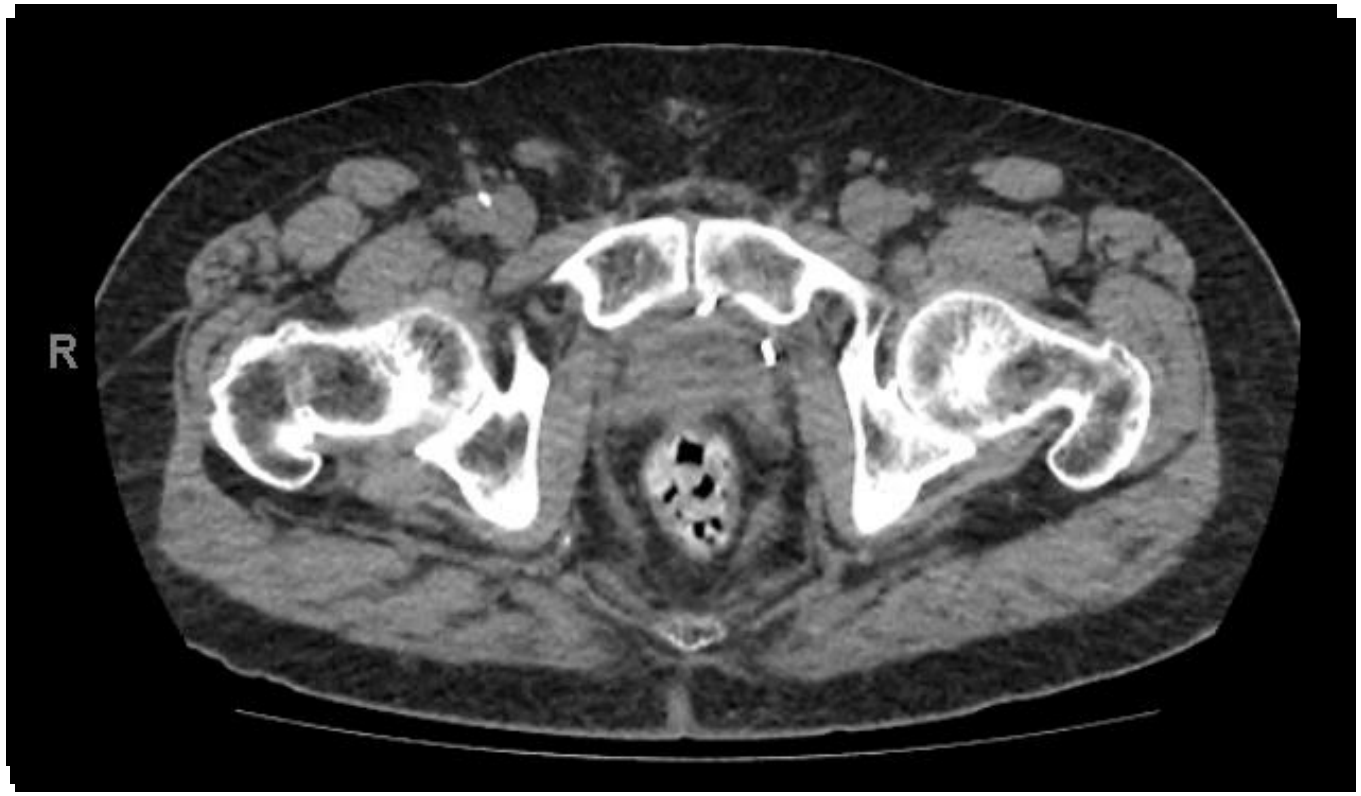
Case 2: Unresectable bladder cancer

- 83yo retired veteran presents with acute renal failure found to be due to obstructive uropathy



Next Steps

- Patient had bilateral percutaneous nephrostomy tubes placed

- Cystoscopy + TURBT outside bulky tumor in bladder trigone, specimen high grade urothelial cancer invasion into lamina propria, no muscularis propria present

What to Do

- Repeat cystoscopy 5cm mass excised, EUA with fixed irregular mass fixed to anterior rectum

DIAGNOSIS

(A) BLADDER TUMOR:
HIGH GRADE UROTHELIAL CARCINOMA, WIDELY INVASIVE INTO MUSCULARIS PROPRIA. (SEE COMMENT)
LYMPHOVASCULAR INVASION IS PRESENT.

