Case 1: Newly diagnosed RCC

- 2009: 69 yo male with new gross hematuria
- Found to have a left renal mass; localized predominantly clear cell RCC (staging unavailable)
- 2/2009: underwent left renal nephrectomy

What would you do at this point?

1. Adjuvant sunitinib
2. Surveillance with follow-up imaging in 6 months and then annual imaging
3. Adjuvant nivolumab
Q1 What would you do at this point?

1. Adjuvant sunitinib
2. Surveillance with follow-up imaging in 6 months and then annual imaging
3. Adjuvant nivolumab

Case 1 continued

- 11/2010: restaging scans reveal new lung nodules
  - Initiates sunitinib with partial response
- 12/2010: scrotal US/bx done for enlarging right testicle which reveals
- 1/2011 right orchiectomy for 8.5 cm mass; found to be predominantly clear cell RCC, 8.5 cm, involving rete testis
- 8/2011 changed to everolimus 10 mg daily for progression on sunitinib

---

Case 1 Continued

- 10/2011: Significant side effects/progression on everolimus
- 11/2011: initiates sorafenib
- 4/2012: Partial response and then progression
- 04/2012: initiates Pazopanib 800 mg/day
- 07/2012: Imaging reveals further interval progression of pulmonary nodules
- ~08/2012: Stopped Pazopanib

Q2: What would you do at this point?

1. Avastin
2. Nivolumab
3. Axitinib
4. Cabozantinib
5. retry Sunitinib or pazopanib
Answer: various options

- **Avastin**: Bevacizumab plus IFNa or IFNα alone
  - PFS 8.5 versus 5.2 months; HR 0.71, 0.61-0.83
- **Cabosun**: 157 patients assigned to Cabozantinib vs. Sunitinib
  - Cabozantinib improved median PFS (8.2 vs. 5.6 months) and was associated with a 34% reduction in progression or death
- **Nivolumab vs. Everolimus**: 821 patients with RCC after 1 or 2 regimens, assigned to nivolumab vs. everolimus 1:1.
  - OS: 25.0 months with nivolumab and 19.6 months with everolimus.
  - The hazard ratio for death was 0.73
- **Retreatment**: 22% of patients re-treated with sunitinib had a partial response (PFS with initial treatment: 13.7 months vs. 7.2 months with re-treatment)

Case 1 Continued

- 8/2012 - 10/2012: Bevacizumab monotherapy
- 10/22/12: Imaging demonstrated interval progression of disease
  - Increasing size/number of pulmonary metastases, increasing size of soft tissue nodules near diaphragm along pleural surface, liver lobe metastasis increased in size, new pathologic fracture of R posterior 5th rib.

Rationale for Phase 1 study of Pazopanib in Combination with Abexinostat

- Epigenetic modulation with a histone deacetylase inhibitor (HDACi) prevents outgrowth of resistant phenotype and reverse resistance to PAZ monotherapy
- PBMC histone acetylation and/or HDAC expression may predict for the subset of patients most likely to achieve benefit
Summary of Dose-Limiting Toxicities

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
<th>Level</th>
<th>N (36)</th>
<th># DLTs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAZ 600 mg/d + ABX 45 mg/m²</td>
<td>ABX 5/7 days</td>
<td>1A</td>
<td>4</td>
<td>2</td>
<td>Grd 3 thrombocytophenia (N = 2)</td>
</tr>
<tr>
<td>PAZ 400 mg/d + ABX 30 mg/m²</td>
<td>ABX 5/7 days</td>
<td>2A</td>
<td>6</td>
<td>1</td>
<td>Grd 3 fatigue</td>
</tr>
<tr>
<td>PAZ 600 mg/d + ABX 30 mg/m²*</td>
<td></td>
<td>3A</td>
<td>4</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>PAZ 800 mg/d + ABX 30 mg/m²</td>
<td>ABX 4/7 days</td>
<td>4A</td>
<td>8 (6 evaluable)</td>
<td>2</td>
<td>Grd 3 fatigue Grd 2 AST + ALT</td>
</tr>
<tr>
<td>PAZ 600 mg/d + ABX 45 mg/m²</td>
<td>ABX 4/7 days</td>
<td>1B</td>
<td>6</td>
<td>1</td>
<td>Grd 3 AST/ALT</td>
</tr>
<tr>
<td>* PAZ 800 mg/d + ABX 45 mg/m²</td>
<td></td>
<td>2B</td>
<td>8 (6 evaluable)</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>
* Recommended Phase 2 Dose

