New Developments in Thyroid Cancer

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Disclosure

Dr. Sherman has the following relevant financial relationships with commercial interests to disclose:

• Consultant: Bristol-Myers Squibb
Classification & Incidence of Thyroid Cancer

Follicular cell origin

- Differentiated
  - Papillary  80%
  - Follicular 10%
  - Hurthle cell 3-5%
- Undifferentiated
  - Anaplastic 1-2%

Parafollicular cell origin

- Medullary 5%
Rising Incidence of Thyroid Cancer
Thyroid Cancer Research

• Lack of research for years
• ASCO Annual Meetings abstracts of clinical studies involving thyroid cancer (chemotherapy related)

• 2000-2005 – No Abstracts
• 2006-2010 – 38 Abstracts
RAI-REFRACTORY DISEASE

- 25-50% of metastatic thyroid cancers lose iodine concentrating ability

- Standard chemotherapy has disappointing response rates and significant toxicity
  - Not well studied; limited prospective evidence
# Doxorubicin: Single-agent Activity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb et al.</td>
<td>1972</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Frei et al.</td>
<td>1972</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td>Gottlieb and Hill</td>
<td>1974</td>
<td>5/15 (33%)</td>
</tr>
<tr>
<td>O'Bryan et al.</td>
<td>1977</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>Kolaric et al.</td>
<td>1977</td>
<td>5/16 (31%)</td>
</tr>
<tr>
<td>Burgess and Hill</td>
<td>1978</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td>Leeper and Shimaoka</td>
<td>1980</td>
<td>2/7 (28%)</td>
</tr>
<tr>
<td>Benker and Reinwein</td>
<td>1983</td>
<td>8/11 (73%)</td>
</tr>
<tr>
<td>Pacini et al.</td>
<td>1984</td>
<td>4/5 (90%)</td>
</tr>
<tr>
<td>Droz et al.</td>
<td>1990</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>42/109 (38.5%)</strong></td>
</tr>
</tbody>
</table>
Role of Molecularly Targeted Agents in Thyroid Cancer
Targets in Thyroid Cancer

- Angiogenesis pathway (all subtypes)
- Follicular Cell Derived Thyroid Cancer
  - MAPK pathway \((RET-BRAF-RAS)\)
  - PI3K/AKT/mTOR \((RET-RAS-PTEN-PIK3CA-AKT1)\)
- Medullary Thyroid Cancer
  - \(RET\)
Medullary Thyroid Cancer

RET
Medullary Thyroid Cancer

- Synaptophysin
- Chromogranin
- CEA
- Calcitonin
MTC: hereditary vs sporadic?

- 20 - 25% of MTC are hereditary
  - Germline mutations in RET proto-oncogene (Rearranged during Transfection)
  - Autosomal dominant inheritance
- Three subtypes:
  - MEN2A
  - MEN2B
  - Familial medullary thyroid cancer (FMTC)
Sporadic MTC
Frequency of RET mutations

Vandetanib

- Tyrosine Kinase Inhibitor targeting VEGF-R 1 to 3, PDGFR, RET
- Recently approved by the US-FDA for advanced MTC
- First-in-class agent to be approved for this disease setting
Patients with unresectable locally advanced or metastatic MTC (N=331)

2:1 randomization

Vandetanib 300 mg/day
n=231
Follow for progression
Discontinue blinded treatment at progression
Optional open-label vandetanib 300 mg/day
Follow for survival

Placebo
n=100
Follow for progression

Provided By Sam Wells
PFS (primary endpoint)

Hazard ratio = 0.46 (0.31–0.69); \( P < 0.0001 \)

Median: not reached (vandetanib); 19.3 months (placebo)

Hazard ratio <1 favors vandetanib
### Objective tumor assessments

<table>
<thead>
<tr>
<th></th>
<th>Vandetanib 300 mg (n=231)</th>
<th>Placebo (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate</strong></td>
<td>45% (104)</td>
<td>13% (13)</td>
</tr>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td>5.48 (2.99–10.79), P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- 12 of 13 responses on the placebo arm occurred while patients were receiving vandetanib in the open-label phase.
- Objective responses were durable; median duration of response not reached at 24 months of follow-up.

Odds ratio >1 favors vandetanib

*Including all scans until progression according to central read.

