Genitourinary Cancer Update 2009

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Dr. Quinn has received honoraria and served on advisory boards for Glaxo Smith Kline and Genentech
After reading and reviewing this material, the participant should be better able to:

• List the major potentially practice changing presentations in the field of GU cancer from ASCO 2009
  - Assess their merit
  - As applicable applied their content to clinical practice
• Understand the implications of material presented that may impact clinical practice in GU oncology in the coming years
• Recognize that Dr. Quinn has a somewhat obtuse and off-beat sense of humor
Genitourinary Cancers - Best of ASCO 2009: Key abstracts

Rini, B. Bevacizumab plus Interferon-alpha versus Interferon-alpha monotherapy in Patients with Metastatic Renal Cell Carcinoma: Results of Overall Survival for CALGB 90206 #5019

Escudier, B. Final results of the phase III, randomised, double-blind AVOREN trial of first-line bevacizumab + interferon-a2a in metastatic renal cell carcinoma. #5020

Sternberg, C. A randomized, double-blind phase III study of Pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma #5021

Scher, H. Antitumor activity of MDV3100 in a Phase 1-2 study of Castration-Resistant Prostate Cancer. #5011

In addition, we will look at the following abstracts in some detail

5018 - bevacizumab with Cisplatin and Gemcitabine in TCC

AUA 1408 - Sipuleucel in CRPC
ASCO 2009: Renal Cell Cancer Highlights

Bevacizumab adds to RR, PFS & toxicity from Interferon-α OS, cost benefit analyses inconclusive #5019, 5020, 5112

Pazopanib - doubles PFS in RCC compared to placebo ... #5021, 5110

VEGF TKi de ja vu? Real advance or just another choice?

..And there are more in the pipeline for next year: AV-951, BAY 73-4506, ABT-869, Axitinib #5032, 5033, 5036

Neoadjuvant VEGF pathway therapy: beautiful science, but warts in practice #5004, 5096

Predicting toxicity from VEGF TKIs #5005, 5006, 5045; Predictors of outcome: CA9, #5003; Chr 9p #5090; More data on Papillary RCC #5091, 5092, 5103, 5146, e16020

New therapies?

Combination targeted therapy – mTORi + VEGF ligand blockade may work #5039, 5104; S1, oral modulated fluoropyrimidine, activity in Japanese pts #5100; Perifosine, Akt inhibitor - modest activity #5034, 5101
Survival by the Memorial Sloan-Kettering Cancer Center Risk Factor Model

Risk factors associated with worse prognosis:
- KPS < 80
- Low serum hemoglobin (13 g/dL/11.5 g/dL: M/F)
- High corrected calcium (10 mg/dL)
- High LDH (300 U/L)
- Time from Dx to IFN-α < 1 yr

- 0 risk factors (164 patients, 30 alive)
- 1 or 2 risk factors (348 patients, 23 alive)
- 3, 4, or 5 risk factors (144 patients, 1 alive)

Years following systemic therapy
RCC: Role of VHL, HIFs and Growth Factors in Disease Progression

Paracrine Function

Autocrine Function

Tumor cell

Pericyte

Endothelial cell

EGF

PDGF

VEGF

HIF-1α

HIF-1α

HIF-1α

HIF-1β

RAS

RAF

MEK

ERK

PI3K

mTOR/Akt

p38MAPK

Paracrine Function

Paracrine Function

Pericyte

Endothelial cell
Treatment options for RCC have been revolutionized in a short period of time...

...but this rapid change has left many unanswered questions, including the optimal sequence of therapy.


High dose interleukin-2

Interferon-α

Sorafenib

Sunitinib

Temsirilimus

Everolimus

Bevacizumab + IFN?

Pazopanib?

Axitinib?

Interferon-α

1992–2005

2005

2006

2007

2008

2009
Final Overall Survival

- **Sunitinib (n=375)**
  - Median: 26.4 months
  - (95% CI: 23.0 - 32.9)

- **IFN-α (n=375)**
  - Median: 21.8 months
  - (95% CI: 17.9 - 26.9)

Hazard Ratio = 0.821
(95% CI: 0.673 - 1.001)

p = 0.051 (Log-rank)

nDeath/nRisk Sunit
375
61 / 295
46 / 242
48 / 229
52 / 187
14 / 61
4 / 2

nDeath/nRisk IFN-α
375
44 / 326
38 / 283
42 / 180
25 / 149
15 / 53
1 / 1

Figlin R et al., ASCO 2008, abstract #5024
TARGET: Preplanned Secondary Analysis
OS Data With Placebo Patients Censored

Sorafenib (n=451) = 17.8 months
Placebo (n=452) = 14.3 months
HR (sorafenib/placebo) = 0.78
95% CI: 0.62–0.97
P=0.0287*

Approximate start of crossover is 30 June 2005.

