Onco-Nephrology in the Era of Targeted Therapies
(case based approach)

Ilya Glezerman
Memorial Sloan Kettering Cancer Center
DISCLOSURE

Pfizer Stock
Targeted Therapy — "Proliferation of Agents"

Multiple tumor types are being treated with new medicines launched over the past five years. New Molecular Entity Launches 2010-14 by Indication.

Validated pathways reduce clinical trial risk, facilitating "fast follower" strategies with rising competitive intensity.

Pipeline by Number of Targeted Agents and Selected Pathways:

Phase II and above

- Breast Cancer
- NSCLC
- CRC
- Prostate Cancer
- HCC
- NHL
- Gastric Cancer
- Leukemia
- Pancreatic Cancer
- Renal Cancer
- Head, Neck (incl. Thyroid) Cancer

ANTI-ANGIOGENIC DRUGS AND THE KIDNEY
What is Angiogenesis?

- Angiogenesis essential for cancer growth
- Complex signaling process
- VEGF-important signal
- Angiogenesis-promoted by VEGF binding to VEGFR family (Tyrosine Kinase Receptors)

- VEGF in the Kidney
  - Expressed in podocytes
  - Signaling to glomerular endothelium via VEGFR2 and VEGFR3
  - Autocrine regulation of podocytes via VEGFR1
    - Cytosolic Ca levels
    - Macromolecular selectivity

VEGF AND BLOOD PRESSURE

- Endothelium-dependent vasorelaxation
- Upregulation of endothelial nitric oxide synthase
- VEGF inhibition exacerbates high salt intake HTN
- Prostacyclin (PGI2) release
- Capillary rarefaction??
- Increased large artery stiffness

ANTI-ANGIOGENIC AGENTS

- Anti-VEGF antibody-bevacizumab
- Anti-VEGFR-2 antibody-ramucirumab
- VEGF trap-soluble “decoy” receptor binding VEGF
- Multi-target Tyrosine Kinase inhibitors (small molecule mTKI)
CASE PRESENTATION

59 y.o. male with h/o glioblastoma treated with temozolomide and bevacizumab (10mg/kg biweekly). Pt’s baseline SCr was 1.0 mg/dl.

Four months after initiation of chemotherapy patient developed HTN, AKI (SCr 1.9mg/dl), severe thrombocytopenia and anemia, high LDH and undetectable haptoglobin. UA was bland and Uprot/Ucreat<0.1.

Kidney biopsy showed TMA with mesangiolysis and microthrombi. Despite d/c of bevacizumab pt progressed to ESRD
Deletion of VEGF gene in podocytes at 3, 12, 24 weeks
Similar findings at all time points
Proteinuria, HTN; schistocytes
Thrombotic microangiopathy-podocyte effacement; intra glomerular thrombi; endotheliosis.

RENAL EFFECTS OF ANTI-ANGIOGENIC AGENTS

- Hypertension
- Proteinuria/nephrotic syndrome
- Thrombotic microangiopathy
- AIN
ANTI-VEGF THERAPIES AND HTN

• Bevacizumab-1850 pts meta-analysis
  • Incidence
    • Low Dose (<7.5mg/kg)- 2.7%-32% RR of 3.0 (95% CI 2.2-4.2)
    • High Dose (>10mg/kg) -17.6%-36% RR of 7.5 (95% CI 4.2-13.4)
      • Grade III (150/100; requiring ≥2 drug or more intense therapy than baseline)
        • Low Dose-8.7%
        • High Dose -16%
        • Controls – 1.7%

• Sunitinib (mTKI)-meta-analysis of 4,609 pts (RCC and GIST)
  • Incidence of HTN
    • All grade-21% RR 3.44 (p=0.16)
    • High grade(>150/100 requiring ≥2 drugs)-6.8% RR 22.72 (p<0.001)

• VEGF-Trap
  • All grade 42.4% OR 4.47, p < 0.001
  • High Grade 17.4% OR 4.97 p < 0.001

Zhu X. AJKD. 2007; Vol 49 (2): 186-193
**ANTI-VEGF THERAPIES AND PROTEINURIA**

- Bevacizumab-Meta Analysis – 12,268 pts (proteinuria not listed at baseline)
  - All grade 13.3% RR 2.79 (P<0.001)
  - Grades III/IV (>3.5gm/24hr or 4+dipstick) 2.2% RR-4.79 (P>0.001)
  - Nephrotic syndrome- 0.8% RR 7.78 (P=0.006)
  - No PFS or OS benefit

