Oncology Highlights: ASCO 2009
Genitourinary Cancers

Abstracts: 5011, 5018, LBA5019, 5020, 5021, 5047, 5048, 5049

Andrea Harzstark, M.D.
Assistant Professor of Clinical Medicine
Helen Diller Family Comprehensive Cancer Center
Department of Medicine
University of California, San Francisco

Slides courtesy of Charles Ryan, M.D.

<table>
<thead>
<tr>
<th>Number</th>
<th>Disease</th>
<th>Author</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
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<td>Prostate Ca</td>
<td>Scher</td>
<td>MDV3100 – Novel Anti-Androgen</td>
</tr>
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<td>5018</td>
<td>Bladder Ca</td>
<td>Hahn</td>
<td>Gem/Cis/Bev in metastatic Urothelial Ca</td>
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<td>5047</td>
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<td>REID</td>
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<td>5048</td>
<td>Prostate Ca</td>
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<td>Abiraterone in Docetaxel refractory PC</td>
</tr>
<tr>
<td>5049</td>
<td>Prostate Ca</td>
<td>Fleisher</td>
<td>CTC in Abiraterone treated patients</td>
</tr>
</tbody>
</table>
Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer


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

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
MDV3100
A Second-Generation Antiandrogen

1. Engineered for activity in prostate cancer cells that overexpress the androgen receptor (AR).
2. Binds the AR more potently than bicalutamide.
3. Unlike bicalutamide, MDV3100 inhibits nuclear translocation of the AR and its binding to DNA.
4. Induces apoptosis in prostate cancer cells.

Trial Design

Cohort 1
- Single Dose 6 days
- Continuous Dosing
- Assess Monthly; Q3 Month Imaging
- Long-Term Dosing

Cohort 2
- After 28 Day Safety
- Single Dose 6 days
- Continuous Dosing
- Assess Monthly; Q3 Month Imaging
- Long-Term Dosing Indefinite

Subsequent Dose Levels
- Cohort expansion at ≥ 60 mg/day
- 12 pre- and 12 post-chemotherapy
- Post-chemotherapy only at ≥ 480 mg/day

Abstract # 5011
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. There were 2 witnessed seizures (1 each at 600 and 360 mg/day) and a possible unwitnessed seizure (at 480 mg/day).
   - 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

Abstract # 5011

Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naïve (N=65)  Post-Chemotherapy (N=75)

62% (40/65) ≥50% Decline
51% (38/75) ≥50% Decline

Abstract # 5011
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

5. MDV3100 is generally well-tolerated

6. A Phase 3 placebo-controlled survival trial in post-docetaxel CRPC patients is beginning this year
   Dose selected to be 240 mg/day based upon:
   - Significant anti-tumor effects plateau at this dose
   - Few side effects
   - Benefit:risk ratio

Abstract # 5011
Abiraterone

Abstracts 5047, 5048, 5049
Phase 2 multicenter study of abiraterone acetate plus prednisone therapy in docetaxel treated CRPC patients: Impact of prior ketoconazole.

Danila D\textsuperscript{1}, de Bono J\textsuperscript{2}, Ryan C\textsuperscript{3}, Denmeade S\textsuperscript{4}, Smith M\textsuperscript{5}, Taplin ME\textsuperscript{6}, Bubley G\textsuperscript{7}, Molina A\textsuperscript{8}, Haqq C\textsuperscript{9}, Scher H\textsuperscript{9}

\textsuperscript{1}Department of Medicine, Joan and Sanford E. Weill College of Medicine of Cornell University, New York, New York; \textsuperscript{2}Cancer Research UK Centre for Cancer Therapeutics, Institute of Cancer Research, Royal Marsden Hospital, UK; \textsuperscript{3}University of California-San Francisco Comprehensive Cancer Center, San Francisco CA; \textsuperscript{4}Chemical Therapeutics Program, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD; \textsuperscript{5}Division of Hematology-Oncology Massachusetts General Hospital, Boston, MA; \textsuperscript{6}Dana-Farber Cancer Institute, Harvard Medical School, Boston MA; \textsuperscript{7}Beth Israel Deaconess Medical Center, Boston, MA; \textsuperscript{8}Department of Clinical Research and Development, Cougar Biotechnology, Los Angeles, CA; \textsuperscript{9}Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY.