Provided by Sam Wells
XL184 Preclinical Rationale

- Potent inhibitor of MET, VEGFR2, and RET
- Active against common mutants of MET and RET

Promotes angiogenesis, tumor cell proliferation, migration, and survival

Induces angiogenesis

Involved in the pathogenesis of MTC; Partially controls MET expression
Best Timepoint Response for 35 MTC Patients with Measurable Disease, Per Investigator Report

- 49% (17/35) experienced a tumor shrinkage of ≥ 30% on at least one post-baseline scan
- 29% (10/35) of patients with measurable disease had confirmed PR

Tumor shrinkage was observed regardless of RET mutation status
Best Timepoint Response for TKI Naïve versus TKI Pre-Treated MTC Patients

TKI Naïve (n = 19)  TKI Pre-Treated (n = 15)

TKI, tyrosine kinase inhibitor; V, vandetanib

• Three patients with known prior vandetanib therapy had tumor shrinkage

Patient was on randomized trial and may have received vandetanib
Angiogenesis Inhibition
VEGF and Thyroid Cancer

↑↑ VEGF levels

↑ Recurrence

↓↓ DFS

– Malignant thyroid tissue vs. Benign thyroid tissue

Sorafenib

- Tyrosine Kinase Inhibitor
- Target VEGF-R 1 to 3, PDGF receptor, RET
- In addition it is a RAF kinase inhibitor

- Currently FDA-approved for the treatment of kidney and liver cancers
Sorafenib
University of Pennsylvania

- Group: Iodine-Refractory Thyroid Cancer
  - Papillary (60%)
  - Follicular Cell/Hurthle Cell (30%)
  - Anaplastic/poorly differentiated (7%)
  - Medullary (3%)
- Number: 30 (although continues to accrue)
- Phase II Study; Sorafenib 400 mg po bid

Sorafenib
University of Pennsylvania

- Complete Response Rate – 0 (0%)
- Partial Response Rate – 7 (23%)
- Stable Disease – 16 (53%)

- Median Progression-Free Survival:
  – 79 Weeks


Head and Neck Cancer
7th Annual Multidisciplinary Symposium
November 19th, 2011 • Hyatt at the Bellevue • Philadelphia, PA
Sorafenib
Ohio State

- RAI-Refractory Thyroid Cancer
- Group A:
  - Papillary thyroid cancer, chemotherapy naïve, and available archival tissue
  - 19 total patients
- Group B:
  - All others
  - 22 with papillary thyroid cancer
  - 37 total patients
### Response Rates

**Ohio State**

<table>
<thead>
<tr>
<th></th>
<th>PTC, chemo-naïve (33 pts)</th>
<th>PTC, prior chemo (n=8)</th>
<th>HTC/FTC (n=11)</th>
<th>Anaplastic (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial Response</strong></td>
<td>5 (15%)</td>
<td>1 (13%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>19 (57%)</td>
<td>6 (75%)</td>
<td>9 (82%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>4 (12%)</td>
<td>1 (12%)</td>
<td>1 (9%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td><strong>PFS, median, months</strong></td>
<td>16</td>
<td>10</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td><strong>OS, median, month</strong></td>
<td>23</td>
<td>37.5</td>
<td>24.2</td>
<td></td>
</tr>
</tbody>
</table>
## Response Rates

### Ohio State versus Penn

<table>
<thead>
<tr>
<th></th>
<th>Ohio State (56 pts)</th>
<th>U. of Penn (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>6 (11%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>35 (63%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>9 (16%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Cell Types with responses</td>
<td>Papillary</td>
<td>Papillary, Follicular, Hurthle</td>
</tr>
</tbody>
</table>
Lenvatinib (E7080)

Background

- Lenvatinib (Adopted USAN for E7080):
  - Small molecule, tyrosine kinase inhibitor administered orally by once daily continuous dosing

- Targets
  - VEGFR1-3, FGFR 1-4, RET, PDGFR and KIT

Sherman et al. ASCO 2011 abstract 5503
# Response Rate

**Investigator Assessment**

<table>
<thead>
<tr>
<th></th>
<th>Prior VEGFR-targeted therapy N=17 (%)</th>
<th>No prior VEGFR-targeted therapy N=41 (%)</th>
<th>Overall N=58 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR) (95% CI)</td>
<td>7 (41%)</td>
<td>22 (54%)</td>
<td>29 (50%) (36-63%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>9 (53%)</td>
<td>17 (42%)</td>
<td>26 (45%)</td>
</tr>
<tr>
<td>Durable SD</td>
<td>6 (35%)</td>
<td>13 (32%)</td>
<td>19 (33%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (6%)</td>
<td>1 (2%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD)</td>
<td>16 (94%)</td>
<td>39 (95%)</td>
<td>55 (95%)</td>
</tr>
</tbody>
</table>