- Aflibercept-4,596 pts
  - All grade 33.9% (RR = 1.41, 95% CI: 1.13–1.77)
  - High grade 7.9%(RR = 6.18, 95% CI: 3.78–10.12)

- TKI
  - Seven patients with pre-eclampsia like syndrome
    - HTN-new or exacerbated
    - Proteinuria (mean 3.8 g/g)
    - Edema
    - Resolution after d/c of TKI
  - 60 patients treated with axitinib for Thyroid CA
    - All grades-18%
    - Grade III/IV-5%

Patel A. JNCI, Vol 100(4): 282-284
Renal Pathology Findings
VEGF Antagonists

8-year Observational Study – 100 pts

- 73pt-TMA
  - 61 on Bevacizumab/5 VEGF Trap/ 3 TKI
  - HTN 83%
  - MDRD mean 71.33±28.6
  - Proteinuria (g/dl) 2.58±2.64 (proteinuria <1g/d-31.5%)
  - Onset of renal disease (median) 3 mo (0.25-26)
  - 50% renally localized
  - 3/4 re-challenged w/o worsening renal function

- 21pt MCN/cFSGS
  - 21 TKI/ 1 Bevacizumab
  - HTN 48.1%
  - MDRD mean 68.88 ±28.75
  - Proteinuria 3.15±3.86 (proteinuria <1g/d-29.6%)
  - Onset of renal disease (median) 2 mo (0.25-30)

AIN and anti-VEGF therapy

- Literature Review
- Biopsy proven
  - Bevacizumab-2 case reports
  - Sunitinib-2 cases
  - Sorafenib-1 case
  - Cediranib-1 case (concurrent FSGS)
- Clinically diagnosed
  - Sunitinib-3 case

TKI AND ANTI-VEGF ANTIBODY

- Sunitinib and Bevacizumab
- 26 patient
  - Grade III-IV
    - HTN-60%
    - proteinuria-36%
    - thrombocytopenia-24%
  - 5 patients developed MAHA; HTN; Anemia; AKI
    - 2 patients with severe symptoms incl. RPLS
    - One pt tolerated re-challenge with single agent TKI for 8mo.
- 88% of patients s/p nephrectomy-hyperfiltration injury?

MANAGEMENT OF COMPLICATIONS OF ANTI-ANGIOGENESIS THERAPY

- Monitor BP and proteinuria routinely
- Discontinue if HTN develops?
- HTN may be a marker of response to therapy
  - mRCC pts
    - OS was 30.9 months, 95% CI = 27.9 to 33.7 vs 7.2 months, 95% CI = 5.6 to 10.7 months; $P < .001$
  - NSCLC
    - Chemo vs Chemo+Bev
      - Figure 1 $p=0.0002$

Rini B., et al. JNCI (2011) 103(9): 763-773
MANAGEMENT OF COMPLICATIONS OF ANTI-ANGIOGENESIS THERAPY (cont)

- How to treat HTN?
- ACEI/ARB also decrease proteinuria
- Improved survival in mRCC pts
  - 1487 Users vs. 3249 Non-users
    - OS 26.68 vs 17.05 months \( p=0.009 \)
- Synergistic effect with VEGF TKI
  - 1192 Users vs 2319 Non-users
    - OS 31.12 vs 20.21 months \( p<0.0001 \)
- VEGF TKI Therapy pts who developed HTN
  - 982 users vs 1484 non-users
    - OS 33.19 vs 24.64 months \( p=0.0004 \)

NEPHROTIC RANGE PROTEINURIA AND BEVACIZUMAB (CASE)

• 62 yo female with mBC in 2005 (bone/lung)
• Started on bevacizumab 15mg/kg
• New onset HTN requiring 2 >meds
• 36 months-U prot/U creat ratio >3 despite ACEI/ARB
• No biopsy
• Able to continue bevacizumab with dose adjustment 7.5mg/kg
• Discontinued due to POD in 2011
• HTN and proteinuria resolved
• Pt remains alive
MANAGEMENT OF COMPLICATIONS OF ANTI-ANGIOGENESIS THERAPY

• Patients with sub nephrotic range proteinuria may have TMA/FSGS on biopsy

• In patients on intermittent regimens—HTN and proteinuria may be intermittent

• HTN and proteinuria resolves after discontinuation

• Be aware that thrombocytopenia and anemia may also be early signs of TMA (not just due to chemotherapy). Obtain LDH, haptoglobin, and peripheral smear.