Responses can be durable in VEGF Pre-Treated Patients

Take Home Points

- Epigenetic modifiers may ‘reset’ responsiveness to VEGF-targeting agents
- Randomized study planned to further test this hypothesis
- Patients with renal cell carcinoma who are refractory to multiple lines of prior therapy may still derive therapeutic benefit from investigational agents/combinatorial therapy

References:

Case 2
Stanford Developmental Therapeutics
Shivaani Kumar

Case 2: BRAF V600E + melanoma

- 2008: 51 yo F with stage IIIA melanoma with mixed superficial spreading and desmoplastic features on the right upper back. Sentinel LN bx c/w micrometastatic disease, resection followed by one yr of interferon
- Recurred in 2012-1.25 mm depth, Clark level III, resected with negative margins, sentinel LN negative
- Recurred in 2/2016- L5 vertebral body, bx confirmed, BRAF V600E+. Ipilimumab + nivolumab
  - Developed new mets in acetabulum and vertebrae, local radiosurgery
  - s/e hypopituitarism, neuropathy
- 11/2016- Dabrafenib with trametinib
  - day 4 developed fevers, rash, weakness, ataxia
  - Symptoms resolved on stopping

Question 1:

1) Switch to checkpoint blockade +/- anti-CTLA4 antibody?
2) Switch to vemurafenib + another MEK inhibitor?
3) Switch to vemurafenib alone?
4) Reduce dose of Dabrafenib with trametinib and re-challenge?

What next?

Patient re-challenged with dabrafenib with trametinib at a reduced dose

- Symptoms recurred
- Treatment discontinued
- Now what?
Case (cont’d)

- Patient switched to Vemurafenib with cobimetinib
  - Day 8 developed high fevers (102-103°F), diffuse facial swelling, rash, diffuse shotty adenopathy, diarrhea, abdominal pain, arthralgias, sensory neuropathy, worsening ataxia.
  - Are these expected toxicities of BRAF inhibitors? MEK inhibitors?
  - Does this patient have DRESS syndrome?

What is DRESS Syndrome?

- Drug reaction with eosinophilia and systemic symptoms (DRESS), is a life-threatening multi-organ system reaction induced by drugs
  - Possible causes:
    - Lack of genetic detoxifying enzymes, so metabolites collect causing damage
    - Specific HLA phenotypes
    - Viral infections: has been associated with sequential reactivations of herpesviruses.
  - 10% mortality
  - RegiSCAR criteria for diagnosis of DRESS
    - Hospitalization
    - Reaction suspected to be drug-related
    - Acute rash
    - Fever >38°C
    - Enlarged lymph nodes at a minimum of 2 sites:
    - Involvement of at least 1 internal organ:
    - Blood count abnormalities:
      - Lymphocytes above or below normal limits
      - Eosinophils above the laboratory limits
      - Platelets below the laboratory limits

3 of the 4 criteria with * have to be met for dx; a scoring system is also used
Vemurafenib-induced DRESS syndrome

- 3 cases reported in the literature
- Symptoms recur even at reduced dose
- High complication rate, mortality
- Discontinue vemurafenib
- Cross-reactivity between vemurafenib and dabrafenib has not been reported and dabrafenib has less cutaneous toxicities
- With our patient, she developed similar symptoms with both drugs


What next?

- Patients immune system is stimulated so no further therapy
- Immune checkpoint blockade?
- Newer generation BRAF inhibitors?
- Chemotherapy?
- Regulatory T cells (Tregs) are expanded during the acute stage of DRESS but, upon clinical resolution, their function becomes gradually defective, which could increase the risk of developing autoimmune sequelae
- Systemic steroids have been shown to prevent Treg dysfunction

Case 2 (cont’d)

