Thyroid Cancer

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Objectives

• Review thyroid cancer types
• Review thyroid cancer epidemiology and risk factors
• Review thyroid cancer presentation
• Review thyroid cancer staging
• Review thyroid cancer treatment
Thyroid function:

- Affects nearly all organs
- Regulates metabolism
- Calcium and phosphorus homeostasis
Thyroid Histology

- **Follicular Cells**: stimulated by TSH to convert thyroglobulin to T4
- **Parafollicular (C) cells**: synthesize calcitonin
- **Colloid**: storage material for thyroglobulin
Thyroid Malignancies

• **Cancers of Follicular Epithelial Cells**
  – Differentiated Thyroid Cancer
    • Papillary Thyroid Carcinoma
    • Follicular Thyroid Carcinoma
    • Hurthle Cell Carcinoma
  – Poorly Differentiated Thyroid Cancer
    • Derived from Follicular or Papillary Thyroid Carcinomas?
  – Undifferentiated Thyroid Cancer
    • Anaplastic Thyroid Carcinoma

• **Cancer of Parafollicular (C) Cells**
  – Medullary Thyroid Carcinoma
## Thyroid Malignancies

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Prevalence</th>
<th>Age</th>
<th>Distant Metastases</th>
<th>Survival rate (5yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid carcinoma</td>
<td>85-90%</td>
<td>20-50</td>
<td>5-7%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Follicular thyroid carcinoma</td>
<td>&lt;10%</td>
<td>40-60</td>
<td>20%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Poorly differentiated thyroid carcinoma</td>
<td>Rare-7%</td>
<td>50-60</td>
<td>30-80%</td>
<td>50%</td>
</tr>
<tr>
<td>Undifferentiated thyroid carcinoma</td>
<td>2%</td>
<td>60-80</td>
<td>20-50%</td>
<td>1-17%</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>3%</td>
<td>30-60</td>
<td>15%</td>
<td>30-80%</td>
</tr>
</tbody>
</table>

Thyroid Cancer Epidemiology

• Thyroid Cancer is the most common endocrine malignancy

• Age- and gender-adjusted incidence has increased faster than that of any other malignancy
  – 23,500 cases in 2005
  – 37,200 cases estimated in 2009
  – 44,670 cases estimated in 2010

• Prevalence is high and increasing
  – 2004: 366,000 men and women alive with history of thyroid cancer
  – 2006: 434,256

US Death Rate Increasing

Highest rate of increase in any cancer for both men and women < and > 65
Death rate increasing for men and women
Differentiated Thyroid Cancer
(Papillary and Follicular)
Differentiated Thyroid Cancer (DTC) Epidemiology

• Gender: female: male = 2.5:1
• Race: Caucasian: African Americans = 2:1
• Median age at diagnosis for PTC:
  – Women: 40-41 years
  – Men: 44-45 years
• Median age at diagnosis for FTC:
  – Women: 48 years
  – Men: 53 years
Differentiated Thyroid Cancer (DTC) Risk Factors

• Radiation exposure
  – Survivors of atomic fall-out
  – Children exposed to external beam radiation
  – Children living in Chernobyl (nuclear accident)
  – Younger age at exposure: Higher risk
    • Controversial whether exposure after age 15 confers increased risk
Differentiated thyroid cancer (DTC)
Risk Factors

• Genetic
  – Component of several inherited syndromes:
    • Familial adenomatous polyposis, Gardner syndrome, Cowden disease, Turcot syndrome, Carney complex
  – “Familial nonmedullary thyroid carcinoma”
    • Appears to be low penetrance, heterogeneous
    • Case control study (n=339)
      – 10-fold increased risk of thyroid cancer in relatives of thyroid cancer patients
    • Swedish retrospective analysis (n=1953 cases)
      – Familial risk:
      – 3.21 when a parent is diagnosed
      – 6.24 when a sibling is diagnosed
      – 11.19 if a female has a sister diagnosed

Pal T; J Clin Endocrinol Metab 2001
Hemminki K; J Clin Endocrinol Metab 2005
# Thyroid Cancer AJCC Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Follicular or Papillary*</th>
<th>Medullary</th>
<th>Anaplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45yo</td>
<td>&gt;45yo</td>
<td>Any age</td>
</tr>
<tr>
<td>I</td>
<td>M0</td>
<td>T1</td>
<td>T1</td>
</tr>
<tr>
<td>II</td>
<td>M1</td>
<td>T2-3</td>
<td>T2-4</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>T4 or N1</td>
<td>N1</td>
</tr>
<tr>
<td>IV</td>
<td>M1</td>
<td>M1</td>
<td>Any T, N, or M</td>
</tr>
</tbody>
</table>
### Thyroid Cancer Stage Distribution