• Asymptomatic nephrotic range proteinuria—cont. chemo?

• When to stop?
  • Nephrotic syndrome
  • TMA with MAHA and AKI
Immunotherapy—"Pipeline"

Molecular Mechanisms of CheckPoint Inhibition

- Checkpoint Pathways-PD-1
- Checkpoint Pathway-CTLA

Postow et al. JCO 33 (17) 2015
Case: PD-1 inhibitor

- 71 y.o. female with Met NSCLC with baseline sCr of 0.8mg/dL received treatment with pemetrexed (500mg/m²); Cisplatin (75mg/m²) and nivolumab 10mg/kg for 3 cycles (3rd dose of Cisplatin was held due to CG CrCl of 42ml/min

- Two weeks after last dose of Chemo (six weeks after last cisplatin) pt presented with dysphagia to liquids.

- On admission
  - sCreat 4.1mg/dL
  - Home meds: Levothyroxine, omeprazole (started 3 mos prior), LMWH
  - BP 118/84, P 103 RR 18
  - PE was unremarkable
  - US-no obstruction
  - UA-WBC>50/HPF; U Prot/U Creat 0.7
Case: PD-1 (cont.)

- Patient started on Prednisone 60mg daily-2 weeks followed by a taper (red arrow)

- Remained on various doses of prednisone (20-40mg) for non renal indications for most of post AKI course until death due to POD 18 mos later
Renal PD-1L Expression


PD-L constitutively expressed on proximal tubular epithelial cells
PD-1 Role in Tubulo-interstitial Inflammation

- Adriamycin nephrosis (AN)-murine and rat model
- PD-1 cortical mRNA increases on days 3,7,14,28
- Strong cortical interstitium immunohistochemistry staining for PD-1 in AN
- Administration of PD-1 antibody worsened tubulo-interstitial disease

CTLA-4 in cold ischemia/reperfusion injury

Incidence of AKI

- CTCAE V 4.0

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Risk of IRAE by Agent

Cortazar F. et al. KI, 2016
# Renal iRAE-Cumulative Dose

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<tr>
<th>Pt</th>
<th>Age/sex</th>
<th>Malignancy</th>
<th>SCr/eGFR (dipstick)</th>
<th>Proteinuria</th>
<th>Comorbidities</th>
<th>Checkpoint inhibitor regimen</th>
<th>Cumulative dose</th>
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<td>1</td>
<td>70/M</td>
<td>Melanoma</td>
<td>0.9/86</td>
<td>NA</td>
<td>Asthma, osteoarthritis, basal cell carcinoma, and squamous cell carcinoma</td>
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<td>2</td>
<td>64/M</td>
<td>Melanoma</td>
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<td>CKD, hypertension, and BPH</td>
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<td>74/M</td>
<td>Melanoma</td>
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<td>Hypertension</td>
<td>Ipi 3 mg/kg + Nivo 0.3 mg/kg q 3 wks × 2, followed by Ipi 3 mg/kg × 1 (7.5 wks later)</td>
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<td>62/F</td>
<td>Melanoma</td>
<td>0.7/92</td>
<td>Trace</td>
<td>CHF and atrial fibrillation</td>
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<td>Nivo 0.6 mg/kg</td>
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<td>Ipi 9 mg/kg</td>
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Cortazar F. et al. KI, 2016

Memorial Sloan Kettering Cancer Center
Clinical Features-Renal IRAE

Cortazar F. et al. KI, 2016

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<tr>
<th>Pt</th>
<th>5–10 WBCs</th>
<th>Proteinuria (dipstick/UPCR)</th>
<th>Day of AKI</th>
<th>Days since last dose of CP</th>
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<th>HTN</th>
<th>Oliguria</th>
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<td>0–3 RBCs</td>
<td>2+–0.12</td>
<td>42</td>
<td>21</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>R 12.4</td>
<td>L 13.0</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>8 RBCs</td>
<td>1+/0.73</td>
<td>120</td>
<td>57</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 8.0</td>
<td>L 10.0</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3 WBCs</td>
<td>3 RBCs</td>
<td>1+/0.18</td>
<td>18</td>
<td>14.7% No No</td>
<td>No</td>
<td>NA</td>
<td>13.3</td>
<td>3 HD treatments starting on day 21</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–2 RBCs</td>
<td>50–100 WBCs</td>
<td>21</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 10.7</td>
<td>L 11.9</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>20–50 WBCs</td>
<td>0–2 RBCs</td>
<td>21</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 11.9–13.1</td>
<td>3.6–7.3</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

