



Case discussions

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1



Case #1

CC: 46 yo M with renal mass

HPI: hematuria (pink urine) x1. One prior episode 1 year ago

PMHx, FHx, SHx, Meds, Allergies: non-contributory

Exam: ECOG PS 0.

Lab: Normal CBC, CMP. Urinalysis with 2+ blood

Imaging: CT abdomen/pelvis with right renal mass

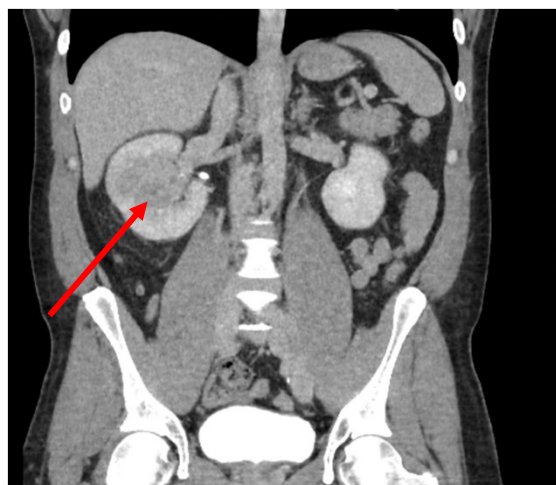
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2

Abdominal imaging



**7.7 x 5.7 x
7.0cm right
renal mass**

**Heterogeneous
enhancement
in renal vein**

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Case #1 continued

Imaging:

CT abdomen/pelvis with right renal mass (clinical T3)
CT chest with no evidence of metastatic disease

Surgery: right radical nephrectomy

Pathology:

pT3a Nx (right renal vein invasion) – **STAGE III**
clear cell, 25% sarcomatoid differentiation, grade 4
Negative margins. +Necrosis

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4



ADVANCES IN
Cancer 10
IMMUNOTHERAPY™ ANNIVERSARY

Discussion

**pT3a grade 4
ccRCC + sarcomatoid features**

How would you manage this patient?

Adjuvant pembrolizumab?

Adjuvant sunitinib?

Observation?

Other?

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5



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Adjuvant therapy for RCC in the cytokine era:

| Trial | Population | Arms | N | Primary | Outcome |
|------------------------|--|--------------------------------|-----|--------------|---------------|
| Porzsolt (1992) | pT3-4N0 or pTxN1-3 | IFN-α vs observation | 270 | TTF/survival | No difference |
| Trump et al (1996) | pT3-4aN0 or pTxN1-3 | L-IFN vs observation | 294 | Recurrence | No difference |
| Pizzocaro et al (2001) | pT3-4aN0 or pTxN1-3 | IFN-α vs observation | 247 | 5-year DFS | No difference |
| Messing et al (2003) | pT3-4aN0 or pTxN1-3 | IFN-α vs observation | 283 | 5-year OS | No difference |
| Clark et al (2003) | pT3b-4Nx or pTxN1-3 | IL-2 vs observation | 138 | 2-year DFS | No difference |
| Atzpodien et al (2005) | pT3b-4Nx or pTxN1-3 | IL-2/IFN-α/5-FU vs observation | 203 | 2-year DFS | No difference |
| Aitchison et al (2014) | pT3b-4Nx or pTxNa-2 or +margin/vascular invasion | IL-2/IFN-α/5-FU vs observation | 309 | 3-year DFS | No difference |

Cytokine therapy with no clear benefit in adjuvant setting

Adapted from:
McKay, ASCO Annual Meeting, 2021
Choueiri, IKCS, 2021

Porzsolt F, Proc Amer Soc Clin Oncol, 1992;
Trump, Proc Am Soc Clin Oncol, 1996;
Pizzocaro, J Clin Oncol, 2001;
Messing EM, J Clin Oncol, 2003;

Clark JL, J Clin Oncol, 2003;
Atzpodien, Br J Cancer, 2005;
Aitchison, Eur J Cancer, 2014