- Does our pt have DRESS Syndrome?
  - Hospitalization Y
  - Reaction suspected to be drug-related Y
  - Acute rash Y
  - Fever >38°C Y
  - Enlarged lymph nodes at a minimum of 2 sites Y
  - Involvement of at least 1 internal organ Y
  - Blood count abnormalities Y
    - Lymphocytes above or below normal limits Y
    - Eosinophils above the laboratory limits normal
    - Platelets below the laboratory limits 100K (below normal)
  - Skin bx: Superficial perivascular dermatitis with eosinophils
  - PCR did not identify any viral activation including HSV
  - Started on 60 mg prednisone with continued worsening of symptoms - admitted and received IV steroids - gradual improvement in symptoms

Case 3

UC Davis Developmental Therapeutics

Tina Li, Arta Monjazeb and Karen Kelly
Case 3: Newly Diagnosed Metastatic NSCLC

- A 71-year-old White man
  - Presents with persistent, right rib cage pain after lifting luggage. CXR revealed a right lung mass. Denies cough, shortness of breath, and dyspnea on exertion. No hemoptysis. Good appetite. No weight loss
  - Former smoker (>15 PY, quit 50 yrs ago)
  - ECOG PS=1

- Staging workup:
  - A PET/CT scan reveals a 2.0-cm, spiculated RLL mass, a 0.5-cm RUL mass, multiple pleural based masses in the right hemithorax, liver and bone metastasis.
  - A brain MRI scan reveals no metastatic disease.
  - Clinical stage IV (T1abNxM1b)

Case 3 Continued:

- Diagnosis: Core needle biopsy of right chest wall mass and right posterior, paraspinal chest wall mass.

<table>
<thead>
<tr>
<th>CT-guided FNA</th>
<th>Right chest wall mass</th>
<th>Right posterior, perispinal chest wall mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>adenocarcinoma</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Grade</td>
<td>poorly differentiated</td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>CK7+, CK-20-, TTF-1+</td>
<td>AE1/AE3 +, CK7 -, CK20-, TTF-1-, HMB45-, S100-, CK5/6, rare, focal positive, P40 +, Napsin A</td>
</tr>
<tr>
<td>PD-L1 22C3 Pharm</td>
<td>--</td>
<td>Positive (95%, 3+)</td>
</tr>
<tr>
<td>Tumor genotyping</td>
<td>Quality insufficient</td>
<td>Not ordered</td>
</tr>
</tbody>
</table>

- Plasma circulating tumor DNA (ctDNA) by a >50-gene panel next generation sequencing (NGS) assay revealed KRAS K12C (3.65%) and two p53 mutations (TP53 splice site 673-1G>T and V225F, 36.0% and 36.1%, respectively).

Q1.1  What would you recommend ?

1. Re-biopsy for broad tumor genomic profiling of adenocarcinoma
2. First line immunotherapy with pembrolizumab
3. First line combination immunotherapy on a clinical trial
4. A trial targeting KRAS mutation (if available)
5. First line platinum-containing chemotherapy

Case 1 Continued:

- Patient had clinical and radiographic responses in almost all existing tumors after 3 cycles of pembrolizumab monotherapy.
- However, he had extensive tumor progression after 6 cycles of pembrolizumab.
- Patient has good performance status (KPS 80%) and normal organ function

Baseline

After 3 cycles

After 6 cycles
Q1.2 What would you recommend?

1. Re-biopsy for broad tumor genomic profiling test and PD-L1 IHC of a growing tumor
2. Second line immunotherapy
3. Platinum-based combinational chemotherapy
4. Docetaxel monotherapy
5. Clinical trial targeting KRAS (trametinib and docetaxel)

Case 3 Continued:
Tumor re-biopsy showed adenocarcinoma with PD-L1 IHC 2% and plasma cfDNA confirmed raising KRAS K12C mutation.

Q1.3 This patient is eligible for several clinical trials. What would you recommend as a second line trial?

1. An PD-L1 inhibitor
2. Second line immunotherapy
3. Platinum-based combinational chemotherapy
4. Docetaxel monotherapy
5. Clinical trial targeting KRAS (trametinib and docetaxel)

Take Home Points

- Immune checkpoint inhibitors produce rapid objective response in 20% of patients.
- Variable tumor response patterns have been observed.
- Further mechanistic studies are needed to understand the exceptional response, primary resistance, adaptive resistance and acquired resistance.
- cfDNA for next generation sequencing is a non-invasive test that can provide rapid similar “actionable results” to tumor tissue analysis.
References