Entire report and diagnosis completed by Priya Rao MD 12141

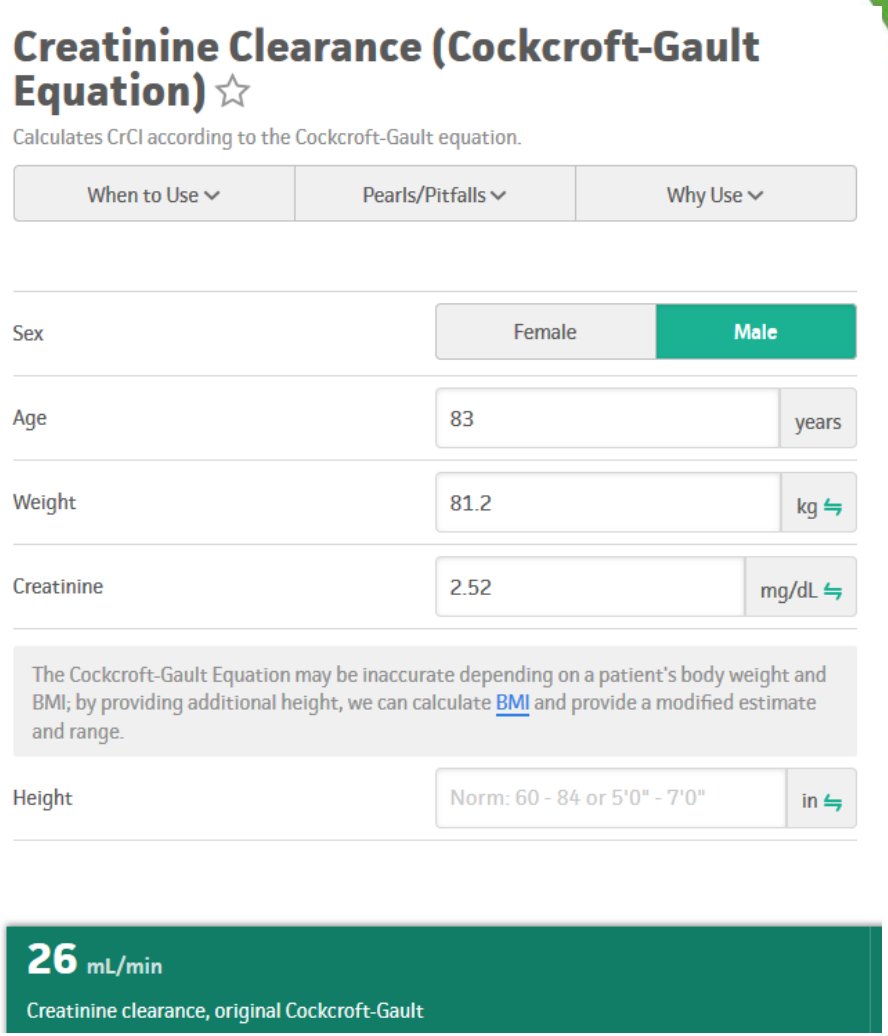
- What additional information would be helpful?

Labs

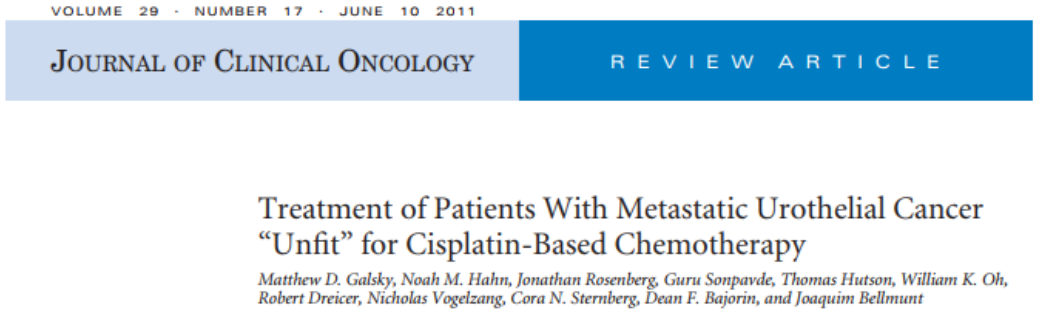
- Hgb 7.9
- BUN 18, Cr 2.52
- ECOG PS 2

- LVEF 52%
- Severe AS, AVA
  0.5cm2/m2

Imaging no distant sites of disease



Eligibility for chemotherapy


VOLUME 29 · NUMBER 17 · JUNE 10 2011

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Treatment of Patients With Metastatic Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy

Matthew D. Galsky, Noah M. Hahn, Jonathan Rosenberg, Guru Sonpavde, Thomas Hutson, William K. Oh, Robert Dreicer, Nicholas Vogelzang, Cora N. Sternberg, Dean F. Bajorin, and Joaquim Bellmunt

Ineligibility for cisplatin per expert recommendations:

1. GFR <60
2. ECOG ≥ 2
3. Neuropathy grade ≥ 2
4. Multirange hearing loss
5. Heart failure NYHA ≥ 3

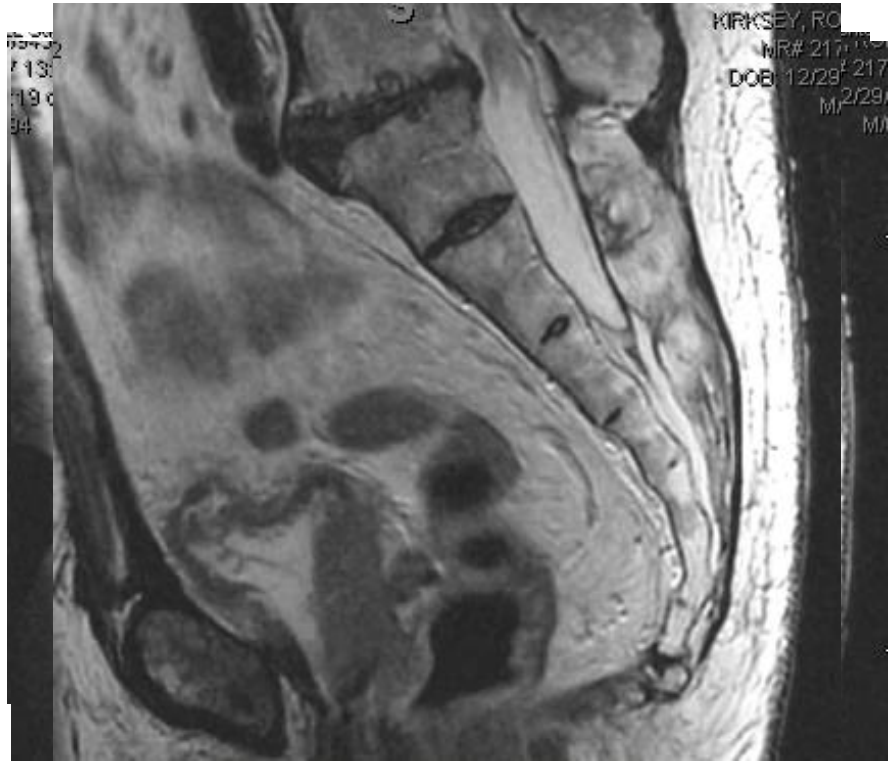
What is the definition for carboplatin ineligibility?

