Novel Therapies for Advanced Thyroid Cancer

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Objectives

• Review the current treatment of Iodine Non-Avid, Metastatic Thyroid Cancer.
• Introduce New Agents in Currently in Clinical trials.
• Present our current experience treating these patients with sorafenib

– Marcia S. Brose MD PhD

Disclosure Elements

• Relevant Financial Disclosures
  – My goal is to present information on a several investigational agents currently under investigation for the treatment of advanced thyroid cancer including our clinical trial of sorafenib for metastatic thyroid cancer. This trial was investigator initiated at the University of Pennsylvania. Only study drug was provided by Bayer/Onyx pharmaceuticals.
  – I have received honoraria/consulting fees in the past from Onyx pharmaceuticals and Bayer Healthcare.

– Marcia S. Brose MD PhD

Thyroid Cancer in the United States

• Thyroid cancer is the most common endocrine neoplasm.
• Thyroid cancer will be diagnosed in 33,550 individuals (8,070 men and 25,480 women) this year.
• From 1997-2004 incidence of thyroid cancer increased by 6.2% mostly due to increased detection.
• From 1985 to 2004 mortality rate increased by 0.3% a year.
Initial disease stage predicts OVERALL SURVIVAL

Stage I: 75% of all tumors
Stage II: 25% of all tumors
Stage III: 25% of all tumors
Stage IV: 0%

Initial disease stage predicts OVERALL SURVIVAL

Stage I: 75% of all tumors
Stage II: 25% of all tumors
Stage III: 25% of all tumors
Stage IV: 0%

Thyroid Cancer in the United States

Lymphoma
Medullary
Anaplastic

Follicular
Papillary
Histopathologic Subtypes

- Thyroid follicular cell: Papillary, Follicular, Hurthle
- Poorly differentiated carcinoma
- Anaplastic thyroid cancer
- C-cell: Medullary Thyroid Cancer

Thyroid Cancer in the United States

New Diagnosis
- Hürthle 3%
- Anaplastic 2%
- Follicular 15%
- Papillary 86%

Cancer Deaths
- Anaplastic 11%
- Hürthle 12%
- Follicular 27%
- Papillary 50%

Metastatic Thyroid Cancer: Treatment Strategy
- Low Risk: (Age <45, female, local dz only, interthyroidal, <4cm)
  - Thyroidectomy (all nodules greater than 1cm)
- High Risk: (Age >45, male, metastasis, extrathyroidal extension, >4cm)
  - Total Thyroidectomy
  - RAI ($^{131}$I) Ablation
  - TSH Suppression Therapy
  - Follow Serial Thyroglobulin Levels (Tg)
  - XRT for recurrent local disease/positive margins

RAI-Refractory Disease
- 25-50% of Metastatic Thyroid Cancers lose ability to take up Iodine
- Iodine Uptake inversely correlates with Survival
- This is attributed to down regulation of the Na+/I- Symporter (NIS)
- Standard Chemotherapy has minimal efficacy
FDG-PET Predicts for survival in patients with metastatic thyroid cancer

- 176/179 alive (FDG-negative)
- 156/223 alive (FDG-positive)
- Median survival ~ 53 mo.

RAI-Refractory Disease

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- This is attributed to down regulation of the Na+/I- Symporter (NIS)
- Standard Chemotherapy has minimal efficacy

FDA Approval of Adriamycin for treatment of metastatic thyroid cancer

“Adriamycin appears to be a promising new regimen for patient with progressive metastatic thyroid cancer”

ECOG E2375: Randomized Trial of Adriamycin vs Adriamycin + Cisplatin

- Shimoaka et al., Cancer, (1985) 56:2155
Molecular Subtypes

<table>
<thead>
<tr>
<th>Molecular Subtypes</th>
<th>Thyroid Cancer Subtype</th>
<th>Status</th>
<th>Company</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-RAF V600E</td>
<td>All</td>
<td>Accruing</td>
<td>Bayer/Onyx</td>
<td>UPenn, Case, Cleveland Clinic, OSUMC</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>ATC (single agent) MTC (with chemos)</td>
<td>Accruing</td>
<td>Novartis</td>
<td>U. Michigan</td>
</tr>
<tr>
<td>RAS</td>
<td>ATC</td>
<td>Accruing</td>
<td>Pfizer</td>
<td>Univ Hospital, Bordeaux, France</td>
</tr>
<tr>
<td>PAX8-PPARγ</td>
<td>ATC</td>
<td>Open/Not Accruing</td>
<td>AstraZeneca</td>
<td>Wash U (Sam Wells)</td>
</tr>
<tr>
<td>RET</td>
<td>ATC</td>
<td>Open/Not Accruing</td>
<td>AstraZeneca</td>
<td>Wash U (Sam Wells)</td>
</tr>
<tr>
<td>100% Hereditary MTC</td>
<td>Open/Not Accruing</td>
<td>Pfizer</td>
<td>Univ of Chicago, FACC, MDAnderson</td>
<td></td>
</tr>
<tr>
<td>40% Sporadic</td>
<td>Open/Not Accruing</td>
<td>Pfizer</td>
<td>MDAnderson</td>
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</tbody>
</table>

