ASCO 2011 – Genitourinary Cancer

Expanding Options for Chronic Diseases?

Walter Stadler, MD, FACP
University of Chicago

Disclosures
(All Non-University &/or Financial Dealings with Potential, Real, or Perceived Conflicts of Interest)

• Consultant:
  – Novartis, Pfizer/Wyeth, Roche/Genentech, Takeda, Caremark/CVS, Aveo, Ligand Pharmaceuticals, NCI/SAIC-Frederick

• Speakers Bureau:
  – CME providers (sponsorship unknown): Imedex, CME Innovations, Research-to-Practice, Clinical Care Options, Medical Communications Media
  – Pfizer, Bayer

• Grant/Research Support:
  – Active Biotech, Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Novartis, Genentech (Roche), Glaxo-Smith-Kline, Medarex, Medivation, Solvay (Abbott), Pfizer, ImClone (Lilly), Amgen, Takeda (Millenium), NIH, CALGB

• Stockholder:
  – Abbott (Spouse)

• Expert Witness
  – None

• Miscellaneous:
  – Kidney Cancer Assoc, Bladder Cancer Advocacy Network, Up-To-Date, NexCura
Renal Cancer: What we Knew

- Disease natural history is highly variable
  - Prognostic models capture some, but not all of variability
- VEGF pathway inhibitors slow disease progression
  - Likely improve survival
  - Sequential inhibitors have activity
- mTOR inhibitors have modest anti-tumor activity
  - Survival improved in untreated poor prognosis patients
  - Progression slowed in post-VEGFR TKI setting
- Combination therapy has increased toxicity

Available VEGF Pathway Inhibitors

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Comparator</th>
<th>No Prior Therapy</th>
<th>Prior IL2 or IFNA</th>
<th>Prior VEGF Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab/IFNA</td>
<td>IFNA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>IFNA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Placebo</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Axitinib</td>
<td>Sorafenib</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tivozanib*</td>
<td>Sorafenib</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Data pending
Rini, et al: AXIS Trial (abstract 4503)

Treatment-refractory metastatic RCC

Randomization stratified by ECOG PS and type of prior treatment

†Starting dose 5 mg BID with option for dose titration to 10 mg BID

- Metastatic RCC with clear cell histology
- Measurable disease per RECIST criteria
- RECIST-defined progressive disease after one prior sunitinib, bevacizumab
  + IFN-α, temsirolimus, or cytokine-based regimen
- ECOG Performance Status 0 or 1

AXIS Results

- Quality of life similar in both arms (abstract 4504)
- Composite “time-to-deterioration” better with axitinib
### PFS by Prior Regimen

<table>
<thead>
<tr>
<th>Prior Treatment Regimen</th>
<th>Axitinib (n=361)</th>
<th>Sorafenib (n=362)</th>
<th>HR</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines (n=251)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>12.1</td>
<td>6.5</td>
<td>0.464</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Investigator</td>
<td>12.0</td>
<td>8.3</td>
<td>0.636</td>
<td>0.005</td>
</tr>
<tr>
<td>Sunitinib (n=389)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>4.8</td>
<td>3.4</td>
<td>0.741</td>
<td>0.011</td>
</tr>
<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.636</td>
<td>0.0002</td>
</tr>
<tr>
<td>Temsirolimus (n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>10.1</td>
<td>5.3</td>
<td>0.511</td>
<td>0.142</td>
</tr>
<tr>
<td>Investigator</td>
<td>2.6</td>
<td>5.7</td>
<td>1.210</td>
<td>0.634</td>
</tr>
<tr>
<td>Bevacizumab (n=59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>4.2</td>
<td>4.7</td>
<td>1.147</td>
<td>0.637</td>
</tr>
<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.753</td>
<td>0.213</td>
</tr>
</tbody>
</table>

*One-sided log-rank test stratified by ECOG PS

---

### Aitchison, et al: Adjuvant Immunochemotherapy (abstract 4505)

- High risk localized disease following nephrectomy
  - IL2/IFNA/5FU versus observation
  - 3 year DFS from 50% to 65 % with 90% power and 2-sided alpha = 0.05
- 35% of pts in experimental arm unable to complete therapy due to toxicity
- No difference in outcome
What we learned - RCC

• Confirmed that sequential VEGFR TKI can have activity

• Standard of care for locally advanced renal cancer following resection is observation

What Do We Need to Know?

• What are the predictors of benefit from IL2 based, VEGF, or mTOR pathway directed therapy?
  – Tumor characteristics
  – Stroma characteristics
  – Host characteristics

• Is continued/life-long VEGF pathway inhibition important?
  – What are the mechanisms of resistance to VEGF pathway inhibition
What Do We Need to Know?