So What Next

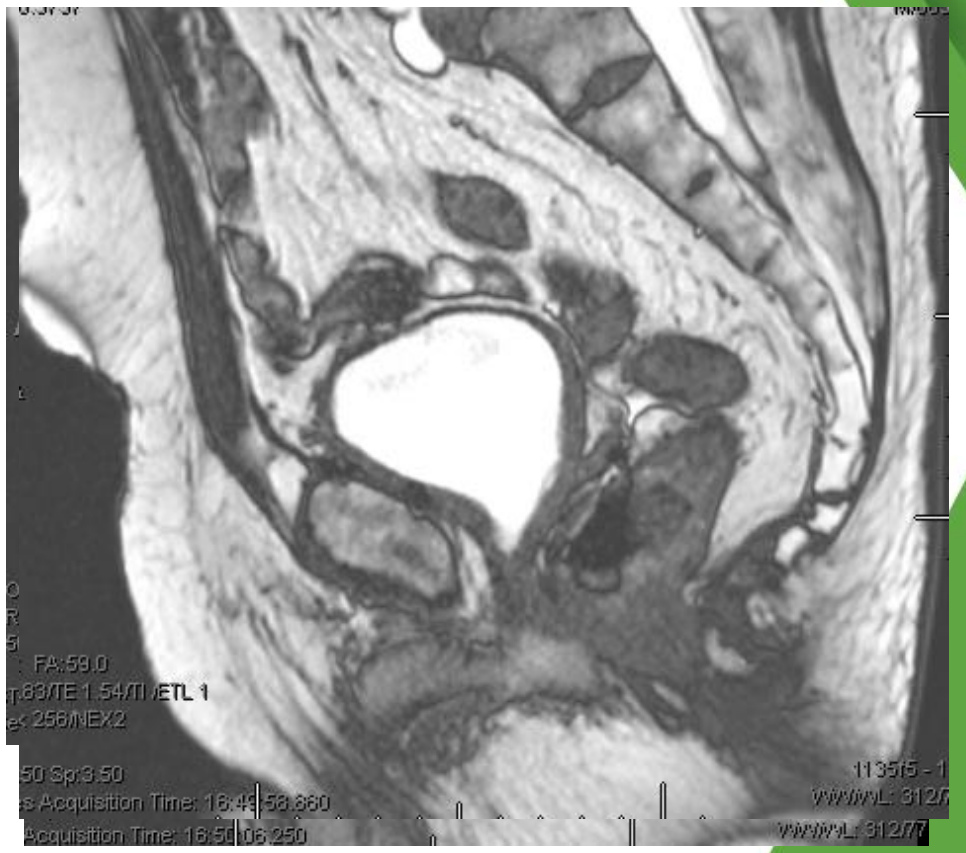
- On work up T4bN0M0 stage IV
- Ordered biomarkers, MSI status, molecular alterations panel, Her2neu status, PD-L1 testing
- Valve replaced
- Started on pembrolizumab

Patient started on immunotherapy

Pre-treatment



Post-treatment



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Repeat Cystoscopy with TURBT

OPERATIVE FINDINGS:

1. Urethra: No tumor noted
2. Ureteral orifices: Clear efflux at end of case from right.
3. Bladder: The bladder showed no tumors, stones, or other abnormalities of the mucosa. The area of the prior tumor appeared to have converted to fibrotic tissue and hence was biopsied to confirm no tumor histologically.
4. Size of tumor: Aggregate size of resection/biopsy site approximately 3 cm. Largest tumor/lesion size approximately 3 cm
5. EUA: some thickening in area of tumor.
6. Good hemostasis at end of procedure

SPECIMENS: Bladder tumor/biopsy specimens as noted.

DIAGNOSIS

(A) BLADDER BIOPSY TRIGONE:
Partially denudated urothelial mucosa with acute and chronic inflammation, no tumor present.
Muscularis propria is present.

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Unanswered Questions

- Does this patient need a cystectomy? Would this warrant a rectal resection if so?

- How long does the patient need to be continued on therapy?

- The patient receives pembrolizumab for 15 months and then calls the clinic with severe fatigue, excessive urination
- In the EC found to have glucose of 569, sodium of 128, anion gap of 17
- What is the likely diagnosis?

- In patients diagnosed with immune mediated endocrinopathies what is your approach?

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Case 3: Fatal Toxicity

- 69-year-old man with metastatic bladder cancer s/p gemcitabine and carboplatin chemotherapy
- PMH: renal insufficiency with GFR 40 ml/min due to h/o obstructive uropathy, CAD s/p CABG 5 years ago, HTN, DM2 on oral agents
- No autoimmune disease, though admits to irritable bowel symptoms, last colonoscopy normal 4 years ago.