Sherman et al. ASCO 2011 abstract 5503
## Differentiated Thyroid Cancers
### Phase II studies – Multitargeted TKIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>#</th>
<th>PR/CR</th>
<th>SD</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>56</td>
<td>11%</td>
<td>63%</td>
<td>Ohio State</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25</td>
<td>23%</td>
<td>53%</td>
<td>Univ. of Pennsylvania</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>29</td>
<td>28%</td>
<td>48% (?)</td>
<td>Univ. of Washington</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>35</td>
<td>17%</td>
<td>74%</td>
<td>Univ. of Chicago</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>37</td>
<td>49%</td>
<td>43% (?)</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Axitinib</td>
<td>45</td>
<td>31%</td>
<td>42%</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Motesanib</td>
<td>93</td>
<td>14%</td>
<td>67%</td>
<td>Amgen</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>58</td>
<td>59%</td>
<td>36%</td>
<td>Multi-Site</td>
</tr>
<tr>
<td>Afiblercept (VEGF trap)</td>
<td>40</td>
<td>0%</td>
<td>83%</td>
<td>MSKCC</td>
</tr>
</tbody>
</table>
## Differentiated Thyroid Cancers
### Phase II studies – Multitargeted TKIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>#</th>
<th>PR/CR</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>56</td>
<td>11%</td>
<td>VEGFR, PDGFR, RAF, RET</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25</td>
<td>23%</td>
<td>VEGFR, PDGFR, RAF, RET</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>29</td>
<td>28%</td>
<td>VEGFR, PDGFR, c-kit, RET</td>
</tr>
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<td>35</td>
<td>17%</td>
<td>VEGFR, PDGFR, c-kit, RET</td>
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<td>14%</td>
<td>VEGFR, PDGFR, c-kit</td>
</tr>
<tr>
<td>E7080</td>
<td>58</td>
<td>59%</td>
<td>VEGFR1-3, FGFR 1-4, RET, PDGFR, c-kit</td>
</tr>
<tr>
<td>Afiblercept (VEGF trap)</td>
<td>40</td>
<td>0%</td>
<td>VEGF</td>
</tr>
</tbody>
</table>
Conclusion

- Many Phase II studies have been done in thyroid cancer showing activity

- We do not know
  - Best agent
  - Important target
  - Real benefit
MAPK pathway in Thyroid Cancer
Genetic Alterations in Thyroid Cancer

- mTOR
- mRNA Translation
- PI3K
- Akt/PKB
- PTEN
- T308
- TSC2
- TSC1
- RheB
- S473
- TK (RET, NTRK)
- RET/PTC, TRK rearrang

Cell survival, growth, X

70% of all PTC with activated MAPK

Transcriptional Activation (Elk-1, Ets, c-jun, c-fos etc...)

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Concordance of genetic alterations in MAPK but not PI3K pathway oncogenes in patients with multiple tumor specimens
BRAF Target
B-Raf Mutation Portends Worse Prognosis

PLX4032/Vemurafenib
Kinase selectivity translates from biochemical to cells to tumor models

Selective for $BRAF^{V600E}$ kinase
70 kinases screened

Selective in cellular assays

<table>
<thead>
<tr>
<th>Phospho-ERK</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A375</td>
<td>20</td>
</tr>
<tr>
<td>COLO829</td>
<td>10</td>
</tr>
<tr>
<td>COLO205</td>
<td>30</td>
</tr>
<tr>
<td>SW620</td>
<td>&gt;40,000</td>
</tr>
<tr>
<td>SKMEL2</td>
<td>14,000</td>
</tr>
</tbody>
</table>

Selective regression of V600E tumors

Selective $BRAF^{V600E}$ binding

PLX4720 co-structure [2008 PNAS]
Vemurafenib Waterfall Plot in Extension Cohort

Interim Vemurafenib phase I Kaplan-Meier plot: V600E+ vs V600E− melanoma patients (≥ 240mg BID)

As of May 13 2009

<table>
<thead>
<tr>
<th></th>
<th>Median PFS Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>44</td>
</tr>
<tr>
<td>V600E</td>
<td>175</td>
</tr>
</tbody>
</table>
V600E+ melanoma patient on 720 mg BID
85% tumor shrinkage in visceral lesions
Vemurafenib

• In Phase I Study
  – 1/3 thyroid cancer pts. had response; other 2 with stable disease
  – Median PFS = 12 months