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>I (%)</th>
<th>II (%)</th>
<th>III (%)</th>
<th>IV (%)</th>
<th>Unknown (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>46.9</td>
<td>14.4</td>
<td>10.3</td>
<td>2.1</td>
<td>16.4</td>
<td>34,794</td>
</tr>
<tr>
<td>Follicular</td>
<td>41.2</td>
<td>26.7</td>
<td>6.9</td>
<td>7.2</td>
<td>17.9</td>
<td>5271</td>
</tr>
<tr>
<td>Hurthle Cell</td>
<td>20.8</td>
<td>35.1</td>
<td>9.3</td>
<td>5.7</td>
<td>29</td>
<td>1310</td>
</tr>
<tr>
<td>Undifferentiated/Anaplastic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>741</td>
</tr>
<tr>
<td>Medullary</td>
<td>16.5</td>
<td>29.6</td>
<td>26.9</td>
<td>11</td>
<td>16</td>
<td>1550</td>
</tr>
<tr>
<td>Total</td>
<td>51.5</td>
<td>16.8</td>
<td>10.3</td>
<td>4.8</td>
<td>16.6</td>
<td>43,666</td>
</tr>
<tr>
<td>Cases</td>
<td>22,486</td>
<td>7335</td>
<td>4491</td>
<td>2091</td>
<td>7263</td>
<td></td>
</tr>
</tbody>
</table>

50% of Differentiated Thyroid Cancers are Stage I
Prognosis of Differentiated Thyroid Cancer

- One of the least morbid solid tumors
- Regional lymph node metastasis does not correlate with overall survival—does correlate with local recurrence
- 2/3 of patients have local disease at dx
- 33-61% of patients with PTC have clinically apparent cervical lymph node involvement at dx
- 1-2% PTC have distant mets at dx
- 2-11% FTC have distant mets at dx
- Distant mets at dx: 43-90% of patients will die of thyroid cancer
## TNM Stage and Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15.4</td>
<td>1.7</td>
</tr>
<tr>
<td>II</td>
<td>22</td>
<td>15.8</td>
</tr>
<tr>
<td>III</td>
<td>46.4</td>
<td>30</td>
</tr>
<tr>
<td>IV</td>
<td>66.7</td>
<td>60.9</td>
</tr>
</tbody>
</table>

N = 700 (PTC=620, FTC=80)
Median follow-up duration = 10.6 yrs
Loh, et al. JCEM 1997
Age and Prognosis in Metastatic Differentiated Thyroid Cancer

Shoup, et al. JCAS 2003
SUV and number of PET-avid lesions influences prognosis in differentiated thyroid cancer.

• FNA is standard diagnostic procedure when a thyroid nodule is found
• Most thyroid nodules are benign
  – 5-10% chance of malignancy
  – Higher rate of cancer in:
    • Men
    • Age < 20 or > 70
    • History of childhood neck radiation:
      – 33-37% chance malignancy
    • Enlarging nodule
    • Fixed nodule/vocal cord paralysis
    • h/o Graves’ disease
    • Family h/o PTC, MTC, MEN 2
  – Up to 90% of women > 70 and up to 60% men > 80 have nodular goiter
### FNA RESULTS

<table>
<thead>
<tr>
<th>FNA result</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>526</td>
<td>87.7</td>
</tr>
<tr>
<td>Malignant</td>
<td>28</td>
<td>4.7</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>Insufficient material</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>600</td>
<td>100</td>
</tr>
</tbody>
</table>

Ultrasound

- Size assessment of nodule
- Detection of multiple nodules not discerned by palpation
- Assisting in FNA
- Distinguishing benign from malignant thyroid nodules—characteristics suggestive of malignancy
  - Microcalcification
  - irregular margins
  - spotty intranodular flow
  - hypervascularity
What is the appropriate operation for differentiated thyroid cancer?
American Thyroid Association Management Guidelines  THYROID  vol 16, 2006

FNA BIOPSY

Nondiagnostic or “suspicious”

Patient prefers limited procedure

• Tumors > 4cm with marked atypia
  • “suspicious for papillary thyroid cancer”
  • family history of thyroid cancer
  • radiation exposure