- Pt had partial response to gemcitabine and carboplatin chemotherapy, and stopped treatment and was observed

Case 3: Continued

- Scans showed increased size of multiple pulmonary metastases, previously subcentimeter, and new retroperitoneal lymphadenopathy

- After discussion of risks and benefits, pt was initiated on pembrolizumab monotherapy 200 mg IV q3 weeks
- Imaging after 3 cycles showed response, that was durable
- After 2 years of treatment, pembrolizumab was stopped

Case 3: continued

- The patient was subsequently lost to follow up and did not return calls
- 9 months after stopping pembrolizumab, the patient was brought by ambulance to the hospital ER with hypotension, dehydration, and a history of 10 days of progressively worsening diarrhea and abdominal pain

- Pt was volume resuscitated and was found to be in acute renal failure with a creatinine of 4.5. A non-contrast CT showed pan-colitis of the colon several areas of colonic perforation.

Case 3: continued

- The patient was taken emergently to the OR for a colectomy and received high dose corticosteroids.
- The patient developed severe sepsis postoperatively and expired 5 days later.

Delayed toxicity

- Autoimmune toxicity occurs predominantly during treatment
  - late toxicity occurs comparatively infrequently
- These can affect any organ system but most frequent are colitis, rash, and pneumonitis
- Up to 5% of patients may be affected post-cessation of treatment
- Early recognition of these late adverse events are needed to ensure optimal outcomes

Owen et al. Ann Oncol 2021

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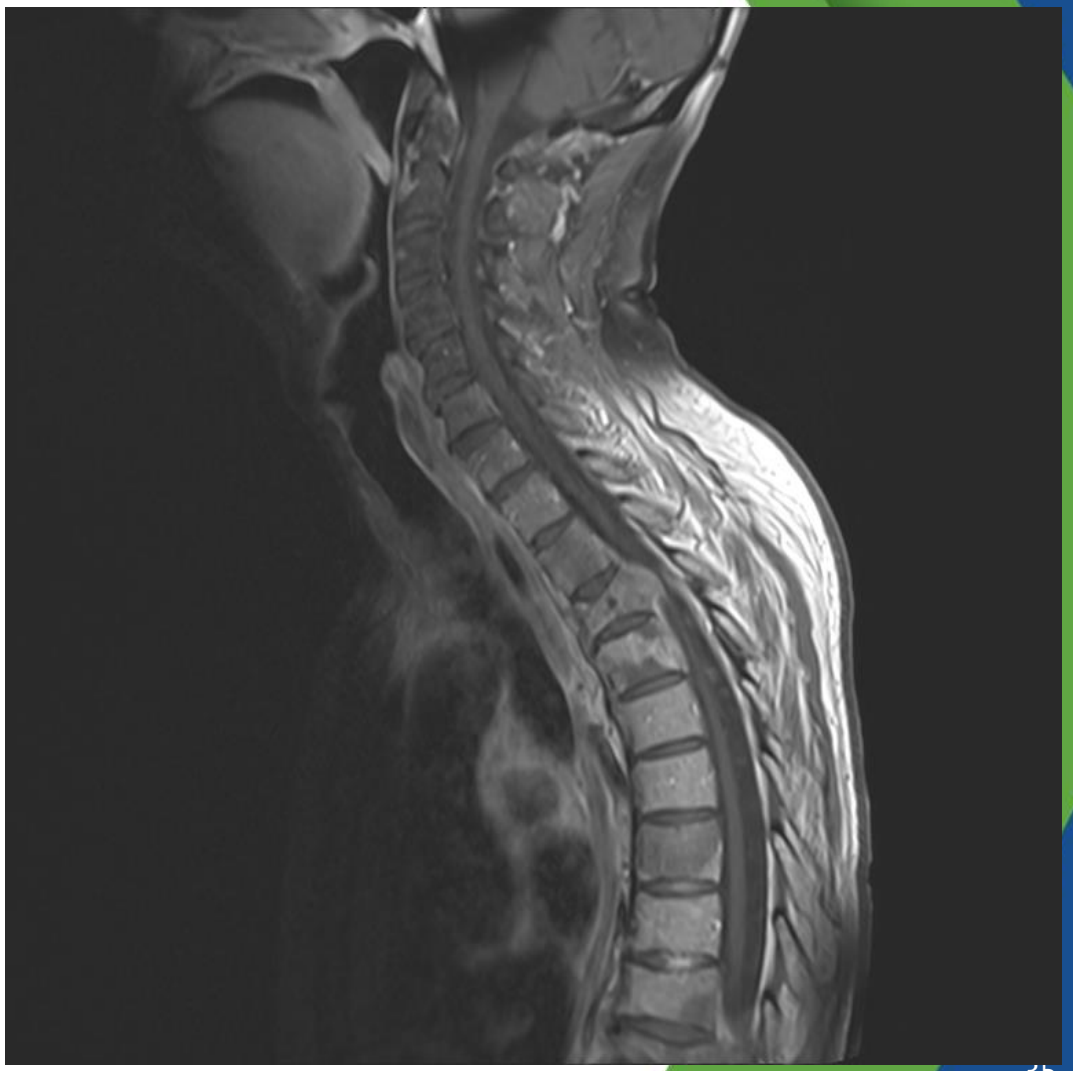
Case 4: An aggressive presentation

- A 70 yo male, never smoker, presents with gross hematuria and is found to have evidence of a mid ureteral tumor and evidence of hepatic metastases on presentation along with bone metastases and lung metastases



Case 4 continued

- The patient admitted with spinal cord compression and provided with steroids/XRT from T1-T12.
- He presents to the office 10 days after completion of XRT.
- His GFR is 80ml/min, ECOG PS is 2, he has no significant neuropathy, he reports no hearing deficits.
- He has significant support at home with his wife and two adult children that live within 2 city blocks.