*Statistically significant: O’Brien–Fleming threshold for statistical significance □=0.037. Adapted from Bukowski RM et al. Presented at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.
Bevacizumab + IFN-α: Phase 3 Trials in mRCC

Patient population
Clear-cell mRCC

CALGB 90206
N=700

Randomization

IFN-α
9.0 MU TIW

IFN-α
9.0 MU TIW
+ Bevacizumab
10 mg/kg d 1, 15

BO17705 (Roche)
N=638

Randomization

IFN-α
9.0 MU TIW
+ Placebo
d 1, 15

Studies powered to detect increase in median survival >13.0–17.0 months

HR=0.63, p<0.0001
Median progression-free survival:
- Bevacizumab + IFN = 10.2 months
- Placebo + IFN = 5.4 months

Probability of being progression-free

**Progression-free survival (investigator assessed)**

Bevacizumab plus Interferon-alpha versus Interferon-alpha Monotherapy in Patients with Metastatic Renal Cell Carcinoma: Results of Overall Survival for CALGB 90206

Abstract 5019

Brian I. Rini¹, Susan Halabi²,³, Jonathan E. Rosenberg⁴, Walter M. Stadler⁵, Daniel A. Vaena⁶, James N. Atkins⁷, Joel Picus⁸, Piotr Czaykowskii⁹, Janice Dutcher¹⁰ and Eric J. Small⁴

1. Cleveland Clinic Taussig Cancer Institute, Cleveland, OH
2. Department of Biostatistics / Bioinformatics, Duke University Medical Center, Durham, NC
3. CALGB Statistical Center, Durham, NC
4. University of California San Francisco, San Francisco, CA
5. University of Chicago Medical Center, Chicago, IL
6. University of Iowa, Iowa City, IA
7. Southeast Cancer Control Consortium Inc.
8. Washington University, St. Louis, MO
9. University of Manitoba, Winnipeg, Manitoba; NCI Canada, Kingston, ON, Canada
10. New York Medical College, NY, NY; Eastern Cooperative Oncology Group, Boston, MA
Final Overall Survival by Treatment Arm: CALBG 90206

Kaplan-Meier Overall Survival Curves by Treatment Arm

Stratified log-rank p=0.069

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>BEV/IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>363</td>
<td>369</td>
</tr>
<tr>
<td>6</td>
<td>286</td>
<td>314</td>
</tr>
<tr>
<td>12</td>
<td>221</td>
<td>242</td>
</tr>
<tr>
<td>18</td>
<td>177</td>
<td>190</td>
</tr>
<tr>
<td>24</td>
<td>148</td>
<td>160</td>
</tr>
<tr>
<td>30</td>
<td>118</td>
<td>139</td>
</tr>
<tr>
<td>36</td>
<td>98</td>
<td>116</td>
</tr>
<tr>
<td>42</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>48</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>54</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

IFN: Median OS 17.4 months
BEV/IFN: Median OS 18.3 months
## Frequency of selected grade 3 or 4 AEs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Bevacizumab + IFN (n=366)</th>
<th>IFN (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 adverse event</td>
<td>79%</td>
<td>61%</td>
</tr>
<tr>
<td>Fatigue/asthenia/malaise</td>
<td>37%</td>
<td>30%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>Arterial ischemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Conclusions (Rini)

• **Overall survival** is greater in patients with metastatic clear cell RCC receiving bevacizumab plus interferon as initial systemic therapy compared to interferon alone, **but does not meet pre-defined criteria for significance**.

• Although the favorable effect of bevacizumab plus IFN on OS is preserved regardless of subsequent treatment, the most robust OS is achieved in patients with **favorable underlying disease biology** who are able to receive subsequent therapy.

• The combination of bevacizumab and IFN as initial therapy in metastatic RCC patients results in a significantly greater progression-free survival and objective response rate versus IFNA monotherapy.

• **Toxicity is greater** in the combination therapy arm, including more fatigue, anorexia, hypertension and proteinuria.
Final overall survival from phase III, randomised, double-blind AVOREN trial of first-line bevacizumab + interferon-α2a in metastatic renal cell carcinoma

Abstract 5020

IFN + Bevacizumab (n=327)
IFN + placebo (n=322)
HR=0.86 (95% CI: 0.72–1.04)
p=0.1291 (stratified*)

*Stratified by Motzer score and region

No difference in overall survival in either study

**CALGB 90206**
Rini, et al. Abstract # 5019

**AVOREN**
Escudier, et al. Abstract # 5020

**Median OS:** 23.3 vs. 21.3 months
**HR=0.86, p=0.1291**
Estimated 3 year OS (BEV/IFN) ~34%

**Median OS:** 18.3 vs. 17.4 months
**HR=0.86, p=0.069**
Estimated 3 year OS (BEV/IFN) ~31%

**Sunitinib vs. IFN phase III trial:**

**Median OS:** 26.4 vs. 21.8 months
**HR = 0.82, p = 0.051**
Estimated 3 year OS (sunitinib) ~ 42%

- Figlin, et al ASCO 2008
## Subsequent therapies

More patients in the control arm (IFN alone) received subsequent therapy, potentially blunting an overall survival endpoint.

<table>
<thead>
<tr>
<th>Treatment, n (%)</th>
<th>AVOREN (n=327)</th>
<th>IFN + placebo (n=322)</th>
<th>CALGB (n=351)</th>
<th>IFN monotherapy (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with &gt;1 treatment</td>
<td>55%</td>
<td>63%</td>
<td>54%</td>
<td>62%</td>
</tr>
<tr>
<td>VEGF Inhibitors</td>
<td>35%</td>
<td>37%</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>3%</td>
<td>4%</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Investigational therapy: Other, mTOR*</td>
<td>6%</td>
<td>4%</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Cytokines</td>
<td>10%</td>
<td>16%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Chemotherapy §</td>
<td>9%</td>
<td>15%</td>
<td>18%</td>
<td>14%</td>
</tr>
</tbody>
</table>
CALGB 90602: Median OS (months) according to treatment arm and subsequent therapy