- Are there other/better therapeutic targets than the mTOR and VEGF pathways?
- Are there better ways to therapeutically target VHL pathway inactivation in ccRCC?
- What are the most appropriate therapeutic targets in papillary or chromophobe RCC?
- Can we afford “personalized” long-term therapy?
  - $  
  - Toxicity

Prostate Cancer: Androgen Ablation
Androgen Ablation & Prostate Ca

- The androgen receptor is the most important therapeutic target in PCa
  - Targeting AR is effective in >90%
  - The AR is critical even in the castrate resistant state
  - Targeting AR is not curative
- Androgen ablation has toxicity
  - Bone, muscle, sex
  - Toxicity minimal in comparison to other cancer therapies

Intermittent vs. Continuous

- Intermittent therapy not associated with worse outcome
- Intermittent LHRH agonist is not intermittent ADT
- Suggestion of improved sexual function and QOL
- Similar observations in post-RT population (Crook, et al, abstract 4514)
- How early should ADT start?
Abiraterone/TAK-700

COU-AA-301 Study Design

**Patients**
- 1195 patients with progressive mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel

**Study Design**
- Phase III, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)
- Stratification according to
  - ECOG performance status (0-1 vs 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs 4-10 [present])
  - Prior chemotherapy (1 vs 2)
  - Type of progression (PSA only vs radiographic progression with or without PSA progression)

**Efficacy endpoints (ITT)**
- Primary end point
  - OS (25% improvement; HR 0.8)
- Secondary endpoints (ITT)
  - TTPP
  - PFS
  - PSA response

**Abbreviations:**
- BPI= Brief Pain Inventory; TTPP=time to PSA progression; ITT=intent to treat; mCRPC= metastatic castrate-resistant prostate cancer.
- **Source:** Clinicaltrials.gov identifier: NCT00638690.
COU-AA-301: Abiraterone Acetate Improves OS in mCRPC

HR = 0.646 (0.54-0.77) \( P < 0.0001 \)

Abiraterone: 14.8 months (95% CI: 14.1, 15.4)
Placebo: 10.9 months (95% CI: 10.2, 12.0)

Overall Survival, %

Days from Randomization

Logothetis, et al: Symptomatic Improvement Pain Intensity Palliation (abstract 4520)

\[ P = 0.0002 \]

155/349 (44.4%) vs 44/163 (27.0%)

Patients experiencing palliation

AA (n = 797) vs Placebo (n = 398)
Scher, et al: CTC as Surrogate Endpoint (LBA 4517)

- In the context of the Abiraterone phase 3 trial:
  - CTC prognostic
  - CTC decline predictive of trial survival outcome
- Applicable to other trials?
- Applicable to individual patients?

Hussain, et al: Cabozantinib (abstract 4516)

- 12-Week Lead-In Stage: Open-Label Cabozantinib 100 mg PO, QD
- Week 12 Tumor Staging
- PD
- SD
- PR or CR

- Unblind at Progression
- Placebo Cross-Over to Cabozantinib
- Discontinue Cabozantinib

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease (per mRECIST 1.0)
mCRPC Patient Disposition

Enrolled: N = 171
Randomization was suspended after 122 patients because of early clinical benefit

Open-Label Extension ≥ Week 12
n = 79 (46%)

Randomized at Week 12
n = 31 (18%)

Off Study Treatment ≤ Week 12
n = 61 (36%)

- Disease Progression 28 (16%)
- Adverse Event 25 (15%)
- Death 1 (1%)
- Otherb 7 (4%)

Cross-over to Cabozantinib 14

*Includes patients with SD at Week 12 following suspension of randomization

b Includes withdrawal (n = 2), not compliant (n = 1), request (n = 3), lost to follow up (n = 1)

Progression-Free Survival for Patients Randomized to Placebo or Cabozantinib (N = 31)

Median PFS
- Cabozantinib (n = 14) 21 weeks
- Placebo (n = 17) 6 weeks

(HR 0.13; log-rank p-value 0.0007)

PFS (95% CI) # Events
- Cabozantinib (11, NE) 6
- Placebo (5, 12) 11
Bone Scan Effects: Representative Images

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 12</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel-pretreated</td>
<td>Docetaxel-pretreated</td>
<td>Docetaxel-pretreated</td>
<td>Docetaxel-naïve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each Patient had PR + Pain Improvement

Best Overall Effect on Bone Scan

<table>
<thead>
<tr>
<th>Bone scan evaluable (N = 108)(^a)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resolution</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>61 (56)</td>
</tr>
<tr>
<td>Stable</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

\(^a\) Bone metastases at baseline and ≥ 1 post-baseline bone scan available
A Met/VEGFR inhibitor?

- VEGF pathway inhibition not effective
  - CALGB docetaxel ± bevacizumab
  - Prednisone/Sunitinib vs. Prednisone (abstract 4515)
- No similar dramatic reports in early phase studies of reported Met or HGF inhibitors
  - Others being tested
- Ongoing cabozantanib trials
  - Phase 3 efficacy with pain endpoints
  - Imaging & biopsy trials to understand stromal vs. tumor specific effects

Prostate Cancer 2011

- Advanced prostate cancer pts can have a long history
  - Opportunity for multiple therapies
  - Toxicities and quality of life important
  - Issues of co-morbid disease and aging
- Philosophy of chronic d. management
- Androgen receptor pathway targeting is key
- DNA targeted chemotherapy plays a role
- Immunotherapy may play a role
- Bone stromal targeting plays a role
  - Bisphosphonates/denosumab for bony morbidity
  - Radioactive bone targeting nuclides
  - Met inhibitors?
What do we need to know?

• When do we start ADT?
• How early do we start more potent AR targeting agents?
• When do we introduce non-AR targeting therapy?
• Can we afford “personalized” long-term therapy?
  – $ 
  – Toxicity

Bladder Cancer

2012 ???