THYROID LOBECTOMY

Diagnostic for malignancy

• Tumor > 1-1.5 cm
  • contralateral thyroid nodules
  • regional or distant metastases
  • history of head/neck radiation
  • 1st degree family history of thyroid cancer
  • age > 45

NEAR-TOTAL OR TOTAL THYROIDECTOMY

• Small
  • low risk
  • Isolated
  • no cervical nodes
Surgical Resection

Left Thyroid Lobectomy with Severed Left Recurrent Laryngeal Nerve

Anatomy of Neck

Post-operative Condition

- The left recurrent laryngeal nerve is transected, thereby cutting off a portion of the nerve supply to the larynx (voice box).
- Transected left recurrent laryngeal nerve
- Thyroid gland with the left lobe removed.
Postoperative Radioiodine

- Recommended for nearly all patients who get a total or near-total thyroidectomy in the USA
  - Stages III and IV disease
  - All Stage II disease if < 45 yo, most if > 45
  - Selected patients with stage I disease
    - Multifocal disease
    - Nodal mets
    - Extra thyroidal or vascular invasion
    - More aggressive histologies
Postoperative treatment and surveillance are based on differentiated thyroid cancer maintaining characteristics of normal thyroid follicular cells.
Postoperative Radioiodine

- **Goals:**
  - Eliminate post-surgical thyroid remnant
    - Decrease local recurrence
    - Facilitate long-term surveillance with RAI (radioiodine) scans and/or stimulated thyroglobulin measurements
  - Destroy micrometastatic disease

- No prospective studies have been done to determine which patients benefit
- Requires TSH stimulation
  - Can be done by stopping thyroid hormone replacement and allowing endogenous TSH levels to rise
  - For low risk patients, can give rhTSH (thyrotropin)
TSH Suppression Therapy

- Differentiated thyroid cancer cells express the thyrotropin receptor on the cell membrane
  - Responds to TSH stimulation
    - Increases rates of cell growth
- Use supratherapeutic doses of LT4
  - TSH suppression to < 0.1mU/L may improve outcomes in high risk patients
  - TSH 0.1-0.5 is appropriate for low risk patients
- Adverse effects of TSH suppression—subclinical thyrotoxicosis:
  - Exacerbation of angina, increased risk of atrial fibrillation, increased risk of osteoporosis in post menopausal women
Management of recurrent disease

- Surgical resection if neck disease +/- post op TSH-stimulated Tg, DxWBS, and RAI therapy
- If more extensive disease:
  - Radioiodine if uptake on WBS
  - External beam radiotherapy
  - Systemic chemotherapy?
RAI-Refractory Thyroid Cancer

- PET avidity is inversely proportional to RAI uptake
- 25-50% metastatic thyroid cancers lose iodine concentrating ability
- Standard chemotherapy has disappointing response rates, significant toxicity
  - Doxorubicin is only FDA-approved therapy
  - PFS = 2 months
  - OS = 8 months

## Systemic Chemotherapy in Advanced Thyroid Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Subtype (N)</th>
<th>ORR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxorubicin</strong></td>
<td>Differentiated (15) Medullary (5) Anaplastic (9)</td>
<td>37%</td>
<td>4-11 months</td>
</tr>
<tr>
<td>(Gottleib and Hill. 1974 NEJM 290(4); 193-197)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doxorubicin vs. Doxorubicin + Cisplatin</strong></td>
<td>Differentiated (35) Medullary (10) Anaplastic (39)</td>
<td>17 vs. 26%</td>
<td>5 vs. 7 months</td>
</tr>
<tr>
<td>(Shimaoka et al, 1985 Cancer 56 (9); 2155-60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doxorubicin + Cisplatin</strong></td>
<td>Differentiated (7) Medullary (6) Anaplastic (7)</td>
<td>9.1%</td>
<td>11.8 months</td>
</tr>
<tr>
<td>(Williams et al, 1986 Can Treat Rep 70(3); 405)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doxorubicin + Cisplatin + Bleomycin</strong></td>
<td>Differentiated (8) Medullary (9) Anaplastic (5)</td>
<td>42%</td>
<td>11 months</td>
</tr>
<tr>
<td>(De Besi, et al, 1991 J Endo Invest 14; 475-480)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thyroid Cancer Signaling

- TSH
- PI3K
- AKT
- mTOR
- RET
- PTC
- RAS
- BRAF
- MEK
- ERK
- cAMP
- PKA
- Gs
- Transcription

Cell differentiation
Cell growth

Kondo, Nature Reviews, 2006
TARGETS FOR THERAPY

\[ \text{RET/PTC} \]
- 100% hereditary MTC
- 40-60% sporadic MTC

\[ \text{BRAF} \]
- 40% PTC

\[ \text{MEK} \]
- 25% PTC

Other pathways: VEGFR, PI3K, PKC, Wnt, etc.