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + Interferon</th>
<th>Interferon</th>
<th>Total (unstratified log-rank p comparing arms)</th>
<th>Stratified HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Received 2nd-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=408)</td>
<td>31.4</td>
<td>26.8</td>
<td>28.2</td>
<td>0.80 (p=0.055)</td>
</tr>
<tr>
<td><strong>Did not receive 2nd-line therapy</strong></td>
<td>13.1</td>
<td>9.1</td>
<td>10.2</td>
<td>0.82 (p=0.108)</td>
</tr>
<tr>
<td>(n=324)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18.3</td>
<td>17.4</td>
<td>18.1</td>
<td>0.86 (p=0.069)</td>
</tr>
</tbody>
</table>
AVOREN: Overall survival by post-protocol therapies

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
<th>Bevacizumab + IFN vs IFN + placebo (n)</th>
<th>Bevacizumab + IFN (months)</th>
<th>IFN + placebo (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent TKI**†</td>
<td>113 vs 120</td>
<td>38.6</td>
<td>33.6</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.56-1.13)</td>
</tr>
<tr>
<td>Subsequent sunitinib</td>
<td>83 vs 92</td>
<td>43.6</td>
<td>39.7</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.58-1.35)</td>
</tr>
<tr>
<td>Subsequent sorafenib</td>
<td>60 vs 50</td>
<td>38.6</td>
<td>30.7</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.44-1.20)</td>
</tr>
</tbody>
</table>

*Subsequent therapy defined as any post-protocol therapy, any line (before or after PD)
†TKIs include sunitinib, sorafenib, pazopanib, erlotinib, blinded sorafenib, blinded sunitinib and unspecified protein tyrosine kinase inhibitor
Take Home Points:

Bevacizumab + Interferon Phase III Updates

- Median OS and estimated 3 year survival rates for Bev/IFN are lower compared to sunitinib

- Partly explainable by differences in prognostic groups and (unseen) molecular profiles

- Is there a clear patient subset in which BEV/IFN should be used over sunitinib?
  - Good risk patient who may warrant cytokine therapy but who can not be given HD IL2.
  - Pre-existent LV dysfunction

- In light of survival, toxicity profiles, and convenience, sunitinib remains the preferred frontline therapy for most patients with advanced RCC

<table>
<thead>
<tr>
<th></th>
<th>Median OS (months)</th>
<th>3 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (ASCO '08)</td>
<td>26.4</td>
<td>~ 42%</td>
</tr>
<tr>
<td>BEV/IFN (CALGB)</td>
<td>18.3</td>
<td>~ 31%</td>
</tr>
<tr>
<td>BEV/IFN (Avoren)</td>
<td>23.3</td>
<td>~ 34%</td>
</tr>
</tbody>
</table>
Phase III Trial of Pazopanib in Locally Advanced and/or Metastatic Renal Cell Carcinoma

Abstract 5019

Cora N. Sternberg,1 Cezary Szczylik,2 Eun S. Lee,3 Pamela Salman,4 Jozef Mardiak,5 Ian D. Davis,6 Lini Pandite,7 Mei Chen,8 Lauren McCann,8 Robert E. Hawkins9

1San Camillo and Forlanini Hospitals, Rome, Italy; 2Military Institute of Medicine, Warsaw, Poland; 3National Cancer Center, Gyeonggi-do, Korea; 4Fundación Arturo López Pérez, Santiago, Chile; 5National Oncological Institute, Klenová, Bratislava, Slovakia; 6Austin Hospital, Melbourne, Australia; 7GlaxoSmithKline, Inc., Research Triangle Park, NC, USA; 8GlaxoSmithKline, Inc., Collegeville, PA, USA; 9University of Manchester and Christie Hospital NHS Foundation Trust, Manchester, UK
Phase III Trial of Pazopanib in Locally Advanced and/or Metastatic RCC

**Abstract # 5021**

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit (similar to sunitinib and sorafenib).

Patients with advanced RCC (N = 435)

Pazopanib 800 mg qd (n = 290)

Matching Placebo (n = 145)

Option to receive pazopanib via an open-label study at progression.

Stratification:
- ECOG PS 0 vs 1
- Prior nephrectomy
- Rx-naive (n = 233) vs 1 cytokine failure (n = 202)

Randomization 2:1

Sternberg, et al. ASCO 2009
# Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>Pazopanib (n = 290)</th>
<th>Placebo (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (CR + PR), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Cytokine-pretreated</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td><strong>Duration of response, weeks</strong></td>
<td>59</td>
<td>—</td>
</tr>
</tbody>
</table>

Sternberg, et al. ASCO 2009
Hazard Ratio = 0.46
95% CI (0.34, 0.62)
P value < 0.0000001

Median PFS
Pazopanib: 9.2 mo
Placebo: 4.2 mo

Sternberg, et al. ASCO 2009
Sunitinib
Median 11.0 months
(95% CI 10.7-13.4) from the first line study vs. interferon-α similar population

Hazard Ratio = 0.40
95% CI (0.27, 0.60)
*p value < 0.0000001

Median PFS
Pazopanib: 11.1 mo
Placebo: 2.8 mo
**PFS in Cytokine-Pretreated Subpopulation**

<table>
<thead>
<tr>
<th>TARGETs PFS</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>5.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.9</td>
</tr>
<tr>
<td>Hazard ratio (S/P)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Hazard Ratio = 0.54  
95% CI (0.35, 0.84)  
*P* value < 0.001

Median PFS  
Pazopanib: 7.4 mo  
Placebo: 4.2 mo
Pazopanib Summary

• Significant improvement in PFS and RR compared with placebo in treatment-naive and cytokine-pretreated patients

• Significant improvement in PFS was observed in all subgroups

• Acceptable safety profile

• Interim OS data are not mature
Most Common Adverse Events ($\geq 10\%$)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grs</th>
<th>Gr 3</th>
<th>Gr 4</th>
<th>All Grs</th>
<th>Gr 3</th>
<th>Gr 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92</td>
<td>33</td>
<td>7</td>
<td>74</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52</td>
<td>3</td>
<td>&lt; 1</td>
<td>9</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>4</td>
<td>0</td>
<td>10</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>38</td>
<td>&lt; 1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>&lt; 1</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>2</td>
<td>&lt; 1</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13</td>
<td>1</td>
<td>&lt; 1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> 4% of patients in pazopanib arm and 3% of patients in placebo arm had grade 5 adverse events.