• Phase II study in thyroid cancer recently started
  – Sorafenib treated and sorafenib naïve cohorts
  – Pre- and Post-biopsies
GSK2118436

- Small molecule inhibitor that is selective for BRAFV600E mutation
  - 10/16 subjects with melanoma BRAF mutation had response rate
  - 1/2 patients with BRAF (+) thyroid cancer with response; other with 66% decrease in RECIST measurable disease
Summary

• BRAF is a logical target in thyroid cancer
  – BRAF V600 mutation is common
  – Early, conserved mutation
• New inhibitors have shown significant activity in melanomas with BRAF mutations
• May not have same activity in thyroid cancer
• Mechanisms of resistance need to be elucidated
Reacquisition of RAI uptake of RAI-refractory metastatic thyroid cancers by pretreatment with the selective MEK inhibitor AZD6244: A pilot study
Mitogen Activated Protein Kinase (MAPK) Activation Suppresses Expression of NIS in Thyroid Cancer

Debyani Chakravarty and Jim Fagin, JCI (in press)
Pharmacologic inhibition of oncogenic BRAF signaling increases RAI uptake in the dox inducible $BRAF^{V600E}$ model.
Clinical Hypothesis

Treatment of patients with BRAF mutant, RAI-refractory tumors with a MEK inhibitor will result in tumor reacquisition of RAI uptake and susceptibility to therapeutic $^{131}$I.

- RTK
- Ras
- B-Raf
- MEK 1/2
- Erk 1/2
- Thyroid specific gene expression (e.g. NIS)

Selumetinib (AZD6244)
Protocol Schema

AZD6244
75 mg po bid x 4 weeks

(-) RAI Reacquisition
Discontinue AZD6244

(+) RAI Reacquisition
Continue AZD6244 and receive $^{131}$I

(lesion absorbed dose >2,000 cGy)
Objective

Primary Objective:
• To determine whether RAI uptake increases after treatment with MEK inhibitor in patients with RAI-refractory thyroid cancer
  – Association with BRAF mutation
Definition of RAI-Refractory Disease

1) Index metastatic lesion non-RAI avid on a diagnostic RAI scan performed up to 2 years prior to enrolment in the current study.

2) RAI-avid metastatic lesion which remained stable in size or progressed despite RAI treatment 6 months or more prior to entry in the study.

3) Patients with FDG avid lesions.
# Impact of Selumetinib Upon $^{124}$I Incorporation

<table>
<thead>
<tr>
<th>Patients with new/increased $^{124}$I incorporation after selumetinib</th>
<th>N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF WT</td>
<td>7 (of 10 WT)</td>
</tr>
<tr>
<td>BRAF MUT</td>
<td>4 (of 7 MUT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients who received therapeutic RAI</th>
<th>7/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF WT</td>
<td>6</td>
</tr>
<tr>
<td>BRAF MUT</td>
<td>1</td>
</tr>
</tbody>
</table>
$^{124}$I PET scan showing significant increase in tracer activity within the known thyroid pulmonary metastases with some of the non $^{124}$I-avid nodules becoming radioiodine-avid following MEK-inhibitor therapy.
Significant Acquisition of $^{124}$I Tracer Activity within Thyroid Cancer Bone Metastases
Post-therapy SUVmax

Pre-therapy SUVmax

n= 41 lesions

n= 55 lesions

100% (+50%)
(+25%)
(+0%)
(-25%)
(-50%)

MEK

Desiree D'Andreis

Head and Neck Cancer
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Best Response For Patients Treated with RAI

Change in Target Lesions by RECIST (%)

- Confirmed PR
- Confirmed SD
Thyroglobulin Changes

Mean TG Reduction: 91%
Preliminary Conclusions

• Selumetinib can induce/enhance iodine uptake in a subset of patients with RAI refractory thyroid cancer.
• Selumetinib effects upon iodine uptake have been observed in both BRAF wild type and mutant tumors.
• This protocol strategy can reduce tumor size(s) and decrease serum thyroglobulin.
• Patients with RAI refractory tumors that are heterogeneous for iodine uptake and exhibit low FDG avidity may potentially be more susceptible to this strategy.
Potential Future Directions

• Possible follow-up selumetinib (AZD6244) studies:
  – Randomized study of RAI +/- selumetinib in metastatic/recurrent, RAI refractory thyroid cancer
  – Randomized study of RAI +/- selumetinib in the adjuvant setting following resection of high risk thyroid cancer

• Testing alternate inhibitors of the MAPK pathway (BRAF, MEK inhibitors)