RET INHIBITORS

RAF INHIBITORS

MEK INHIBITORS

PI3-K INHIBITORS

VEGFR INHIBITORS
## Differentiated (Papillary and Follicular) Thyroid Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Histology (N)</th>
<th>OR (%)</th>
<th>SD (%)</th>
<th>Benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sorafenib</strong></td>
<td>PTC (41) Shah JCO</td>
<td>15</td>
<td>56</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>DTC/MTC (50) Brose ASCO 2009</td>
<td>36</td>
<td>46</td>
<td>82</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td>DTC (12) Ravaud,ASCO 2008</td>
<td>13</td>
<td>83</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>DTC (35) Cohen ASCO 2008</td>
<td>17</td>
<td>74</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>DTC/MTC (35) Carr CCR 2010</td>
<td>31</td>
<td>46</td>
<td>77</td>
</tr>
<tr>
<td><strong>Motesanib</strong></td>
<td>DTC (93) Sherman, NEJM 2008</td>
<td>14</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td><strong>Pazopanib</strong></td>
<td>DTC (37) Bible, Lancet 2010</td>
<td>49</td>
<td>43</td>
<td>92</td>
</tr>
</tbody>
</table>
Sorafenib

- inhibits RAF, PDGFR, VEGFR2 and 3, RET, KIT
- Rationale for its use in DTC
- Most feel response related to VEGFR inhibition
- Approved for use in renal cell carcinoma and hepatocellular carcinoma
- 2 phase 2 trials in thyroid cancer
- Ongoing phase 3 trial of sorafenib vs. placebo
# Sorafenib Studies

<table>
<thead>
<tr>
<th>University of Pennsylvania Gupta-Abramson, et al</th>
<th>The Ohio State University Kloos, et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>Metastatic, iodine refractory, unresectable or locally advanced (N=30)</td>
<td>Metastatic, iodine refractory, unresectable or locally advanced (N=56)</td>
</tr>
<tr>
<td><strong>Progression needed?</strong></td>
<td><strong>Yes, within 12 mo by RECIST</strong></td>
</tr>
<tr>
<td><strong>Papillary</strong></td>
<td><strong>41</strong></td>
</tr>
<tr>
<td><strong>Follicular/Hurthle Cell</strong></td>
<td><strong>11</strong></td>
</tr>
<tr>
<td><strong>ATC/Poorly Differentiated</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td><strong>Medullary</strong></td>
<td>(reported separately)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Sorafenib 400mg BID</strong></td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td><strong>RECIST response, TTP</strong></td>
</tr>
</tbody>
</table>

*Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719*  
*Journal of Clinical Oncology, Vol 27, No 10 (April 1), 2009: pp. 1675-1684*
### Sorafenib Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7 (23%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>16 (53%)</td>
<td>34 (61%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2 (3%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>PFS</td>
<td>79 weeks (~ 20 mo)</td>
<td>PTC – no prior chemo 16 mo FTC/HCC – 4.5 mo</td>
</tr>
</tbody>
</table>

**Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719**

Sorafenib Best Response

Gupta Abramson, et al

Kloos, et al

Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719

Hand Foot Syndrome

Grade 1
Numbness, dysesthesia or paresthesia, tingling, painless swelling or erythema, and/or discomfort of hands or feet not disrupting normal activities

Grade 2
Painful erythema and swelling of hands or feet and/or discomfort affecting ADLs

Grade 3
Moist desquamation, ulceration, blistering or severe pain of hands or feet, or severe discomfort preventing work or performance of ADLs
Sunitinib

- Multitargeted tyrosine kinase inhibitor approved for renal cell carcinoma and gastrointestinal stromal tumor (GIST)
- Targets VEGFR-1 and 2, PDGFRs, KIT, FLT3, RET
## Sunitinib

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Differentiated or medullary thyroid cancer refractory to curative therapy</td>
<td>Differentiated or medullary thyroid cancer refractory to curative therapy</td>
</tr>
<tr>
<td>Progression needed?</td>
<td>No, disease had to be PET avid</td>
<td>Yes, RECIST progression within 6 months</td>
</tr>
<tr>
<td>Papillary</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Follicular/Hurthle Cell</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>ATC/Poorly Differentiated</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Medullary</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sunitinib 37.5 mg daily</td>
<td>Sunitinib 50 mg QD 4-weeks on/2-weeks off</td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>RECIST response</td>
<td>RECIST response</td>
</tr>
</tbody>
</table>