Abstract No: 5048

<table>
<thead>
<tr>
<th>Baseline Patient Characteristics</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age (Median)</th>
<th>69.5 years (range 44-86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>24 (41.1)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>31 (53.4)</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>2 ( 3.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 ( 1.7)</td>
</tr>
<tr>
<td><strong>Prior Hormonal Therapies:</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>LHRH Agonists</td>
<td>57 (98.3)\textsuperscript{1}</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>53 (91.4)</td>
</tr>
<tr>
<td>Estrogens</td>
<td>9 (15.5)</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Other estrogens</td>
<td>1 ( 1.7)</td>
</tr>
<tr>
<td>Steroids</td>
<td>21 (36.2)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>5 ( 8.6)</td>
</tr>
<tr>
<td>Other Steroids</td>
<td>20 (34.5)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>27 (46.6)</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td>3 ( 5.2)</td>
</tr>
</tbody>
</table>

Abstract No: 5048
In this study, the comparison between the decline in PSA >50% in keto-naïve patients vs. keto exposed patients was not statistically significant (p=0.07).

Abstract No: 5048

Circulating tumor cells (CTC) in patients with metastatic castration-resistant prostate cancer (CRPC) receiving abiraterone acetate (AA) after failure of docetaxel-based chemotherapy.

M. Fleisher, D. C. Danila, M. Leversha, D. Rathkopf, S. Slovin, A. Anand, M. Koscuiszka, C. Haqq, H. I. Scher

Abstract No: 5049
Investigators monitored changes in CTC number with therapy in patients treated with abiraterone therapy

<table>
<thead>
<tr>
<th>Pts # (pts total)</th>
<th>Baseline CTC</th>
<th>Post Therapy CTC</th>
<th>PSA decline&gt;50%</th>
<th>Time on protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (23%)</td>
<td>&gt;5 CTC</td>
<td>&lt;5 CTC</td>
<td>9</td>
<td>Group A</td>
</tr>
<tr>
<td>11 (23%)</td>
<td>&lt;5 CTC</td>
<td>&lt;5 CTC</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>24 (50%)</td>
<td>&gt;5 CTC</td>
<td>&gt;5 CTC</td>
<td>4</td>
<td>Group B</td>
</tr>
<tr>
<td>2 (4%)</td>
<td>&lt;5 CTC</td>
<td>&gt;5 CTC</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Among pts with baseline CTC >5, the CTC decline to <5 was associated with a decline in PSA by >50% (p<0.001).

Changes in CTC with treatment may represent valuable intermediary endpoints for clinical benefit.

Abstract No: 5049
Bladder Cancer

A multicenter phase II study of cisplatin (C), gemcitabine (G), and bevacizumab (B) as first-line therapy for metastatic urothelial carcinoma (UC): 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
Statistical Design

- Primary Endpoint
  - Progression Free Survival (PFS)
    - $(H_0)$ PFS = 7.5 months
    - $(H_1)$ PFS = 11.25 months
    - $\alpha = 0.10$, $\beta = 0.14$
    - Sample size = 40
    - 10% dropout rate expected
    - Final sample size = 45

- Secondary Endpoints
  - Response Rates
  - Toxicity
  - Overall Survival (OS)

Von der Maase H, et al, JCO 2000;17:3068-77

Gem/Cis/Bev - Study Schema

- Maximum of 8 cycles of Cisplatin and Gemcitabine
- Maximum 1 year of Bevacizumab therapy
  *Gemcitabine reduced to 1000 mg/m$^2$ iv d1,8 after first 17 patients due to 7 DVT/PE events

### Eligibility Criteria
- Metastatic UC
- ECOG PS 0-1
- Cr $< 1.5$ mg/dl
- No prior CTx for mUC
- No anticoagulation
- No CNS mets

ENROLLMENT

Cisplatin
70 mg/m$^2$ iv d1

Gemcitabine*
1250 mg/m$^2$ iv d1,8

Bevacizumab
15 mg/kg iv d1

Cycle length = 21 days

Abstract
#5018
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

Abstract #5018

Toxicity and Conclusions

- Bevacizumab adds significant toxicity
- The PFS of 8.2 months did not meet the designed primary endpoint
- The OS of 19.1 months is beyond that expected from cisplatin plus gemcitabine alone