What would you offer as treatment at this time?

A. Gemcitabine/carboplatin
B. Gemcitabine/cisplatin
C. Pembrolizumab
D. Dose dense MVAC
E. Atezolizumab

Case 4 continued

- The patient receives 3 cycles of gemcitabine/cisplatin and has evidence of continued disease progression in his liver. His ECOG PS is 3. Hgb is 8.5g/dL. He wishes to try additional therapy.
- On IHC testing of his initial liver metastasis biopsy, he was found a PDL-1 CPS score of 0. He was found to have evidence of MLH1/PMS2 loss, his molecular testing revealed the following:

AKT1	STK	CREBBP	FGF19	HRAS	MAPK1	NBN	PIK3CB	RAF1	SPOP
AKT2	CBL	CSF1R	FGF3	IDH1	MAX	NF1	PIK3R1	RB1	SRC
AKT3	CCND1	CTNNB1	FGFR1	IDH2	MDM2	NF2	PMS2	RET	STAT3
ALK	CCND2	DDR2	FGFR2	IGF1R	MDM4	NFE2L2	POLE	RHEB	STK11
AR	CCND3	EGFR	FGFR3	JAK1	MED12	NOTCH1	PPARG	RHOA	TERT
ARAF	CCNE1	ERBB2	FGFR4	JAK2	MET	NOTCH2	PPP2R1A	RICTOR	TOP1
ARID1A	CDK12	ERBB3	FLT3	JAK3	MLH1	NOTCH3	PTCH1	RNF43	TP53
ATM	CDK2	ERBB4	FOXL2	KDR	MRE11A	NRAS	PTEN	ROS1	TSC1
ATR	CDK4	ERCC2	GATA2	KIT	MSH2	NTRK1	PTPN11	SETD2	TSC2
ATRX	CDK6	ESR1	GNA11	KNSTRN	MSH6	NTRK2	RAC1	SF3B1	U2AF1
AXL	CDKN1B	EZH2	GNAQ	KRAS	MTOR	NTRK3	RAD50	SLX4	XPO1
BAP1	CDKN2A	FANCA	GNAS	MAGOH	MYC	PALB2	RAD51	SMAD4	
BRAF	CDKN2B	FANCD2	H3F3A	MAP2K1	MYCL	PDGFRA	RAD51B	SMARCA4	
BRCA1	CHEK1	FANCI	HIST1H3B	MAP2K2	MYCN	PDGFRB	RAD51C	SMARCB1	
BRCA2	CHEK2	FBXW7	HNF1A	MAP2K4	MYD88	PIK3CA	RAD51D	SMO	

FINDINGS:

Copy Number Variations

None identified

Somatic Mutations

Gene	Standardized Nomenclature (HGVS)	Location	DNA change	Protein change	COSMIC ID
ATRX	NM_000489.3(ATRX):c.3465_3467del p.S1156del	Exon 9	Deletion	Deletion	
CREBBP	NM_004380.2(CREBBP):c.6395G>A p.G2132D	Exon 31	SNV	Missense	
CREBBP	NM_004380.2(CREBBP):c.2114-1G>T	Splice	Splice?	Unknown	
CREBBP	NM_004380.2(CREBBP):c.5730A>C p.Q1910H	Exon 31	SNV	Missense	
FGFR3	NM_000142.4(FGFR3):c.742C>T p.R248C	Exon 7	SNV	Missense	COSM714
MLH1	NM_000249.3(MLH1):c.546-1G>C	Splice	Splice?	Unknown	
NOTCH3	NM_000435.2(NOTCH3):c.4556T>C p.L1519P	Exon 25	SNV	Missense	
RAD50	NM_005732.3(RAD50):c.2852T>G p.V951G	Exon 18	SNV	Missense	
SETD2	NM_014159.6(SETD2):c.5219G>T p.R1740L	Exon 10	SNV	Missense	