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6



Adjuvant therapy for RCC in the TKI era: *probably no benefit*

| Trial | Experimental Therapy | Therapy Duration, y | Completion | Eligibility | Histology | Enrollment | Endpoint | Statistically Significant? |
|----------------|------------------------|---------------------|-------------|--|-----------------------|------------|------------|----------------------------|
| ASSURE | Sunitinib or sorafenib | 1 | 2010 | ≥T1bNXM0 | Any | 1,943 | DFS | No |
| SORCE | Sorafenib | 3 | 2012 | Leibovich 3-11 | Any | 1,656 | DFS | No |
| S-TRAC* | Sunitinib | 1 | 2016 | High-risk per UISS | Clear cell RCC | 674 | DFS | Yes |
| PROTECT | Pazopanib | 1 | 2016 | pT2, pT3-4N0, or node-positive disease | Clear cell RCC | 1,538 | DFS | No |
| ATLAS | Axitinib | 3 | 2017 | pT2, pT3-4N0, or node-positive disease | Clear cell RCC | 592 | DFS | No |

Adapted from:
Kazarian, *Kidney Cancer*, 2021
McKay, *ASCO Annual Meeting*, 2021

***No overall survival benefit**

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7



Adjuvant therapy for RCC in the ICI era

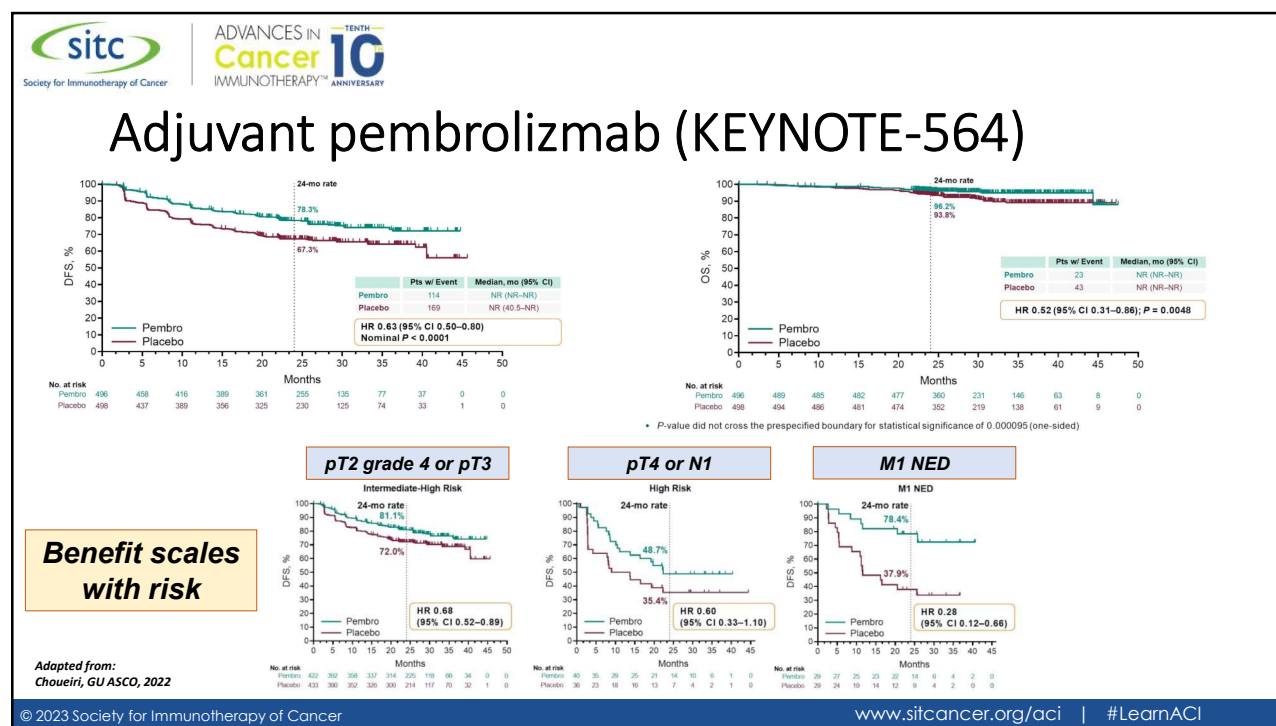
| PROSPER | Sample Size | Inclusion Criteria | Treatment | Primary Endpoint | Statistically Significant? |
|----------------------|-------------|--|---|------------------|--|
| Keynote-564 | 994 | pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell | Pembrolizumab vs placebo | DFS | YES DFS HR 0.63 OS HR: 0.52 (n.s.) |
| IMmotion010 | 778 | pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell | Atezolizumab vs. placebo | DFS | No |
| CheckMate-914 | 1600 | pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell | Nivolumab + ipilimumab vs. nivolumab + placebo vs. placebo (6 months) | DFS | No (Part A; nivo+ipi) |
| PROSPER | 766 | T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology | <u>Perioperative/adjuvant</u> nivolumab vs. observation | EFS | No |
| RAMPART | 1750 | Leibovich score 3-11; any RCC histology | Durvalumab + tremelimumab vs. durvalumab vs. observation | DFS, OS | 7/2024 |