Cortazar F. et al. KI, 2016
# PD-1 Inhibitors Cohort IRAE

<table>
<thead>
<tr>
<th>Case</th>
<th>Pt Age, y</th>
<th>Sex</th>
<th>Comorbid Conditions</th>
<th>Δ In Kidney Function</th>
<th>Laboratory Findings</th>
<th>Timing of AKI</th>
<th>NSCLC Type</th>
<th>Prior Systemic Therapy</th>
<th>Other Potential Nephrotoxins</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>M</td>
<td>HTN, CKD2, prior tobacco use, Afb, treated laryngeal carcinoma</td>
<td>Scr: 1.3–1.9; eGFR: 57–35</td>
<td>Eos: 7%; UPCR: 0.1 mg/mg; bland urine sediment</td>
<td>11 mo after nivolumab started</td>
<td>Advanced squamous</td>
<td>1: cisplatin/vinorelbine, cetuximab; 2: docetaxel; 3: erlotinib</td>
<td>Omoprazole, furacémide (both preceding nivolumab by &gt;1 y)</td>
<td>Omeprazole held; nivolumab continued, w/ Scr varying from 1.4 to 1.7 for 8 mo; Scr ↓ to pre-nivolumab baseline 6 mo after nivolumab held</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>M</td>
<td>HTN, T2DM, prior tobacco use</td>
<td>Scr: 0.9–1.8; eGFR: &gt;60 to 37</td>
<td>Eos: 6%; no protein on UA; sediment: 2 white blood cells/HPF</td>
<td>16 mo after nivolumab started (5 mo after starting celecoxib)</td>
<td>Advanced adenocarcinoma</td>
<td>1: cisplatin, etoposide; 2: docetaxel; 3: pemetrexed/bevacizumab</td>
<td>Omoprazole (preceding nivolumab by &gt;1 y), celecoxib (begun 11 mo after starting nivolumab)</td>
<td>Nivolumab and celecoxib held; treated w/ 1-mo steroid taper, w/ normalization of Scr</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>HTN, prior tobacco use, hypothyroid</td>
<td>Scr: 0.9–5.5; eGFR: &gt;60</td>
<td>Eos: 3%; UPCR: 0.6 mg/mg; sediment: 2–5 white blood cells/HPF</td>
<td>10 mo after nivolumab started</td>
<td>Advanced adenocarcinoma</td>
<td>1: carboplatin/pemetrexed/bevacizumab; 2: docetaxel; 3: pemetrexed</td>
<td>Ibufrofen (intermittent use preceding nivolumab by &gt;1 y, w/ ↓ in use prior to AKI)</td>
<td>Ibufrofen held; treated w/ 1-mo steroid taper, w/ normalization of Scr</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>HTN, COPD, prior tobacco use</td>
<td>Scr: 1.0–1.9 &amp; 1.3–2.5; eGFR: 55–26 &amp; 41–19</td>
<td>No eosinophilia; no protein on UA; sediment: numerous white blood cells/HPF</td>
<td>3 mo after pembrolizumab started</td>
<td>Advanced adenocarcinoma</td>
<td>1: carboplatin/paclitaxel/bevacizumab; 2: docetaxel; 3: pemetrexed</td>
<td>Omoprazole (preceeding pembrolizumab by 3 mo)</td>
<td>Pembrolizumab and omeprazole held; treated w/ 1-mo steroid taper, w/ ↓ of Scr to 1.3; 2 wk after steroid course, Scr ↑ to 2.5; re-treated w/ 3-mo steroid taper, w/ normalization of Scr</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>M</td>
<td>tobacco user</td>
<td>Scr: 0.8–2.5 &amp; 1.3–10.6; eGFR: &gt;60 to 27 &amp; 57–45</td>
<td>Eos: 2%; no protein on UA; sediment: 1 white blood cell/slide</td>
<td>8 mo after nivolumab + ipilimumab started</td>
<td>Advanced adenocarcinoma</td>
<td>none</td>
<td>Omoprazole (begun 3 mo after starting nivolumab/ipilimumab)</td>
<td>Nivolumab, ipilimumab, and omeprazole held; Scr ↓ to 1.3 w/ steroids; nivolumab/ipilimumab re-started, w/ severe AKI (pt reported interim omeprazole use); Scr ↓ to 1.4 w/ 1-mo steroid taper</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>HTN, hypothyroid, prior tobacco use, HPL</td>
<td>Scr: 0.8–2.3; eGFR: &gt;60</td>
<td>Eos: 1%; no protein on UA; sediment: 15–30 white blood cells/HPF</td>
<td>1 y after pembrolizumab started</td>
<td>Advanced adenocarcinoma</td>
<td>Carboplatin/pemetrexed</td>
<td>Pantoprazole (preceeding pembrolizumab by 6 mo)</td>
<td>Pembrolizumab held; treated w/ 1-mo steroid taper, w/ normalization of Scr</td>
</tr>
</tbody>
</table>