Abstract #5018
Renal Cell Carcinoma

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

Brian I. Rini1, Susan Halabi2,3, Jonathan E. Rosenberg4, Walter M. Stadler5, Daniel A.Vaena6, James N. Atkins7, Joel Picus8, Piotr Czaykowski9, Janice Dutcher10, and Eric J. Small4

Bevacizumab FDA approved for use in combination with interferon alpha for metastatic RCC 8/3/09
Study Schema

N=732

Eligibility Criteria
- Confirmed metastatic RCC with a component of clear cell histology
- Karnofsky PS ≥ 70%
- Measurable or evaluable disease (by RECIST)
- No prior systemic treatment
- Adequate end-organ function
- No CNS metastases
- BP < 160/90 with meds
- No DVT within 1 year or arterial thrombotic event within 6 months
- Prior nephrectomy not required

• Patients stratified for nephrectomy status (yes/no) and MSKCC risk group (0 risk factors vs. 1-2 risk factors vs. 3 or more risk factors)*

LBA5019
* Motzer R et al., JCO 20(1), 2002

Kaplan-Meier Progression-Free Survival by Treatment Arm

- Median PFS 8.4 months
- Median PFS 4.9 months
- HR= 0.71 (95% CI=0.6-0.8)

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>BEV/IFN</th>
<th>BEV/IFN 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>363</td>
<td>145</td>
<td>77</td>
<td>47</td>
</tr>
<tr>
<td>47</td>
<td>36</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>26</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

LBA5019
Kaplan-Meier Overall Survival by Treatment Arm

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEV/IFN</td>
<td>18.3</td>
</tr>
<tr>
<td>IFN</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Percentage of patients receiving any second-line therapy:
- Bevacizumab + IFN (n=351): 54%
- IFN monotherapy (n=350): 62%
- VEGF-targeted therapy: 37% (Bevacizumab + IFN) vs 46% (IFN monotherapy)
- Bevacizumab: 6% (Bevacizumab + IFN) vs 14% (IFN monotherapy)
- Chemotherapy: 18% (Bevacizumab + IFN) vs 14% (IFN monotherapy)
- Investigational therapy: 11% (Bevacizumab + IFN) vs 18% (IFN monotherapy)
- Cytokines: 13% (Bevacizumab + IFN) vs 14% (IFN monotherapy)

* Fifty-six percent of patients overall received at least one subsequent systemic therapy
### 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> (n=408)</td>
<td>31.4</td>
<td>26.8</td>
<td>28.2 (p=0.079)</td>
<td>0.80 (p=0.055)</td>
</tr>
<tr>
<td><strong>Did not receive 2nd-line therapy</strong> (n=324)</td>
<td>13.1</td>
<td>9.1</td>
<td>10.2 (p=0.059)</td>
<td>0.82 (p=0.108)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18.3</td>
<td>17.4</td>
<td>18.1 (p=0.097)</td>
<td>0.86 (p=0.069)</td>
</tr>
</tbody>
</table>

### Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Bev + IFN (n=325)</th>
<th>IFN (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response rate</strong></td>
<td>25.5% [95% CI = 20.9-30.6]</td>
<td>13.1% [95% CI = 9.5-17.3]</td>
</tr>
<tr>
<td>CR</td>
<td>3.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>PR</td>
<td>23.4%</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

p < 0.0001

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>Bev + IFN (n=325)</th>
<th>IFN (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.9 months [95% CI = 8.3 – 14.8]</td>
<td>9.7 months [95% CI = 7.6 – 19.8]</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.362

Note: patients with measurable disease only
Final results of the phase III, randomised, double-blind AVOREN trial of first-line bevacizumab + interferon-α2a in metastatic renal cell carcinoma

Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, Ravaud A, Golding S, Jethwa S on behalf of the AVOREN investigators

Abstract # 5020

AVOREN study design

Nephrectomised patients with advanced RCC (n=649)