<sup>b</sup> Included hemorrhage from all sites; 1% patients in pazopanib arm had grade 5 events.

Median exposure: **pazopanib 7.4 (0 - 23) vs placebo 3.8 (0 - 22) months**
## Selected Class Effects

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pazopanib (n = 290)</th>
<th>Placebo (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades, %</td>
<td>All Grades, %</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>6</td>
<td>(&lt; 1)</td>
</tr>
<tr>
<td>Mucositis / Stomatitis</td>
<td>4 / 4</td>
<td>&lt; 1 / 0</td>
</tr>
<tr>
<td>Arterial thromboembolic</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Associated with multi-target receptor tyrosine kinase inhibitors.

<sup>b</sup> 2% of arterial thromboembolic events were ≥ grade 3.
NCCN Guidelines: RCC (v.2.2009)

**First-line Therapy**
- Clinical trial
- Sunitinib [1]
- Temsirolimus ([1] for poor-prognosis patients, [2B] for selected patients of other risk groups)
- Bevacizumab + IFN-α [1]
- High-dose IL-2 for selected patients
- Sorafenib for selected patients
- And best supportive care

**Predominant clear-cell histology**
- Clinical trial (preferred)
- Temsirolimus ([1] for poor-prognosis patients, [2A] for other risk groups)
- Sunitinib
- Sorafenib
- Chemotherapy [3]:
  - gemcitabine or capecitabine or floxuridine or 5-FU or doxorubicin
  - (in sarcomatoid only)
- And best supportive care

**Non-clear cell histology**
- Clinical trial (preferred)
- Everolimus ([1] following TKI)
- Sorafenib ([1] following by cytokine; [2A] followed by TKI)
- Sunitinib([1] following by cytokine; [2A] followed by TKI)
- Temsirolimus ([2A] followed by cytokine and [2B] followed by TKI)
- IFN-α [2B]
- High-dose IL-2 [2B]
- Low-dose IL-2 ± IFN-α [3]
- Bevacizumab [2B]
- And best supportive care

**Subsequent Therapy** (use crossover regimen)
- Clinical trial (preferred)
- Everolimus ([1] following TKI)
- Sorafenib ([1] following by cytokine; [2A] followed by TKI)
- Sunitinib([1] following by cytokine; [2A] followed by TKI)
- Temsirolimus ([2A] followed by cytokine and [2B] followed by TKI)
- IFN-α [2B]
- High-dose IL-2 [2B]
- Low-dose IL-2 ± IFN-α [3]
- Bevacizumab [2B]
- And best supportive care

*Targeted agents are highlighted.

[ ]=NCCN category of evidence and consensus. 5-FU=fluorouracil; IL-2=interleukin-2.
<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapy (level 1)</th>
<th>Other Options (≥ level 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Good or Intermediate risk</td>
<td>Sunitinib</td>
<td>HD IL-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab + IFN</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib(?)</td>
<td>Clinical trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trial</td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>Poor risk</td>
<td>Temsirolimus</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Refractory</td>
<td>Cytokine</td>
<td>Sorafenib</td>
<td>Sunitinib, Bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
<td>Clinical trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td></td>
<td>VEGF; mTOR</td>
<td>Everolimus</td>
<td>Everything</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trial</td>
<td>Other VEGF TKIs</td>
</tr>
</tbody>
</table>

*Adapted from M Atkins, ASCO 2006 & R Bukowski ASCO 2007; Rini B ASCO 2008
Phase III Trial of the Angiogenesis Inhibitor Pazopanib vs Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma

Patients with metastatic RCC, treatment naïve
N~876

Primary end point: PFS
Secondary end point: OS, ORR, time to response, duration of response, safety, and QoL

A Prospective Randomized Trial of the mTOR Inhibitor Temsirolimus vs. Sorafenib in Advanced Renal Cell Carcinoma as Second-Line Therapy in Patients Who Have Failed First-Line Sunitinib Therapy

**Study Design:** International, Prospective, Randomized, Open-label, Outpatient, Multicenter Study

**Randomization**

- **Temsirilimus 25 mg IV q week**
  - n=220

- **Sorafenib 400 mg PO BID**
  - n=220

**Patients with advanced RCC, PD by RECIST criteria while receiving 1st line sunitinib therapy, at least 1 measureable lesion, at least 2 wks since prior treatment with sunitinib, palliative radiation therapy, and/or surgery, and resolution of all toxic effects of prior therapy, age ≥ 18**

**Primary end points:** PFS, safety and tolerability

**Secondary endpoints:** RR (CR & PR), OS, SD at 12, 24, 36 wks, clinical benefit (CR+PR+SD at > 24 wks), duration of response and best tumor shrinkage
AG-013736 (axitinib) vs. Sorafenib as Second-Line Therapy for Metastatic Renal Cell Cancer

Patients after disease progression to one prior systemic first-line treatment (N=540)

Primary end point: Compare PFS of patients receiving AG-013736 versus sorafenib in mRCC after disease progression to one prior systemic first-line regimen containing one or more of the following agents: sunitinib, bevacizumab + IFN alfa, temsirolimus or cytokine(s).