Shirali A et al. AJKD 68(20) 287-291; 2016
## Treatment of AIN

<table>
<thead>
<tr>
<th>Pt</th>
<th>Treatment</th>
<th>Renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pred 60 mg daily, tapered off over 3 mo</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>2</td>
<td>Pred 60 mg daily, tapered off over 6 wks</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>3</td>
<td>Episode 1: Pred 60 mg daily, tapered off over 2 wks; episode 2: hydrocortisone 100 mg i.v. q 12 h × 1 d, then pred 60 mg daily, tapered to 10 mg daily over 3 mo and continued at 10 mg daily for an additional 3 mo</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>4</td>
<td>Conservative management</td>
<td>No recovery</td>
</tr>
<tr>
<td>5</td>
<td>Solu-Medrol 35 mg i.v. daily × 4 d, then pred 80 mg daily, tapered off over 8 wks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>6</td>
<td>Solu-Medrol 500 mg i.v. daily × 3 d, 250 mg i.v. daily × 3 d, then pred 80 mg daily, tapered off over 4 wks</td>
<td>No recovery</td>
</tr>
<tr>
<td>7</td>
<td>Pred 70 mg twice a day, tapered over 3 wks to 10 mg daily, tapered off over 9 wks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>8</td>
<td>Pred 60 mg daily, tapered off over 2 wks</td>
<td>No recovery</td>
</tr>
<tr>
<td>9</td>
<td>Solu-Medrol 500 mg i.v. daily × 3 d, then pred 60 mg daily; 2 wks later pred increased to 80 mg twice a day and MMF 1 g twice a day added</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>10</td>
<td>Conservative management</td>
<td>No recovery</td>
</tr>
<tr>
<td>11</td>
<td>Pred 60 mg daily, tapered off over 4 wks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>12</td>
<td>Solu-Medrol 500 mg i.v. daily × 3 d, then pred 40 mg daily, tapered off over 4 wks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>13</td>
<td>Solu-Medrol 250 mg × 1, then pred 40 mg daily, tapered off over 3 mo</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>

Cortazar F. et al. KI, 2016
IRAE-Response to Therapy

Cortazar F. et al. KI, 2016
Steroid Use During Checkpoint Therapy

Horvat T et al. JCO. 2015. 33(28) pp 3193-3198
PD-1 Receptor Occupancy

- Nivolumab-PD-1 Ab
- Serum $t_{1/2}$ 12-20 days-dose dependent
- PD-1 occupancy on circulating T-cells is dose dependent
  - Mean peak occupancy: 85% (4-24 hrs)
  - Mean plateau occupancy: 72% ($\geq 57$ d)
- Occupancy on lymphocytes in tissue/tumor unknown
- *Duration of treatment for nivolumab induced AIN??*

Case: PD-1 Re-Challenge

• 69 y.o. male with stage IV NSCLC
• S/P 5 cycles of Nivolumab
• Referred for AKI
  • Baseline SCr 1.0-1.3 mg/dl
  • Now SCr 1.7 mg/dl
• Underwent renal biopsy
Clinical Course
## Retreatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Checkpoint Agent</th>
<th>Treatment</th>
<th>Re-challenge checkpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortazar</td>
<td>Ipilimumab (one dose)</td>
<td>Prednisone 60mg/d for 3 months</td>
<td>Pembrolizumab</td>
<td>No IRAE</td>
</tr>
<tr>
<td>Cortazar</td>
<td>Nivolumab (16 doses)</td>
<td>Prednisone (14 weeks taper)</td>
<td>Ipilimumab</td>
<td>No IRAE</td>
</tr>
<tr>
<td>Cortazar</td>
<td>Ipilimumab (4 doses)</td>
<td>Supportive-no recovery</td>
<td>Ipilimumab</td>
<td>Stable</td>
</tr>
<tr>
<td>Shirali</td>
<td>Ipilimumab/nivolumab 8 months</td>
<td>Supportive-recovery</td>
<td>Ipilimumab/nivolumab</td>
<td>Recurrent IRAE/severe AKI</td>
</tr>
</tbody>
</table>
Glomerular IRAEs
Membranous Nephropathy-IRAES?