Adapted from:
McKay, *ASCO Annual Meeting*, 2021
Choueiri, *IKCS*, 2021

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8



9

Case #1 wrap-up and conclusions

Case wrap-up:

- Patient received adjuvant pembrolizumab
- No toxicities; no recurrence

Conclusions:

- Pembrolizumab is approved as adjuvant therapy for intermediate-high risk, high risk, and M1 NED ccRCC
- DFS benefit is modest, scales with risk (highest risk = most benefit)
- OS *trending* positive, but not yet statistically significant
- Low but serious irAEs (adrenal insufficiency, type I DM) can occur

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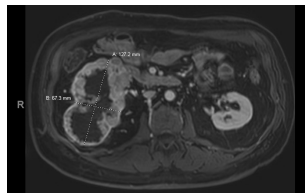
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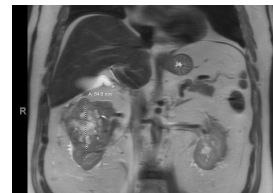
Case #2 - RCC case

- 70yo man presents with gross hematuria
- CT CAP: 13cm R renal cancer, hemorrhage into R ureter and bladder
- Undergoes R radical nephrectomy, pathology showed RCC, clear cell type, 11cm; extensive involvement of renal vein, segmental branches, renal sinus fat; rhabdoid and focal sarcomatoid differentiation, multifocal tumor necrosis; margins neg; pT3aNxMx
- 2 months after nephrectomy, starts adjuvant pembrolizumab

Initial presentation:

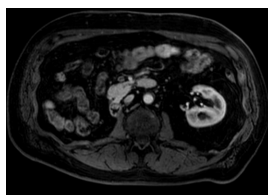


MRI T1 axial



MRI T2 coronal

Post-op:



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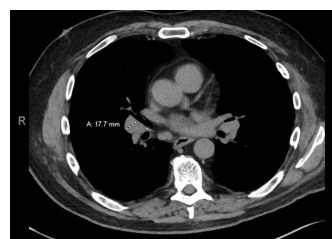
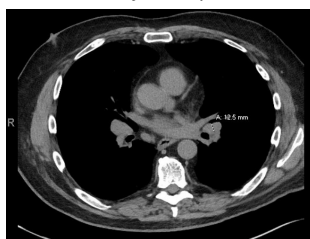
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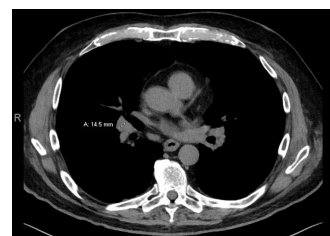
Case #2 continued

- 3 months into adjuvant pembrolizumab, bilateral hilar and mediastinal LNs increased
- Added axitinib to pembrolizumab
- 3 months later, bilateral hilar and mediastinal LNs incrementally improved

3 months after adjuvant pembrolizumab:



3 months after adding axitinib to pembrolizumab:



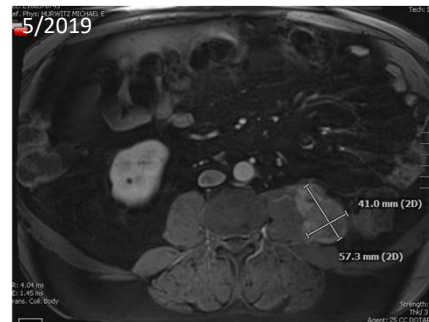
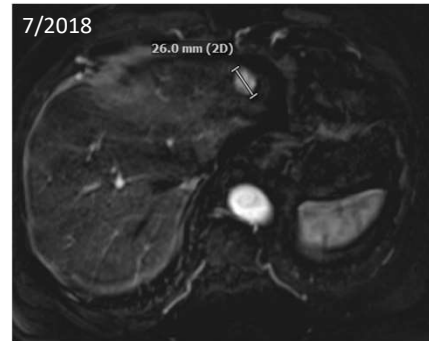
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12