Clin Cancer Res; 16(21) November 1, 2010

ASCO (abstract 6025) 2008, ASCO (abstract 5504) 2010
### Sunitinib

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>10 (28%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>16 (46%)</td>
<td>26 (74%)</td>
</tr>
<tr>
<td>Stable Disease (SD) &gt; 6 months</td>
<td>13 (37%)</td>
<td>?</td>
</tr>
<tr>
<td>Progression</td>
<td>6 (17%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Time To Progression</td>
<td>12.8 mo</td>
<td>28 weeks (7 mo)</td>
</tr>
</tbody>
</table>

- Median duration of response: 8 months
- Median TTP: 12.8 months
A, maximum percent change in target lesions from baseline in all patients with evaluable disease (n = 33; 1 patient was removed from the study because of adverse event before evaluation and 1 patient did not have measurable disease per RECIST at baseline).

# Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study


## RECIST RESPONSE N= 37

<table>
<thead>
<tr>
<th>RECIST RESPONSE</th>
<th>N= 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>18 (49%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Follicular</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Hurthle Cell</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Progression</td>
<td>1 (14%)</td>
</tr>
</tbody>
</table>

### Histologic subtype N= 37

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>N= 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>15</td>
</tr>
<tr>
<td>Follicular</td>
<td>11</td>
</tr>
<tr>
<td>Hurthle Cell</td>
<td>11</td>
</tr>
</tbody>
</table>

\[ p = \text{NS} \]
# Differentiated Thyroid Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Agent and regimen</th>
<th>Radioiodine-resistance required</th>
<th>Threshold for progression</th>
<th>Patients with any RECIST response (n/total [%])</th>
<th>Median survival (months)</th>
<th>Progression-free</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al(^a)</td>
<td>Axitinib 5 mg twice daily</td>
<td>Yes</td>
<td>None</td>
<td>14/45 (31%)</td>
<td>18.1*</td>
<td>NR</td>
</tr>
<tr>
<td>Iten et al(^a)</td>
<td>(197)yttrium-DOTA-TOC minimal cumulative administered activity 12-6 GBq (range 1-7-29-6 GBq)</td>
<td>Yes</td>
<td>&lt;12 months</td>
<td>NR</td>
<td>NR</td>
<td>16.8</td>
</tr>
<tr>
<td>Gupta-Abramson et al(^a)</td>
<td>Sorafenib 400 mg twice daily</td>
<td>Yes</td>
<td>&lt;12 months</td>
<td>7/27 (26%)</td>
<td>19.75</td>
<td>NR</td>
</tr>
<tr>
<td>Kloos et al(^a)</td>
<td>Sorafenib 400 mg twice daily</td>
<td>No</td>
<td>None</td>
<td>6/52 (12%)</td>
<td>12.6</td>
<td>25.5</td>
</tr>
<tr>
<td>Aim et al(^a)</td>
<td>Thalidomide 800 mg daily</td>
<td>Yes</td>
<td>&lt;12 months</td>
<td>5/28 (18%(^\d))</td>
<td>4(^\d)</td>
<td>17(^\d)</td>
</tr>
<tr>
<td>Sherman et al(^a)</td>
<td>Motesanib 125 mg daily</td>
<td>Yes</td>
<td>&lt;6 months</td>
<td>13/93 (14%)</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
<td>Argiris et al(^a)</td>
<td>Interferon alfa 2b, 12 million units/m² subcutaneously on days 1-5, and doxorubicin, 40 mg/m² intravenously on day 3; 28-day cycles</td>
<td>Yes</td>
<td>None</td>
<td>1/14 (7%)</td>
<td>5.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Mrozek et al(^a)</td>
<td>Celecoxib 400 mg twice daily</td>
<td>Yes</td>
<td>&lt;12 months</td>
<td>1/32 (3%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Woyach et al(^a)</td>
<td>Vorinostat 200 mg twice daily (2 weeks on, 1 week off)</td>
<td>Yes</td>
<td>None</td>
<td>0/16</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pennell et al(^a)</td>
<td>Gefitinib 250 mg daily</td>
<td>Yes</td>
<td>None</td>
<td>0/17</td>
<td>3.7*</td>
<td>17.5*</td>
</tr>
</tbody>
</table>

NR=not reported. RECIST=Response Evaluation Criteria in Solid Tumors. \(^*\)Includes patients with anaplastic and medullary thyroid cancers. \(^\d\)Includes patients with medullary thyroid cancers.