* Higher in radiation exposure populations

Phase II Trials of Kinase Inhibitors for Metastatic Thyroid Cancer

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Thyroid Cancer Subtype</th>
<th>Status</th>
<th>Company</th>
<th>Sites</th>
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</thead>
<tbody>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>All</td>
<td>Accruing</td>
<td>Bayer/Onyx</td>
<td>UPenn, Case, Cleveland Clinic, OSUMC</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>ATC (single agent) MTC</td>
<td>Accruing</td>
<td>Novartis</td>
<td>U. Michigan</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>ATC, MTC</td>
<td>Accruing</td>
<td>Pfizer</td>
<td>Univ Hospital, Bordeaux, France</td>
</tr>
<tr>
<td>Vandetinib (Zactima)</td>
<td>ATC</td>
<td>Open/Not Accruing</td>
<td>AstraZeneca</td>
<td>Wash U (Sam Wells)</td>
</tr>
<tr>
<td>Axitinib</td>
<td>ATC</td>
<td>Open/Not Accruing</td>
<td>Pfizer</td>
<td>Univ of Chicago, FACC, MDAnderson</td>
</tr>
<tr>
<td>Motesanib (AMG-706)</td>
<td>ATC</td>
<td>Open/Not Accruing</td>
<td>Amgen</td>
<td>MDAnderson</td>
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</table>

Targets of Kinase Inhibitors for Metastatic Thyroid Cancer

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>VEGFR</th>
<th>BRAF</th>
<th>PDGFR</th>
<th>KIT</th>
<th>RET</th>
<th>EGFR</th>
<th>Other</th>
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<tbody>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>FLT-3</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>FLT-3</td>
</tr>
<tr>
<td>Vandetinib (Zactima)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axitinib (AG-013736)</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Motesanib (AMG-706)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
### Other Phase II Trials for Metastatic Thyroid Cancer

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Therapeutic Targets</th>
<th>Drug Class</th>
<th>Thyroid Cancer Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabretastatin A4</td>
<td>Tubulin-binding protein</td>
<td>Anti-Angiogenic</td>
<td>ATC</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>unknown</td>
<td>Anti-Angiogenic</td>
<td>DTC</td>
</tr>
<tr>
<td>17-AAG, 17-DMAG</td>
<td>HSP-90</td>
<td>HSP-90 Derivative</td>
<td>DTC, MTC</td>
</tr>
<tr>
<td>Depsipeptide (FR901228)</td>
<td>Histone Deacetylase</td>
<td>HDAC Inhibitor</td>
<td>DTC</td>
</tr>
<tr>
<td>Decitabine</td>
<td>DNA Methylase</td>
<td>DNA Methylation inhibitor</td>
<td>DTC</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>26S Proteosome</td>
<td>Proteosome Inhibitor</td>
<td>DTC</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Topoisomerase</td>
<td>Topoisomerase Inhibitor</td>
<td>MTC</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>PPAR-Gamma</td>
<td>PPAR-Gamma Agonist</td>
<td>DTC, ATC</td>
</tr>
</tbody>
</table>

### BRAF V600E in Thyroid Cancer

- **2003** The BRAF V600E mutation is the most common genetic alteration in thyroid cancer, occurring in about 45% of sporadic papillary thyroid cancers (PTCs).

### Sorafenib

- Multi-tyrosine kinase inhibitor targeting RAF kinases, and VEGFR2 among others.

<table>
<thead>
<tr>
<th>(In vitro) Assay</th>
<th>IC50 (mM)</th>
</tr>
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<tbody>
<tr>
<td>CRAF</td>
<td>0.002/0.006</td>
</tr>
<tr>
<td>BRAF wt</td>
<td>0.025</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>0.038</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>0.090</td>
</tr>
<tr>
<td>FLT3</td>
<td>0.058</td>
</tr>
<tr>
<td>c-KIT</td>
<td>0.068</td>
</tr>
<tr>
<td>FGFR1</td>
<td>0.580</td>
</tr>
</tbody>
</table>

Wilhelm (Cancer Research, 2004)

Fabian, MA (Nature Biotechnology, 2005)
Targeting Thyroid Cancer with Sorafenib

- **April 2003**: BRAF identified in 35-69% of papillary thyroid cancers (Kimura et al., Cohen et al., 2004).
- **October 2003**: Patient with metastatic thyroid cancer and multiple pulmonary nodules began treatment with sorafenib at the University of Pennsylvania:
  - Toxicities were all grade 1 (Hand/Foot syndrome, and GI).
  - At 12 weeks patient achieved a PR (50% decrease RECIST).
- **October 2008**: He has completed over 5 years of therapy and he continues to maintain a stable response (70% decrease in tumor by RECIST).
  - At five years he has the longest response to sorafenib.