Case #3

- 62 y.o. man developed gross hematuria
- 12/2017 left radical nephrectomy: 11 cm grade 2/4 ccRCC (pT2)
- 7/2018 new liver and retroperitoneal metastases
- 8/2018 ipi/nivo x4 followed by nivo monotherapy
- 10/2018 stable disease
- 2/2019 improvement in almost all lesions
- 5/2019 growing retroperitoneal masses
- 6-7/2019 RT to growing masses

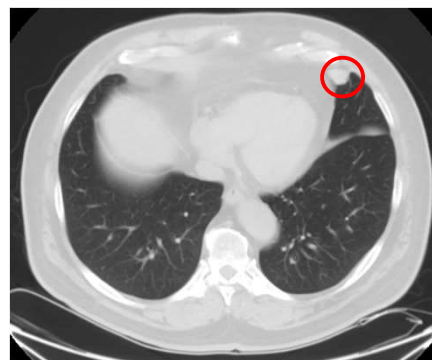


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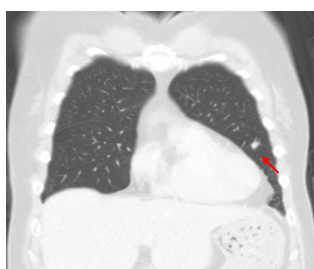
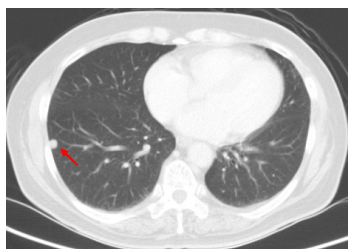
Case #3 continued

- 10/2021 growing lingula mass
- 1/2022 wedge resection of lingula mass: ccRCC
- 3/2023 3 growing lung metastases
- What's our next step for systemic management?



14

Case #4 - Slowly-progressive mRCC



63M with multifocal, pulmonary mets (bx +) 2 years after nephrectomy for locally-advanced clear cell RCC. IMDC favorable. Pt is asymptomatic with normal labs.

- Next step is.....
- 1. Continued observation
- 2. SBRT to all lung nodules
- 3. TKI monotherapy
- 4. Ipi/Nivo
- 5. IO/TKI

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15



Case #5 Urothelial

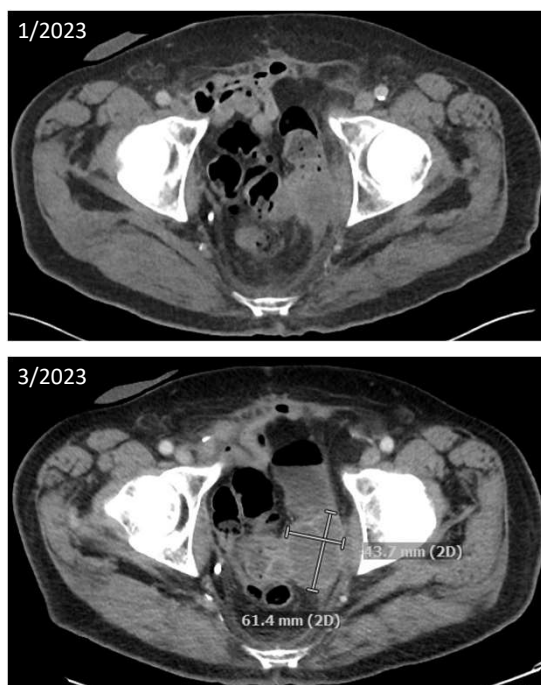
- 77 y.o. man
- 8/2021 CT AP (surveillance for prior Merkel Cell Ca): bladder mass
- 8/2021 TURB: T1
- 11-12/2021 BCG x6
- 2/2022 TURB: extensive disease though no clear muscle invasion
- 3/2022 cystectomy: TCC with sarcomatoid differentiation invading seminal vesicles, 1/3 LN+ and positive margins (T4aN1). **PDL1 90% in tumor cells and 50% in immune infiltrate**

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16

Case #5 continued

- 5-7/2022 Gem/cis (split dose) x4
- 10/2022 new pelvic soft tissue nodule
- 11/2022 biopsy: sarcomatoid TCC
- 12/2022 pembrolizumab 200 mg
- 1/2023 CT: new RP and pelvic adenopathy
- 2/2023 completed 4 cycles of pembrolizumab
- 3/2023 CT: growing adenopathy
- What's next for this patient?