Secondary end point: OS, ORR, evaluate safety and tolerability, DR, compare symptoms’ severity

Randomization 1:1

Axitinib 5 mg BID

Sorafenib (2x200 mg) BID
<table>
<thead>
<tr>
<th></th>
<th>VEGF R1</th>
<th>VEGF R2</th>
<th>VEGF R3</th>
<th>PDGFR α</th>
<th>PDGFR β</th>
<th>KIT</th>
<th>FLT3</th>
<th>RET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>NA</td>
<td>90</td>
<td>100</td>
<td>50-60</td>
<td>80</td>
<td>68</td>
<td>46</td>
<td>100-150</td>
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<tr>
<td>Sunitinib</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>5-10</td>
<td>10</td>
<td>13</td>
<td>1-10</td>
<td>100-200</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>10</td>
<td>30</td>
<td>47</td>
<td>71</td>
<td>84</td>
<td>72</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Axitinib</td>
<td>1.2</td>
<td>0.2</td>
<td>0.3</td>
<td>5</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>AV-951</td>
<td>0.21</td>
<td>0.16</td>
<td>0.24</td>
<td>1.7</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BAY 73-4506</td>
<td>16</td>
<td>5</td>
<td>46</td>
<td>NR</td>
<td>74</td>
<td>7</td>
<td>440</td>
<td>1</td>
</tr>
<tr>
<td>ABT-869</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>35</td>
<td>31</td>
<td>48</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

* Inhibitory concentrations (kinase IC50 in nanomoles) for relevant targets.

The spectrum and potency of VEGF-R inhibitors is not identical.
Renal cancer therapeutics

Systemic therapy

- Surgery and/or cytokine therapy may be curative in some patients.
- Beyond this, Systemic therapy utilizes one of:
  - low dose cytokine treatment - interferon
    - Consider adding VEGF ligand inhibition to interferon
  - VEGF pathway inhibition
  - mTOR pathway inhibition
- Cytokines need to be used early to be effective.
- Therapeutic strategem should then be to maintain effective disease control and potentially prolong survival by providing optimal VEGF or mTOR pathway inhibition with the best side effect profile.
- Choice of therapy then becomes a merry-go-round where you may go back to a previously used drug class depending on past effect and toxicity profile.
- Different agents within the same class of agents may have different therapeutic indices and these indices may vary depending on where in the disease time course patients are exposed to a given drug.

Quinn DI at al. Clinical Cancer Biology for Dummies, in press.
Renal Cell Cancer Summary 2009

- High dose **Interleukin 2** remains the only curative therapy
- Role of **Interferon** alpha is in question
  - May still be useful as an adjunct to angiogenesis inhibitors

- Newer agents targeting angiogenesis such as **Sorafenib**, **Sunitinib** and **Temsirolimus** are approved and **EXTEND SURVIVAL**
- Everolimus is now approved for patients failing sorafenib or sunitinib
- AND finally **Bevazucimab** has been approved by the EMEA as well!
- AND NOW **Pazopanib** and **Axitinib** look promising
  - Delay progression and double PFS
  - Stable disease
  - Few complete responders
  - Directed at patient risk groups based on MSK criteria
- **Optimal dose scheduling** is still to be determined

- Building blocks for further progress
- Studies of tumor biology to identify markers of response are a priority
ASCO 2009: Prostate Cancer Highlights

Lazarus? The Androgen receptor lives! Even in CRPC #5002

Androgen receptor antagonism: MDV3100 #5011

Romancing the Stone? Optimal androgen deprivation: CYP19 inhibitors:
Abiraterone, TAK 700 #5046, 5047, 5048, 5049

Immunotherapy does something!? What? What cost? #5013, 5138, 5144, AUA 1408
Where do IL-6 & CRP fit into this? #5063, 5143, 5168

Epothilones & platins in CRPC: Do they have a place? #5059, 5139, 5140

Are clusterin, Bcl2, Src, mTOR/akt & IGF-1R really therapeutic targets?
#5001, 5012, 5062, 5142, 5147, 5154

SERMs and Rank Ligand inhibition for ADT-induced side effects: #5055, 5056

Gene classifiers - In clinical practice?: CTCs, Blood RNA, PCA3, TMPRSS2 rearrangements, PITX2, gene signatures #5000, 5052, 5054, 5132, 5124, 5162
Southwest Oncology Group S9921: Prolonged event-free survival in high-risk prostate cancer (PC) patients receiving adjuvant androgen deprivation

Abstract 5009


University of Colorado Health Sciences Center, Aurora, CO; Southwest Oncology Group, Seattle, WA; University of Michigan, Ann Arbor, MI; University of Texas Health Sciences Center, San Antonio, TX; University of Southern California, Los Angeles, CA; University of Maryland & CALGB, Baltimore, MD; Fox Chase Cancer Center & ECOG, Philadelphia, PA

• High risk locally advanced prostate cancer treated with RRP (n=859)
• Goserelin and Bicalutamide +/- mitoxantrone 6 cycles
• Data from Z+B arm only (426)
• Sequential PSA and testosterone measures
  • Median time to above castrate: 11.7 months
  • 89% by 18 months
  • 5-year PSA relapse >0.2 ng/ml in only 7.1%

Conclusion:
markedly low PSA relapse and death rates in high risk PC patients who received CAB
In 1940 Huggins reported that testosterone removal (castration) resulted in rapid shrinkage of the enlarged prostate of older dogs.

In 1941 Huggins and Hodges reported that androgen removal greatly aided patients with advanced prostate cancer.

“Prostatic cancer is influenced by androgenic activity in the body.”