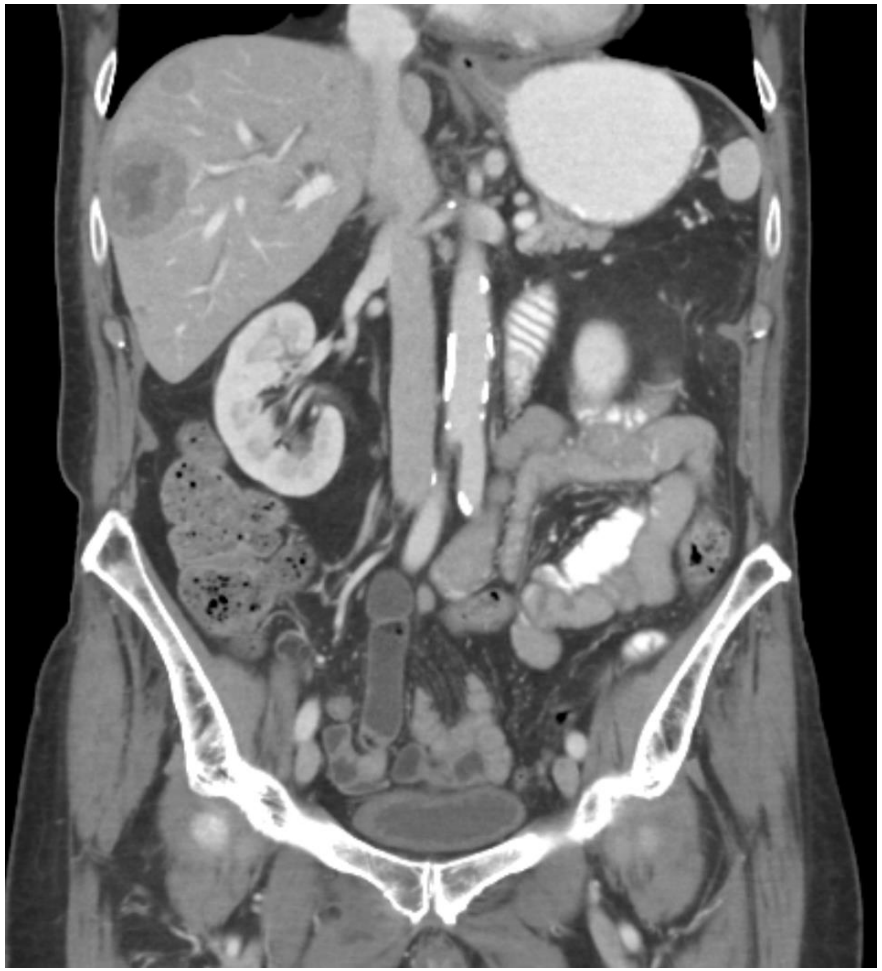
In this patient scenario (cisplatin refractory, ECOG PS 3, PDL-1 negative, dMMR, FGFR3 mutated), what would you offer at this time?

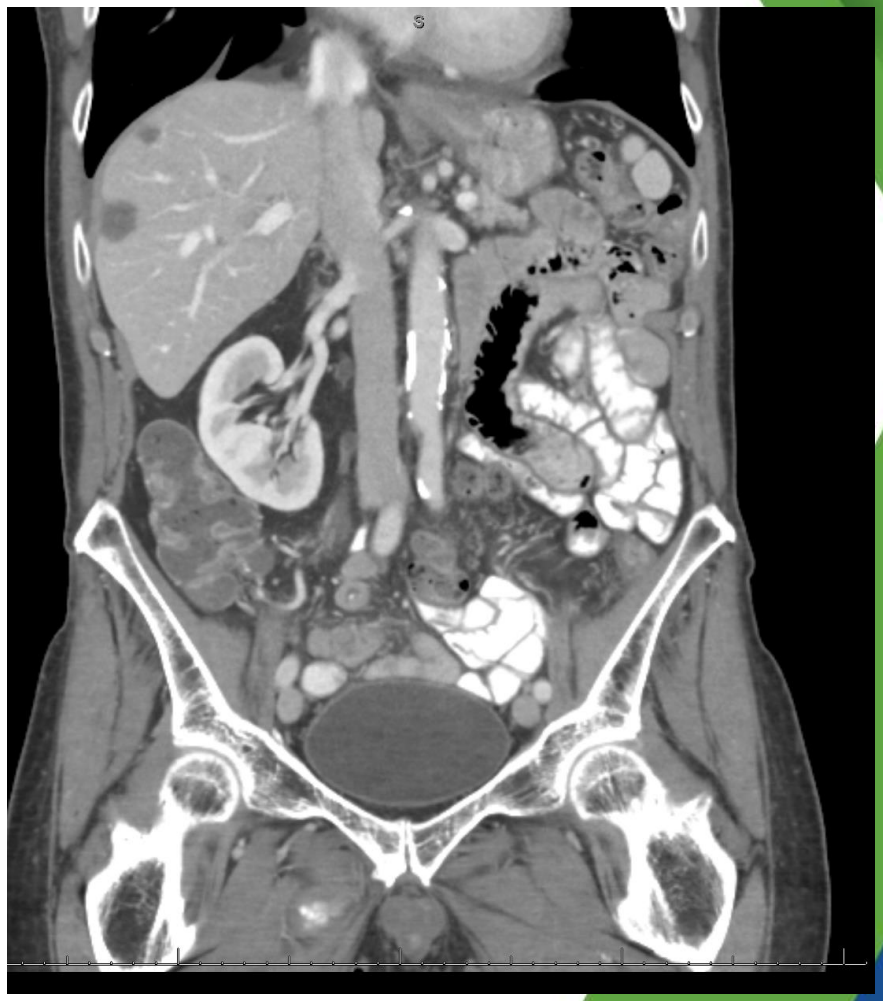
A. Best supportive care/hospice
B. Pembrolizumab
C. Avelumab
D. Enfortumumab vedotin
E. Erdafitinib

If this same patient did not have MMR deficiency but the same characteristics (i.e. cisplatin refractory, PDL-1 negative, FGFR3 mutation, ECOG PS 3), what would you offer?

A. Best supportive care/hospice
B. Pembrolizumab
C. Avelumab
D. Enfortumumab vedotin
E. Erdafitinib

- The patient is started on pembrolizumab. He returns in 3 weeks and clinically feels improved. He receives 3 doses and restaging finds evidence of response.