17



Case Study #6 LN positive bladder cancer

75-year-old man who presents with hematuria noted to have widespread bladder tumor with high grade T1 urothelial carcinoma on TURBT but with scant muscle present in specimen. Subsequent CT CAP shows irregular bladder tumor with prostatic invasion and bilateral pelvic lymphadenopathy.

Patient has ECOG 1, no hearing loss or neuropathy, no cardiac history, CrCl 75 but with ongoing hematuria and hemoglobin 7.5g/dL.

How would you treat this patient?

AK

18

Case #7: Perioperative Therapy for UTUC

- 02/16/22 61 yoM developed gross hematuria
- 03/26/22 Recurrent gross hematuria - went to ED.
 - CTU: Urothelial thickening/filling defect involving the right ureteropelvic junction measuring approximately 1.9 cm in length and resulting in moderate right upstream hydronephrosis and delayed nephrogram. Findings are consistent with urothelial neoplasm.
- 03/31/22 Cysto, clot evac, R ureteroscopy and stent placement. No findings in the bladder. R retrograde pyelogram showed a prox ureteral filling defect. Biopsy taken and stent placed. Pathology: Inconclusive given limited sample, but worrisome for urothelial carcinoma. Cytology was suspicious for HGUC.
- 04/30/22 CT chest: No convincing evidence of metastatic disease above the diaphragm.
- What next?



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19

Case #7: Perioperative Therapy for UTUC

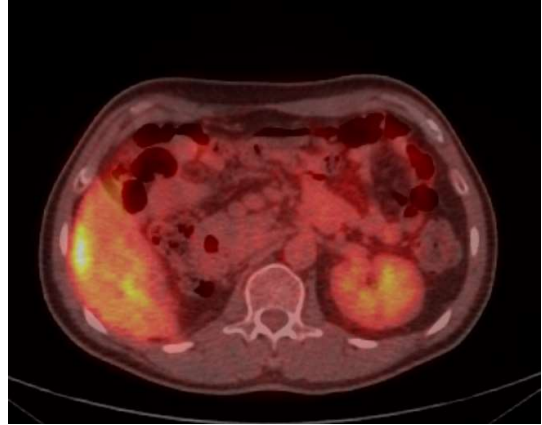
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- 04/30/22 CT chest: No convincing evidence of metastatic disease above the diaphragm.
- 05/05/22 Robotic R-sided nephroureterectomy with excision of bladder cuff. Pathology pT3N0(0/2)



20

Case #7 Continued: Advanced Therapy for UTUC

- RNU for UTUC: pT3N0M0
- Declined adjuvant chemotherapy and nivolumab
- 08/29/22 CT chest/urogram: new multiple liver lesions
- 09/08/22 PET/CT: Multiple hypermetabolic hepatic lesions and retroperitoneal lymph nodes concerning for metastatic disease.
- 09/21/22 Liver Biopsy: metastatic urothelial carcinoma
- 10/20/22 – 12/08/22 Received 3 cycles of carboplatin/gemcitabine
- 12/15/22 PET/CT: Progression of disease – new liver lesions
- What next?



21

Case #8 - Urothelial adjuvant case

67yo man presented with hematuria, on CT has bladder mass and hydronephrosis

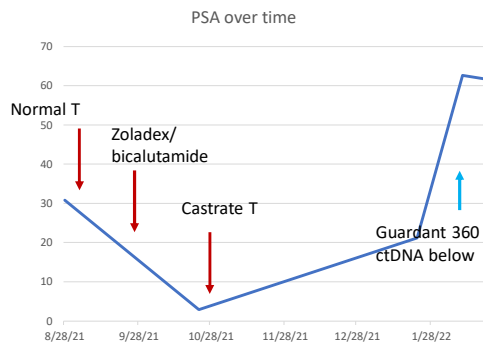
- TURBT: high grade urothelial cancer, papillary type, extensive invasion of muscularis propria; stent placed
- Received 3 cycles ddMVAC
- Radical cystectomy: pathology showed invasive HG UC invading R UVJ, R lateral wall, 6.5x4x1.8cm, invading perivesical soft tissue, margins negative; 2 LNs positive; pT3aN1
- Signatera negative for ctDNA
- Post op 1 month CT: s/p cystectomy, otherwise NED
- Would you offer adjuvant nivolumab?