Later that year, Huggins reported that oral estrogens had the same effect as castration for prostate cancer patients.
Evolution of Hormone Blockade

Orchiectomy | DES | LHRH Agonist | LHRH Agonist + Anti-androgen (CAB) | GnRH Antagonists

<1940 | 1940 | 1985 | 1989 | 2002-03

We were wrong!!

CAB = Complete androgen blockade is a misnomer
Inhibition of androgen receptor (AR) signaling

Androgen receptor

CoR vs Coactivators

NCoR/HDAC

Pol II

Transcription of AR target genes eg PSA

Activation of TMPRSS/ERG fusion

CoR

PSA

Pol II

AR

ARE

AR kinases

testosterone hormone

LHRH agonists / antagonists/ CYP17 inhibitors

Anti-androgens

Bicalutamide

Flutamide

Bicalutamide

Flutamide

AR

AR

AR

AR

AR

Pol II
The debate about AR in castrate resistant prostate cancer

1) AR is irrelevant because
   - it is not expressed in two commonly used prostate cancer cell lines
   - ADT use does not influence outcome in CRPC (it actually can)

2) However, AR activity is restored (e.g., PSA production) by
   - AR amplification
   - increased AR mRNA and protein
   - AR mutation
   - intracrine synthesis of androgens
   - alternative pathways (kinase activation)

3) And AR activation mRNA signatures are increased in high grade and metastatic disease, raising the question of whether AR is still relevant for growth and survival
Androgen Receptor Overexpression is Frequent in Castration Resistant Tumors and is a Target for Therapy

Increased AR protein
AR mRNA overexpression
Increased AR DNA copy number
Increased androgen synthesis
A multicenter phase II study of abiraterone acetate in docetaxel pretreated castration-resistant prostate cancer patients. Abstract 5047

Phase II multicenter study of abiraterone acetate plus prednisone therapy in docetaxel-treated castration-resistant prostate cancer patients: Impact of prior ketoconazole. Abstract 5048

Circulating tumor cells (CTC) in patients with metastatic castration-resistant prostate cancer (CRPC) receiving abiraterone acetate (AA) after failure of docetaxel-based chemotherapy. Abstract 5049
M. Fleisher, D. C. Danila, M. Leversha, D. Rathkopf, S. Slovin, A. Anand, M. Koscuiszka, C. Haqq, H. I. Scher

- Abiraterone produces clinical, PSA, radiological responses in patients with CRPC who have failed docetaxel
- Patients NOT exposed to prior ketoconazole are more likely to respond & have durable response
- Low dose corticosteroid reduces mineralocorticoid related toxicity such as HTN and ↓ K+
- Circulating tumor cell kinetics may predict outcome in patients treated with abiraterone
- Expression data for a variety of molecules in CTCs need to be evaluation for further predictive value

COU-AA-301, a phase III trial for CRPC patients who have received docetaxel based chemotherapy is currently accruing MORE IN 2010!!
Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer

Abstract 5011


Memorial Sloan-Kettering Cancer Center, New York, NY; Oregon Health and Science University, Portland, OR; University of Washington, Seattle, WA; Dana Farber Cancer Institute, Boston, MA; M.D. Anderson Cancer Center, Houston, TX; Medivation, San Francisco, CA; and the Prostate Cancer Clinical Trials Consortium
MDV3100
A Second-Generation Antiandrogen

Why are MDV3100 and similar compounds better than bicalutamide?

1. greater binding affinity for AR

2. different mechanism of AR inhibition
   - reduced nuclear localization
   - impaired DNA binding at AR target genes
   - induces an AR conformation that cannot bind co-activators
   - associated with resistance acquisition
Subcellular localization of GFP-AR is differentially affected by antiandrogens

Vehicle 1nM R1881 10 μM Bic

10 μM RD162 10 μM MDV3100

Yu Chen, Vivek Arora
MDV3100 and similar agents are superior to bicalutamide in the castrate-resistant LNCaP-AR xenograft model.
Phase 1-2 Multicenter Trial in CRPC (Prostate Cancer Clinical Trials Consortium)

- Determine safety
- Determine pharmacokinetics (PK)
- Assess antitumor activity:
  - Prostate-specific antigen (PSA)
  - Soft tissue
  - Bone
- Exploratory:
  - Circulating tumor cells
  - PET: FDG - 18-fluorodeoxyglucose
  - FDHT - 18-fluorodihydrotestosterone
Key Inclusion Criteria

1. Pathologic confirmation of adenocarcinoma of prostate

2. Serum testosterone level <50 ng/dL

3. Progressive disease defined as one or more of:
   - 3 rising PSA levels; screening PSA >2 ng/mL
   - RECIST
   - Two or more new lesions on bone scan

4. No more than 2 prior chemotherapy regimens, at least one of which contained docetaxel
MDV3100 Was Generally Well-Tolerated
Possibly Related Grade 2/3 Adverse Events in >2 Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Doses (N = 140)</th>
<th>240 mg/day (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2</td>
<td>G3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (21%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8%)</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (3%)</td>
<td>–</td>
</tr>
<tr>
<td>Seizure</td>
<td>–</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

1. Only one subject discontinued treatment due to fatigue which coincided with disease progression
2. Two witnessed seizures (one each at 600 and 360 mg/day) and a possible unwitnessed seizure (at 480 mg/day) were reported
   • Both patients with witnessed seizures were taking concomitant medications that can cause seizure
3. MTD determined to be 240 mg/day; patients at higher doses were lowered to 240 mg/day
Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naïve (N=65)

- 62% (40/65) >50% Decline

Post-Chemotherapy (N=75)