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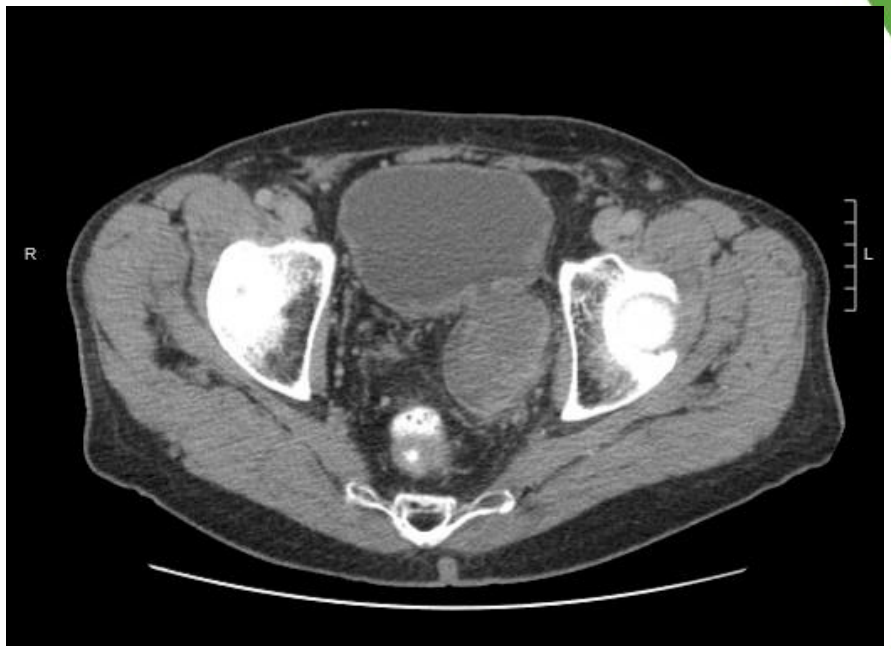
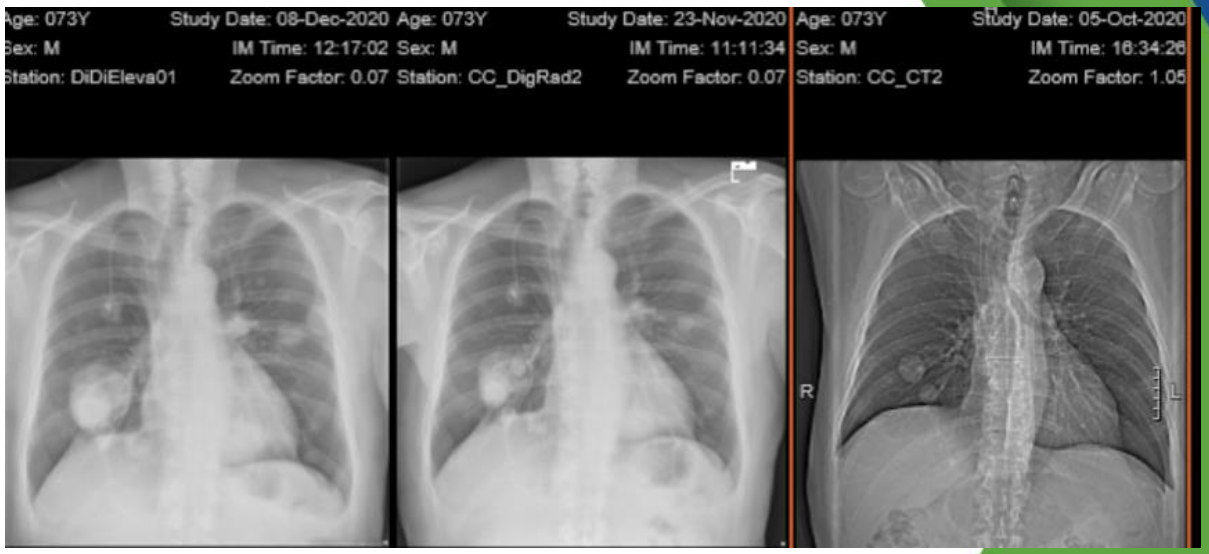
Case 5: “Too Many Times to Count”

- A 73 yo male, never smoker, presented with cloudy urine and weight loss and was found to have a muscle invasive urothelial cancer involving a bladder diverticulum.
- PMH: otherwise healthy
- He was treated with neoadjuvant ddMVACx4 followed by RC/PLND; ypT0N0 urothelial carcinoma.



Case 5: First and Second line treatment

- He then had path confirmation of metastatic disease 18months later
- Treatment in the 1st line metastatic setting:
  - Planned for Gemcitabine and Cisplatin with rotation to Avelumab per Javelin-Bladder 100 data
  - He developed clinical and radiographic progression at 3cycles of Gem – Cis
- Treatment in the 2nd line setting:
  - Anti-PD-1 IV every 3 weeks



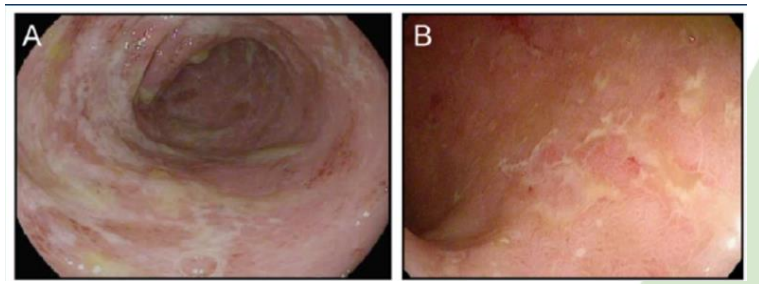
Case 5: Adverse Events on CPI

- Adverse Events while on anti-PD1 therapy:
  - Week 15 : Profuse diarrhea, “*too many times to count*” and crampy abdominal pain.