- 75 yo male with metastatic melanoma treated with nivolumab x6. Developed anasarca after 4 doses. Transferred care to MSK.
  - S Creat 1.2 mg/dl
  - S albumin 1.4 g/dl
  - Urine protein 12g/24 hr
  - UA-bland
  - PLA2R-negative
  - Biopsy c/w membranous nephropathy with negative PLA2R staining
Clinical course

- Grey arrow - Nivolumab dose
- Red arrow - start of prednisone
- Green arrow - ipilimumab administration
# Glomerular IRAE

<table>
<thead>
<tr>
<th>Author</th>
<th>Check Point Inhibitor</th>
<th>Clinical Presentation</th>
<th>Renal Pathology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidd J and Gizaw A</td>
<td>Ipilimumab</td>
<td>AKI, Nephrotic Syndrome</td>
<td>Minimal Change Disease</td>
<td>Steroids (2mg/kg)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Fadel F et al</td>
<td>Ipilimumab (2 doses)</td>
<td>Nephrotic Syndrome</td>
<td>Lupus Nephritis</td>
<td>Prednisone (1mg/kg)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Ray AS et al</td>
<td>Nivolumab</td>
<td>AKI, Nephrotic Syndrome</td>
<td>Collapsing FSGS</td>
<td>IV steroids</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Kitchlu A et al</td>
<td>Pembrolizumab (2 doses)</td>
<td>AKI, Nephrotic Syndrome</td>
<td>Minimal Change Disease</td>
<td>Steroids</td>
<td>Resolved</td>
</tr>
<tr>
<td>Kitchlu A et al</td>
<td>Ipilimumab (4 doses)</td>
<td>Nephrotic Syndrome</td>
<td>Minimal Change Disease</td>
<td>Steroids</td>
<td>Resolved but recurred after re-challenge with ipi</td>
</tr>
<tr>
<td>Bickel A et al</td>
<td>Pembrolizumab (two doses)</td>
<td>AKI, Nephrotic syndrome</td>
<td>Minimal Change Disease</td>
<td>Prednisone (1mg/kg)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Takahashi N et al</td>
<td>Nivolumab (8 doses)</td>
<td>AKI, hematuria and proteinuria</td>
<td>Goodpasture disease</td>
<td>Pulse steroids and plasma exchange</td>
<td>Rapid clinical deterioration and death</td>
</tr>
</tbody>
</table>
# Checkpoint Inhibitors in Kidney Transplant

<table>
<thead>
<tr>
<th>Allograft outcome</th>
<th>Checkpoint inhibitor</th>
<th>Years from tx to ICI</th>
<th>IS regimen</th>
<th>Cancer response</th>
<th>Interval between IS reduction and ICI initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrejected</td>
<td>Ipiilimumab</td>
<td>11</td>
<td>Tac + Pred→ Pred 5 mg daily</td>
<td>PR</td>
<td>6 wk</td>
</tr>
<tr>
<td>Nonrejected</td>
<td>Ipiilimumab</td>
<td>8</td>
<td>MMC + Tac + Pred→ Pred 5 mg daily</td>
<td>PR then PD</td>
<td>&gt; 4 mo</td>
</tr>
<tr>
<td>Rejected</td>
<td>Nivolumab</td>
<td>25</td>
<td>CyA + Pred→ Pred 5 mg daily</td>
<td>PR</td>
<td>&gt; few mo</td>
</tr>
<tr>
<td>Rejected, HD</td>
<td>Nivolumab</td>
<td>5</td>
<td>CyA + pred→ low dose CyA + Pred</td>
<td>N.D.</td>
<td>2 yr</td>
</tr>
<tr>
<td>Rejected, HD</td>
<td>Ipi × 4 then Nivolumab</td>
<td>15</td>
<td>CyA + Pred→ Pred 5 mg daily</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Rejected, HD</td>
<td>Ipi × 2 then Nivolumab</td>
<td>15</td>
<td>Tac + Pred→ Pred 5 mg daily</td>
<td>PR</td>
<td>Days</td>
</tr>
</tbody>
</table>

# Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab

**Table 1.** Immunosuppressive Regimen in a Patient Who Had Undergone Kidney Transplantation.

<table>
<thead>
<tr>
<th>Timing*</th>
<th>Drug and Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wk before</td>
<td>Prednisone — 40 mg daily</td>
</tr>
<tr>
<td>Concurrent</td>
<td>Prednisone — 20 mg daily; sirolimus — target goal, 4–6 ng per milliliter</td>
</tr>
<tr>
<td>1 Wk after</td>
<td>Prednisone — 20 mg</td>
</tr>
<tr>
<td>&gt;2 Wk and ≤6 mo after</td>
<td>Prednisone — 10 mg/day; sirolimus — target goal, 10–12 ng per milliliter</td>
</tr>
<tr>
<td>&gt;6 Mo after</td>
<td>Glucocorticoid — gradually decreased to 5 mg/day; sirolimus — continued to maintain goal of 10–12 ng per milliliter</td>
</tr>
</tbody>
</table>

Barnett R. NEJM 376 (2)191-192; 2017
## Summary

Checkpoint inhibitors cause iRAE at a rate of 1-2% depending on the agent and combination

AIN is the most common manifestation

Nephrotic syndrome also reported

Renal iRAE respond to steroid therapy

Some patients may be re-challenged with immunotherapy if clinically indicated

Check point inhibitors should be used with caution in transplant patients due to risk of rejection
# ASCO Management Recommendations

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: Creatinine level increase of $&gt; 0.3$ mg/dL; creatinine $1.5-2.0 \times $ over baseline</td>
<td>Consider temporarily holding ICPI, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still $&lt; 1.5$ ULN could be meaningful</td>
</tr>
<tr>
<td>G2: Creatinine $2-3 \times$ above baseline</td>
<td>Hold ICPI temporarily; consult nephrology. Evaluate for other causes (recent IV contrast, medications, fluid status, etc.); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents. If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment. If improved to G1 or less, taper corticosteroids over 4-6 weeks. If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.</td>
</tr>
<tr>
<td>G3: Creatinine $&gt; 3 \times$ baseline or $&gt; 4.0$ mg/dL; hospitalization indicated</td>
<td>Permanently discontinue ICPI</td>
</tr>
<tr>
<td>G4: Life-threatening consequences; dialysis indicated</td>
<td>Consult nephrology. Evaluate for other causes (recent IV contrast, medications, fluid status, etc). Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent).</td>
</tr>
</tbody>
</table>

**Additional considerations**
- Monitor creatinine weekly
- Reflux kidney biopsy should be discouraged until corticosteroid treatment has been attempted

---

**6.2 Symptomatic nephritis: follow-up**
CAR-T Cell Kidney Toxicity

BRAF Pathway

- Rapidly Accelerated Fibrosarcoma kinase B (BRAF)-part of MAPK pathway
- V600 E mutation-constitutive activation MAPK
- Melanoma/metanephric adenoma/Erdheim-Chester

Hagen B. J of Adv Pract Oncol. 2014. 5(6) 400-410
BRAF Inhibitors

- Vemurafenib/Dabrafenib
- Vemurafenib-CYP3A4 metabolism (no significant metabolite levels in plasma)
- Excreted predominantly in the feces -94%/urine <1%
- Major Toxicity
  - Photosensitivity –within 2 weeks
  - Skin reactions/rash
  - Hepatotoxicity
  - FAERS (FDA reporting system)-132 cases of AKI with vemurafenib/13 cases with dabrafenib

Jhaveri K. et al. JAMA Oncology. 2015
Hagen B. J of Adv Pract Oncol. 2014. 5(6) 400-410
Case presentation

• 59 yo pt with Erdheim-Chester disease-non Langerhans histocytosis with BRAF V600E positive mutation presented with exophthalm due to infiltrative process.

• CT of Abd/Pelvis c/w perirenal infiltration, hilar involvement and atrophic right kidney

• Baseline Creatinine 1.1mg/dL

• Patient started on vemurafenib 960mg PO BID
Case presentation (cont.)