- 51% (38/75) >50% Decline
## Radiographic Changes in Soft Tissue (N=59) and in Bone (N=109)

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy-Naïve Patients (N=65)</th>
<th>Post-Chemotherapy Patients (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soft Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* (Best Response)</td>
<td>N=25</td>
<td>N=34</td>
</tr>
<tr>
<td>Partial Response</td>
<td>36% (9/25)</td>
<td>12% (4/34)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>44% (11/25)</td>
<td>53% (18/34)</td>
</tr>
<tr>
<td><strong>Bone Scan (Week 12)</strong></td>
<td>N=41</td>
<td>N=68</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>63% (26/41)</td>
<td>51% (35/68)</td>
</tr>
</tbody>
</table>

*59 patients with evaluable soft tissue disease as defined by PCWG2 consensus J Clin Oncol 2008.
Time to PSA Progression For Pre- and Post-Chemotherapy Treated Patients

Pre (Not reached)

Post (186 days)
Time to Radiographic Progression in Pre- and Post-Chemotherapy Treated Patients

- Pre: Not yet reached
- Post: 201 days
Summary and Conclusions

1. MDV3100 is a second-generation antiandrogen engineered for activity in cells that overexpress AR, unique from bicalutamide.

2. The drug is active in CRPC both before and after chemotherapy as shown by:
   - declines in PSA, imaging, CTC conversion rates, and PET

3. MDV3100 is generally well-tolerated

4. A Phase 3 placebo-controlled survival trial in post-docetaxel CRPC patients is beginning 2009

5. Dose selected to be 240 mg/day based upon:
   - Significant anti-tumor effects plateau at this dose
   - Few side effects
   - Benefit:risk ratio
Phase 3 Registration Trial of MDV3100 in Post-Chemotherapy CRPC Patients

Primary Endpoint: 25% survival increase (12 to 15 months)
Sample size: ~1170 (780 and 390)
Statistics: 85% Power; p=0.05, two-sided
Biomarkers: CTC enumeration and profiling with outcome

Scher, H. (North America) and De Bono, J. Co-PI, Medivation
Sipuleucel-T Immunotherapy for Advanced Prostate Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

IMPACT STUDY

David Penson, MD, MPH

For the IMPACT Study Investigators

American Urological Association Annual Meeting

Abstract 1408, April 28, 2009
Sipuleucel-T: Patient-Specific Therapy

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center
Dendreon
Doctor’s Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=512)

Sipuleucel-T Q 2 weeks x 3

Placebo Q 2 weeks x 3

2:1

PROGRESSION

Treated at Physician discretion

Treated at Physician discretion and/or Salvage Protocol

SURVIVAL

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression
Eligibility Criteria

- Metastatic androgen independent prostate cancer
- Life expectancy of at least 6 months
- Serum PSA ≥ 5.0 ng/mL
- Castrate level of testosterone (< 50 ng/dL) achieved via medical or surgical castration
- Adequate hematologic, renal, and liver function
- Negative serology for HIV 1 & 2, HTLV-1, and Hepatitis B & C
IMPACT Overall Survival: Primary Endpoint

Intent-to-Treat Population

\[ P = 0.032 \text{ (Cox model)} \]
\[ \text{HR} = 0.775 \ [95\% \ CI: 0.614, 0.979] \]

Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.
Time to Objective Disease Progression

- Secondary endpoint
- Result
  - Independent radiologic review
  - HR=0.951 (95% CI: 0.77, 1.17); P=0.628 (log rank)
- Consistent with other trials in advanced prostate cancer
- Difficult endpoint to measure reliably and doesn’t correlate with overall survival
### Most Common Adverse Events (≥ 5%)
Higher Rate in Sipuleucel-T (p ≤ 0.05)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Sipuleucel-T N = 338</th>
<th>Placebo N = 168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>54.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>9.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Summary

• First active immunotherapy to demonstrate improvement in overall survival for advanced prostate cancer
• Highly favorable benefit to risk profile
• Short duration of therapy
• Potential to create new treatment paradigm in oncology
ASCO 2009: Urothelial, Testis and Other GU Cancer Highlights

**Bevacizumab**

added to Cisplatin+Gem in adv urothelial cancer (AUC).

High DVT/PE rate; despite this long OS 19.1 months in phase II trial.

Phase III CALGB/Intergroup trial opening soon - tight safety monitoring #5018

Metastatic or unresectable AUC: **Sequenced chemotherapy** directed at >90% response; Doxorubicin, Ifosfamide, CDDP, Gemcitabine

4 regimens using triplets or Cisplatin+Gemcitabine with switch at 6 weeks if cancer volume not decreased by 40% followed by Surgical consolidation

Median OS 19.1 months. Complex. Approach deserves further testing #5071

**Testis cancer**: BEP remains standard first-line therapy. HDCT + SCT with various regimens (VICE, TICE, TAXIFII) for salvage #5016, 5027, 5028

**Adenocortical carcinoma**: Encouraging activity for insulin-like growth factor-1 receptor tyrosine kinase inhibitor (OSI-906)

2 randomized phase II trials to start late 2009: NCI/CTEP trial with mitotane and second line single agent pharmaceutical study #3544
Randomized trial of p53 targeted adjuvant therapy for patients (pts) with organ-confined node-negative urothelial bladder cancer (UBC).