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22

Case #9 – Prostate cancer



Bone scan 1/2022



81yo man, presented 8/2021 with PSA 30, normal T, bone mHSPC at baseline

History of dermatomyositis on weekly MTX

1/2022, increasing hip pain, PSA 21 → held bicalutamide

2/2022, PSA 62, severe pain (fentanyl TD) – 2nd opinion at UTSW

Guardant 360 ctDNA: MSI-high and MSH6 S702* loss; BRCA2 copy number loss;

AR mutations: W742C, W742L, M896V, P893S, S889G

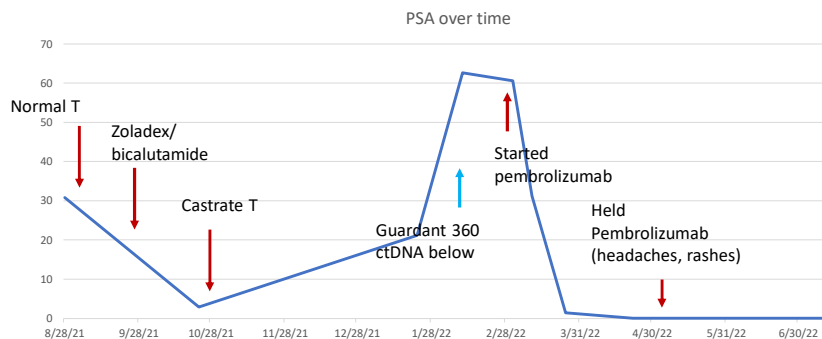
SMAD4 mutations: R361H, L540P, RB1 R661W; TMB 109 mut/Mb

What would you do?

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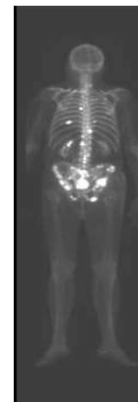
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Case #9 – Prostate cancer



Bone scan 1/2022

Bone scan 2/2023



81yo man, presented 8/2021 with PSA 30, normal T, bone mHSPC at baseline

History of dermatomyositis on weekly MTX

1/2022, increasing hip pain, PSA 21 → held bicalutamide

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Guardant 360 ctDNA: MSI-high and MSH6 S702* loss; BRCA2 copy number loss;

AR mutations: W742C, W742L, M896V, P893S, S889G

SMAD4 mutations: R361H, L540P, RB1 R661W; TMB 109 mut/Mb

Stopped methotrexate; 3/2022, C1 pembrolizumab

1 week later, PSA 31.19

3/2022, C2 pembrolizumab PSA 1.41 → 4/2022, C3 pembrolizumab PSA <0.05, developed headaches responsive to steroids

24



Case Study #10

75-year-old man diagnosed with muscle-invasive bladder cancer. He underwent neoadjuvant chemotherapy with ddMVAC x 4 cycles and radical cystectomy with pelvic lymph node dissection with pathology ypT3a ypN3 urothelial carcinoma. Started on adjuvant nivolumab and after 2 cycles noted to have disease progression with osseous metastases and pathological fracture.

What is your recommended treatment?

AK

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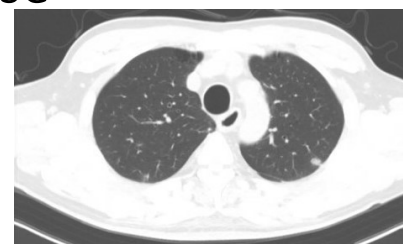
25



Case #11 Urothelial metastatic case

- 74yo man with metastatic urothelial cancer from lung nodule biopsy
- Received 6 cycles carboplatin/gemcitabine with partial response (one lung nodules 1.5cm from 3cm, some resolved)
- What would we recommend?

Baseline lung nodules



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26