- Referred to renal clinic due to AKI
- Rash-diffuse erythematous papular
- Urinalysis was bland
- U Prot/U Creat 0.04
- Pertinent home medications
  - PPI
  - Bactrim
  - Lisinopril
  - Steroids (Rash/Ocular symptoms)
- Renal Doppler US-no evidence of RAS
- Vemurafenib dose reduced from 960mg BID to 480 mg BID
- No kidney biopsy was performed

Arrows represent vemurafenib dose adjustments
BRAF Inhibitors
Renal Toxicity

- 4 patients on vemurafenib
- AKI and Rash
  - 2 cases with eosinophilia
- Pts presented within 1-2 weeks after drug initiation
- Improvement/resolution of AKI after dose reduction/discontinuation

BRAF Inhibitors
Renal Toxicity

• Case series – 8 pts on Vemurafenib
  • Mean baseline GFR 64.25
  • GFR decline 19%-74%-within one month in all but one pt
  • Mild proteinuria <1gm/d
  • Six patients able to continue with up to 50% dose reduction
    • One pt stopped due to POD and AKI
    • One pt stopped due to AKI (died 3 days after stopping the drug)
      • Biopsy c/w ATN
Proteasome Inhibitors-case

• 55 yo male with MM s/p auto HSCT 4 months prior; treated with carfilzomib one year ago and received another dose one week prior
• Fever, diarrhea and AKI;
• PE: BP 154/60
• Creat 14.0; Hgb 9.7 (12.7); Plt 108 (296); 3+schistocytes; LDH 1838; Hapto 73; STEC(-); AdamTS13-68%
• Biopsy-severe acute TMA with microthrombi
PI associated TMA

<table>
<thead>
<tr>
<th>Age and sex</th>
<th>PI used</th>
<th>Timing(^a)</th>
<th>Hgb (g dL(^{-1}))</th>
<th>Platelet count, x10(^9)L(^{-1})</th>
<th>Cr (mg dL(^{-1}))</th>
<th>LDH (U L(^{-1}))</th>
<th>Haptoglobin (mg dL(^{-1}))</th>
<th>ADAMTS13 activity</th>
<th>Dialysis required</th>
<th>TMA on renal biopsy</th>
<th>AST (U L(^{-1}))</th>
<th>G1 sx</th>
<th>Neuro sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 70 M</td>
<td>Bortezomib 21 d</td>
<td>6.9</td>
<td>66</td>
<td>9.9</td>
<td>631</td>
<td>&lt;14</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td>N</td>
<td>50</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2 64 M</td>
<td>Bortezomib 9 d</td>
<td>9.2</td>
<td>17</td>
<td>0.8</td>
<td>659</td>
<td>&lt;14</td>
<td>N</td>
<td></td>
<td>N</td>
<td>N</td>
<td>118</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3 51 M</td>
<td>Bortezomib 21 d</td>
<td>7.5</td>
<td>119</td>
<td>2.65</td>
<td>218</td>
<td>&lt;2</td>
<td>34%</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>49</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4 80 M</td>
<td>Carfilzomib 5 d</td>
<td>11.2</td>
<td>11</td>
<td>6.1</td>
<td>1920</td>
<td>&lt;14</td>
<td>100%</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>96</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>5 79 M</td>
<td>Carfilzomib 8 mo</td>
<td>8.4</td>
<td>18</td>
<td>7.29</td>
<td>3481</td>
<td>Y</td>
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<td>6 67 M</td>
<td>Carfilzomib 17 mo</td>
<td>10.3</td>
<td>20</td>
<td>3.12</td>
<td>642</td>
<td>N</td>
<td>43</td>
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<td>43</td>
<td>N</td>
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<tr>
<td>7 64 F</td>
<td>Carfilzomib 8 mo</td>
<td>11.9</td>
<td>8</td>
<td>1.1</td>
<td>1848</td>
<td>&lt;10</td>
<td>88%</td>
<td>N</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>8 67 F</td>
<td>Carfilzomib 7 d</td>
<td>7.3</td>
<td>34</td>
<td>8.1</td>
<td>698</td>
<td>&lt;8</td>
<td>79%</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>36</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>9 45 M</td>
<td>Carfilzomib 6 mo</td>
<td>4.6</td>
<td>163(^a)</td>
<td>1.75</td>
<td>250</td>
<td>34</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>17</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>10 44 M</td>
<td>Carfilzomib 8 mo</td>
<td>6.7</td>
<td>39</td>
<td>7.28</td>
<td>1220</td>
<td>3</td>
<td>N</td>
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<td>58</td>
<td>Y</td>
<td>58</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>11 49 M</td>
<td>Carfilzomib 8 d</td>
<td>7.2</td>
<td>18</td>
<td>2.4</td>
<td>1129</td>
<td>&lt;14</td>
<td>82%</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>36</td>
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Memorial Sloan Kettering Cancer Center

AMERICAN COLLEGE OF OSTEOPATHIC INTERNS 2018 CONVENTION & SCIENTIFIC SESSIONS OCT 17-21

ORLANDO 2018
THANK YOU