- Workup: Acute abdominal series (X-rays) show non-specific bowel gas pattern and no free air

Case 5: Immune Irritability

- Working up Diarrhea in the patient on a Checkpoint inhibitor:
  - Infectious vs immune mediated colitis
- Workup:
  - Stool sample, c diff, O&P, leuks, culture
  - Colonoscopy: focal erosion in the TI with chronic inflammation. ***Chronic active colitis***
- Treatment:
  - Hold anti- PD1 therapy
  - Hospitalization, IVF
  - Methylpred 2mg/kg/day initial, then Prednisone 100 with slow taper of > 4wks (with prophylaxis- Bactrim, fluconazole)
  - Stools became formed and baseline (1-2 per day) within ~7 days



CPI-associated colitis Ulcerative colitis

Dougan M. *Frontiers in Immunology,* 2017

Case 5: Immune Irritability

- After 2 weeks, while on the Prednisone taper, he developed diarrhea 4 times per day with distention and gas.
- Workup ~ may include stool studies again (such as c diff, etc if warranted)
- Escalate immunosuppression:
  - Check Quantiferon gold, check LFTs
  - Infliximab 5mg/kg is given
- Rapid resolution of the diarrhea and the taper is continued for a total of 40 days.
- The patient complains of insomnia and combative behavior and referred to a psychiatrist
- Given anxiolytics with some improvement

Case 5: Immune Irritability

- SIX weeks later, after finishing the steroid taper, scans show an excellent response to treatment, partial response in all areas including LNs and Pulmonary masses.
- A few days later he comes to the ED with high fever, photophobia, confusion, delirium. He also had a severe headache that began a few days prior.
- What's going on now?

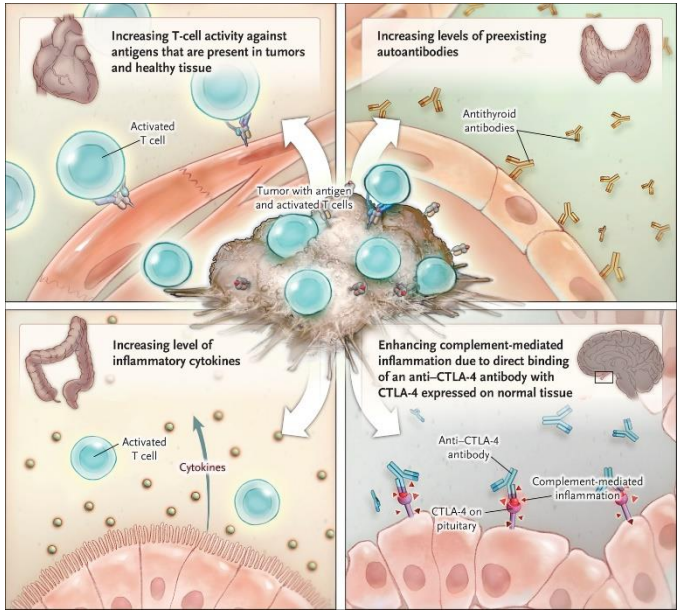
Case 5: Immune Irritability

- Differential:
  - Brain mets, infection (meningo or encephalitis)
  - Immune mediated hypophysitis with pituitary edema
- Workup:
  - Hormone panel, blood and urine cultures
  - MRI brain and sella
  - Results: Suppressed TSH, ACTH, FT4, cortisol, prolactin, and MRI sella showed enlarged pituitary.
- Treatment:
  - Hospitalization, endocrine consult, hormone suppl

Case 5: Immune Irritability

- He is placed on hydrocortisone THEN synthroid, IN THAT ORDER, (avoid adrenal crisis) based on endocrinologist's consultation.
- Headache resolved after 48hrs
- Disease has a complete response at wk 36

Framework for Considering irAE



Mechanism of irAE	Examples	Treatment
Direct binding of ICI antibody to tissue and complement binding	Hypophysitis	Hormone replacement, cortisol, thyroxine, T
T cell mediated destruction (disinhibited)	T1DM (panc islets)	Replacement
T cell cytokine secretion	Colitis/enterocolitis Hepatitis Myocarditis	Interrupt, discontinue Glucocorticoids, Pulse dose Mycophenolate, infliximab (not for hepatitis), Vedolizumab Tocilizumab CTLA agonist : abatacept, Tacrolimus IVIG
B cell, expansion of autoantibodies	Hashimotos (anti Bullous pemphigoid (anti PB180) Neuromusc syndromes (many, but likely not all)	Hormone replacement IVIG Plasmapheresis/PLEX Rituxumab Alemtuzumab

Sullivan and Weber, *Nat Rev DD* 2021
Postow et al. *NEJM* 2018
Iwama et al *Sci Trn Med* 2014
Johnson et al *NEJM* 2016

Key Takeaways

- Patients with bladder cancer have benefited from Immunotherapy approaches for over 6 decades and now plays an important part of the paradigm for treatment from early- to late-stage disease
- Optimal management of Immunotherapy adverse events depends on patient education and guidance on reporting symptoms, a high index of suspicion, and coordinated care across specialties
- As symptoms may involve any tissue or organ, and present with varying degrees of severity, guideline-based care is recommended for diagnosis and management to ultimately maximize the patient's safety as well as realize immunotherapy- related benefits!

Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

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Thank you for attending the webinar!

Questions or comments: connectED@sitcancer.org

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