UPCC 03305: Objectives

- **Primary**
  - Determine the activity of sorafenib in metastatic thyroid cancer (CR/PR rate by RECIST)
- **Secondary**
  - Safety profile of sorafenib in thyroid cancer patients
  - Progression Free Survival
  - Duration of response
  - Overall survival
  - Pharmacokinetics
  - Explore relationships between clinical response and tissue vascular and differentiation characteristics

UPCC 03305: Trial design

- **Design**
  - Phase II, single arm, single institution trial
  - Primary endpoint overall response rate
  - Null Hypothesis: RR=5%
  - Two stage design:
    - Stage I: 30 patients
    - Total accrual of 55 patients
- **Treatment**
  - Sorafenib 400 mg PO BID (starting dose)
  - CT assessment at months 2, 4 and Q 3 months thereafter
### UPCC 03305: Most-Common Treatment-Related Toxicities

- Fatigue
- Hand-Foot
- Rash
- Diarrhea
- Weight Loss
- Musculoskeletal Pain

### D.T. Progression by the radiologist

44.5% PR by RECIST

### UPCC 03305: Stage I Patient Demographics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>15/15</td>
<td>50</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>18</td>
<td>60%</td>
</tr>
<tr>
<td>Follicular/Hurthle cell variant</td>
<td>9</td>
<td>30%</td>
</tr>
<tr>
<td>Medullary</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Poorly Differentiated/Anaplastic</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Prior Surgery</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Prior ¹³¹I Therapy</td>
<td>28</td>
<td>93%</td>
</tr>
<tr>
<td>Prior Chemotherapy/Adriamycin regimen</td>
<td>3/2</td>
<td>10/7</td>
</tr>
<tr>
<td>Other investigational agents</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>PET completed/FDG uptake positive</td>
<td>29/29</td>
<td>97/97</td>
</tr>
</tbody>
</table>

Age Range: 30-86

90% DTC

### UPCC O3305: Stage I analysis

<table>
<thead>
<tr>
<th>Table 2. Patient Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n)</td>
</tr>
<tr>
<td>Total evaluable patients</td>
</tr>
<tr>
<td>Best response by RECIST (n)</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response (≥30%)</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>Overall Median Progression Free Survival</td>
</tr>
<tr>
<td>for patients with Differentiated thyroid</td>
</tr>
<tr>
<td>cancer only</td>
</tr>
</tbody>
</table>
**UPCC 03305: February 2006-Present**  
Stage I analysis at 30 patients

- Results: 25 evaluable patients
  - PR 23% (7pts)
  - SD 54% (16 pts)
  - **Clinical benefit 77% (23)**
- Exact Binomial Confidence Interval excludes the null hypothesis (p<.0001)
- Response Rate in PTC vs. FTC is not statistically significant although power is low
- Progression free survival is 79 weeks. 84 weeks in patients with Differentiated thyroid cancer.

**Other Treatment Related Grade 3+ Adverse Events***

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Hand Foot</td>
<td>2</td>
<td>(7)</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>(7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Pruritis/Skin Discomfort</td>
<td>2</td>
<td>(7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>(10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>(7)</td>
</tr>
<tr>
<td>LFT elevation (grade 5)</td>
<td>1</td>
<td>(3)</td>
</tr>
</tbody>
</table>

*relationship 3-possible to 5-probable
**UPCC 03305: Progression Free Survival**

Kaplan Meier curves reveal a PFS of 72 weeks for all patients on study (A), and a PFS of 84 weeks for DTCs alone (B). Data reflect outcomes as of May for the first 30 patients enrolled through October 2007, used for the planned interim analysis.

**Conclusions Phase I**

- Several new agents in the clinic show promise in improving PFS in patients with advanced thyroid cancer.
- The agents furthest along in development are kinase inhibitors (Axitinib, Vandetanib, and Sorafenib) all of which target VEGFR2.
- These agents are safe, taken orally and have manageable side effect profiles.
- Sorafenib is a multi-kinase inhibitor which targets RAF and VEGFR2 among others.
- Sorafenib has anti-tumor activity with a response rate of 21% and SD of 59% for an 80% clinical benefit in advanced thyroid cancer.
Two Targets of sorafenib: Vascular endothelial cells and the tumor cells

Quantitation and Analysis of Pharmacodynamics Using Histocytometry in Patients treated on UPCC 03305

Pre-therapy

On-therapy (1 week)

Quantitation and Analysis of Pharmacodynamics (Bill Lee): p-AKT immunostaining in thyroid carcinoma treated with sorafenib

Pre-therapy

On-therapy (1 week)
Future Directions

• Understand the Basis of Progression by examining biomarkers in tissue that predict for response, and examine the activity of molecular targets at the time of progression (genotyping and other analysis)

• Open additional trials to expand options for patients with advanced disease to investigate new agents for patients that have progressed on sorafenib.

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  - Michael Feldman MD PhD
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