- Stratification: Country
- MSKCC risk group

IFNα + Bevacizumab (n=327) → PD

1:1

IFNα + placebo (n=322) → PD

• Endpoints
  - primary: OS
  - secondary: PFS, TTP, TTF, RR, safety

• Treatment
  - bevacizumab/placebo 10mg/kg i.v. q2w
  - IFN 9MIU s.c. t.i.w. (maximum 52 weeks)

Abstract # 5020

*PFS is the primary endpoint for regulatory approval in the USA
Summary of published AVOREN data

• Final analysis of PFS performed at the time of the interim analysis
  – significant increase from 5.4 to 10.2 months when bevacizumab is combined with IFN (HR=0.63; p=0.0001)\(^1\)
  – good safety profile

• By reducing the IFN dose for safety issues
  – PFS benefit is maintained\(^2\)
  – decreased incidence of grade 3/4 events\(^2\)

Abstract # 5020

Objectives

• Final analysis of OS
• Clinical cut-off September 2008
• Median follow-up: 22 months
• Statistical considerations
  – required 445 events from 649 randomised patients
  – 80% power to detect an improvement in OS from 13 to 17 months
  – corresponding to an HR of 0.76 at a two-sided overall significance level of 0.05

Abstract # 5020
Final OS

- 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

OS by post-protocol therapies

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
<th>IFN + Bevacizumab vs IFN + placebo (n)</th>
<th>Median OS (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>0.80</td>
</tr>
<tr>
<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>0.88</td>
</tr>
<tr>
<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>0.73</td>
</tr>
<tr>
<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 TKI

Abstract # 5020
Phase III Trial of Pazopanib in Locally Advanced and/or Metastatic Renal Cell Carcinoma

Cora N. Sternberg,1 Cezary Szczylík,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

Abstract No: 5021

Pazopanib

• An oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit

• Clinical efficacy demonstrated in advanced RCC in a Phase II study1

Kinase affinity profile

<table>
<thead>
<tr>
<th>Kinase</th>
<th>$K_{app}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-1</td>
<td>15</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>8</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>10</td>
</tr>
<tr>
<td>PDGFR-α</td>
<td>30</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td>14</td>
</tr>
<tr>
<td>c-Kit</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abstract No: 5021

Study Design

Patients with advanced RCC (N = 435)

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

Randomization 2:1

Pazopanib 800 mg qd (n = 290)
Matching Placebo (n = 145)

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

PFS in Overall Study Population

Hazard Ratio = 0.46
95% CI (0.34, 0.62)
P value < 0.0000001

Median PFS
Pazopanib: 9.2 mo
Placebo: 4.2 mo

Proportion Progression-Free

Patients at risk
Pazopanib 290 159 76 29 6
Placebo 145 38 14 2
PFS in Treatment-Naive Subpopulation

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

Median PFS
Pazopanib: 11.1 mo
Placebo: 2.8 mo

Subgroup Analysis of PFS

Baseline Factor

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
</tr>
<tr>
<td>MSKCC risk: Favorable</td>
</tr>
<tr>
<td>MSKCC risk: Intermediate</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age &lt; 65 yrs</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
</tr>
<tr>
<td>ECOG PS 0</td>
</tr>
<tr>
<td>ECOG PS 1</td>
</tr>
</tbody>
</table>

P < 0.001 by log-rank test for all.
Interim Analysis of Overall Survival

- **Hazard Ratio**: 0.73
- **95% CI**: (0.47, 1.12)
- **P value**: 0.02 (1-sided)

[Graph showing Kaplan-Meier survival curves for Pazopanib and Placebo.]

- **Median OS**: Pazopanib: 21.1 mo, Placebo: 18.7 mo
- **Proportion Surviving**
- **Hazard Ratio** = 0.73
- **95% CI**: (0.47, 1.12)
- **P value**: 0.02 (1-sided)

Most Common Adverse Events (≥ 10%)

<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 Grs</td>
<td>Gr 3</td>
</tr>
<tr>
<td>Any event*</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>38</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhageb</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

*4% of patients in pazopanib arm and 3% of patients in placebo arm had grade 5 adverse events.

b 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
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
- The safety profile was acceptable
- Interim OS data are not yet mature
- FDA decision expected November 2009

- Probably the last placebo arm study in TKI naïve patient population

Thank you