Abstract 5017

University of Chicago, Chicago, IL; Baylor College of Medicine, Houston, TX; University of Southern California, Los Angeles, CA; Cleveland Clinic, Cleveland, OH; University of Michigan, Ann Arbor, MI; Sunnybrook Medical Center, Toronto, ON, Canada; Piedmont Urology Associates, High Point, NC

• p53 status may be prognostic in early bladder cancer
• The effect appears to extend to T2 bladder cancer
  • in which chemotherapy in neo-adjuvant setting is not of proven benefit
• Presented study profile 499 cases in a prospective fashion for p53 accumulation
  • 55% (n=272) p53 positive
• Offered randomization to MVAC x 3 or observation
  • 158 patients refused, 114 randomized: 58 MVAC, 56 observation
  • No difference in RFS or OS

Conclusions:
• The putative predictive value of p53 for chemotherapy benefit was NOT confirmed
• Randomization for these patients was a major challenge: closed for futility
A multicenter phase II study of cisplatin, gemcitabine, and bevacizumab as first-line therapy for metastatic urothelial carcinoma: Hoosier Oncology Group GU04-75

Abstract #5018

N. M. Hahn¹, W. M. Stadler², R. T. Zon³, D. Waterhouse⁴, J. Picus⁵, S. Nattam⁶, C. S. Johnson⁷, S. M. Perkins⁷, M. J. Waddell¹, C. J. Sweeney¹,⁸

¹Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, ²University of Chicago Cancer Research Center, Chicago, IL, ³Northern Indiana Cancer Research Consortium, South Bend, IN, ⁴Oncology and Hematology Care Inc., Cincinnati, OH, ⁵Washington University School of Medicine Siteman Cancer Center at Barnes-Jewish Hospital, St. Louis, MO, ⁶Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, ⁷Indiana University School of Medicine, Division of Biostatistics, ⁸University of Adelaide, Adelaide, Australia
Eligibility Criteria
- Metastatic UC (mUC)
- ECOG PS 0-1
- Cr < 1.5 mg/dl
- No prior CTx for mUC
- No anticoagulation
- No CNS mets

Maximum of 8 cycles of Cisplatin and Gemcitabine
Maximum 1 year of Bevacizumab therapy
*Gemcitabine reduced to 1000 mg/m² iv d1,8 after first 17 patients due to 7 DVT/PE events

Cisplatin
70 mg/m² iv d1

Gemcitabine*
1250 mg/m² iv d1,8

Bevacizumab
15 mg/kg iv d1

Cycle length = 21 days

Hahn, et al. ASCO 2009
## Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Gem 1250 (n=18)</th>
<th>Gem 1000 (n=25)</th>
<th>Total (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 3-4 %</td>
<td>Gr 3-5 %</td>
<td>Gr 3-5 %</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>39</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>HTN</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
<td>12*</td>
<td>7*</td>
</tr>
</tbody>
</table>

*One treatment related death due to cerebral hemorrhage was observed*
### Tumor Response

<table>
<thead>
<tr>
<th>Response Type</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong>*</td>
<td>6</td>
<td>14 (5-28)</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>19</td>
<td>44 (29-60)</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>13</td>
<td>30 (17-44)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>4</td>
<td>9 (3-22)</td>
</tr>
<tr>
<td><strong>Not Evaluable</strong></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Note: 3 patients underwent cystectomy for clinical CR. Pathologic results included - pT0 N0, pT1 N2, pT3 N0
Toxicity Timing

- Clin Sig Tox (n=18):
  - Cycles 1-2: 39%
  - Cycles 3-4: 28%
  - Cycles 5-6: 17%
  - Cycles 7-8: 17%

- DVT/PE (n=9):
  - Cycles 1-2: 67%
  - Cycles 3-4: 33%
  - Cycles 5-6: 0%
  - Cycles 7-8: 0%
Progression Free Survival

Median PFS = 8.2 m (95% CI 6.5 – 10.0)
Median follow-up = 14.6 m (Range 2-37)
12-month PFS = 29%

Overall Survival

Median OS = 19.1 m (95% CI 11.5 – 23.4)
Median follow-up = 14.6 m (Range 2-37)
12-month OS = 65%
Randomized phase III study of gemcitabine and cisplatin with or without bevacizumab in patients with advanced transitional cell carcinoma

**Schema**
1 cycle = 21 days

**ARM A**
- Gemcitabine 1000 mg/m² IV on Day 1 and Day 8 of every cycle
- Cisplatin 70 mg/m² IV on Day 1
- Placebo 15 mg/kg IV on Day 1

**Placebo** 15 mg/kg IV every 21 days

**ARM B**
- Gemcitabine 1000 mg/m² IV on Day 1 and Day 8 of every cycle
- Cisplatin 70 mg/m² IV on Day 1
- Bevacizumab 15 mg/kg IV on Day 1

**Bevacizumab** 15 mg/kg IV every 21 days

Treatment with gemcitabine and cisplatin should continue for a maximum of 6 cycles. Treatment with bevacizumab/placebo alone will continue until disease progression or unacceptable toxicity.
Conclusions: ASCO/AUA 2009

• Two new therapeutic agents in Renal Cell Carcinoma
  - Bevazicumab will likely have very specific approval with Interferon-α and in the first line
  - Pazopanib will likely have a broader approval
  - For the oncologist to decide on sequence of therapy

• AR continues to be a viable target in CRPC
  - CYP17 inhibitors: abiraterone, TAK 700
  - New second line AR antagonists: MDV3100

• Immunotherapy may be efficacious in CRPC
  - Data on Sipuleucel will be assessed in detail by the FDA

• Bevazicumab adds toxicity to GC for Urothelial Cancer but may also improve survival
  - Well orchestrated phase III trial will dissect the risk:benefit ratio

• Insulin-like growth factor-1 receptor modulation may have activity in adrenocortical carcinoma – 2 trials planned.