Table 4: Summary of results of published clinical trials in differentiated thyroid cancers
DC after 12 weeks of sorafenib

5/08 CT

10/08 CT
Anaplastic Thyroid Cancer
Anaplastic Thyroid Cancer

• Undifferentiated tumors
• Aggressive
  – Disease-specific mortality near 100%
• Annual incidence: 2/1,000,000
• Mean age at diagnosis: 65
• 60-70% occur in women
• 20% of patients have history of differentiated thyroid cancer (DTC)
• 20-30% have concurrent DTC
Anaplastic Thyroid Cancer

• Up to 90% have regional or distant metastases at presentation
  – Lungs most common site

• Clinical presentation:
  – Rapidly enlarging neck mass
    • Pain, upper airway compression, dyspnea, dysphagia, hoarseness, cough
  – Constitutional symptoms:
    • Anorexia, fever, weight loss
Anaplastic Thyroid Cancer

• Diagnosis:
  – FNA
  – CT neck and chest

• Prognosis:
  – Considered Stage IV at diagnosis
  – Patients with disease confined to the thyroid/regional disease survive longer than patients with distant mets
  – Tumor size:
    • < 6 cm: 2 yr survival 25%
    • > 6 cm: 2 yr survival 3-15%

• Other: older age, male sex, dyspnea: poorer prognosis
Anaplastic thyroid cancer

• Treatment:
  – Surgery: ONLY if tumor appears localized to the thyroid
    • Lobectomy with wide margins
    • Total thyroidectomy does not prolong survival and has higher complication rate
  – Adjuvant therapy:
    • No data other than uncontrolled observation
    • Most will treat with concurrent chemoradiotherapy
Metastatic or advanced ATC

- No effective therapy, uniformly fatal
- Median survival: 3-7 months
- One year survival: 20-35%
- Five year survival: 5-14%
- Death most often due to airway compromise (50-60%)
- Chemotherapy and/or radiation do not prolong survival
- Patients should participate in clinical trials
FACT Trial (Fosbretabulin + Carboplatin/Paclitaxel vs. Carboplatin/Paclitaxel Alone in ATC

• Results reported September 2010
• Phase II/III Randomized Trial
• 80 patients
  – Largest ATC trial
  – First randomized trial
  – 55 patients Fosbretabulin/Carbo/Taxol
  – 25 patients Carbo/Taxol alone
Overall Survival
Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>CA4P+C/P (n=55)</th>
<th>C/P (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (%95 CI)</td>
<td>5.1 (3.1, 9.2)</td>
<td>4.1 (2.8, 8.9)</td>
</tr>
<tr>
<td>Hazard Ratio (%95 CI):</td>
<td>0.71 (0.42, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Reduction in Risk:</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>6 month survival</td>
<td>48%</td>
<td>37%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>23%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Patients at Risk:
- CA4P+C/P (n=55): 36, 25, 18, 9, 6, 2, 2, -
- C/P (n=25): 15, 8, 6, 2, 2, 1, 1, 1, -

Data Cutoff: 08 August 2010
Overall Survival
Age ≤ 60

Median (%95 CI)
CA4P+C/P (n=24)  10.9 (3.1: 11.1)
C/P (n=11)  3.1 (1.7, 9.5)

Hazard Ratio (%95 CI): 0.38 (0.16, 0.88)
Reduction in Risk: 62%

Patients at Risk:
CA4P+C/P (n=24)  18 14 11 5 4 1 1 - - -
C/P (n=11)  6 4 3 0 0 0 0 0 0 0

Data Cutoff: 08August2010
Anaplastic Thyroid Cancer Treated With Combretastatin, Carboplatin, Paclitaxel

Vague thickness, difficult to see or measure any tumor.
Medullary Thyroid Cancer
Medullary Thyroid Cancer

- Neuroendocrine tumor of the parafollicular (C cells)
- Produce calcitonin
- 80% are sporadic
- 20% are familial: MEN type 2 syndromes
- Sporadic MTC presents 50s-60s
- Familial MTC (MEN2) presents younger (30s)
  - Children with MEN 2B undergo thyroidectomies in infancy
  - Children with MEN 2A undergo thyroidectomies by ages 5 or 6
Medullary Thyroid Cancer

• Clinical presentation:
  – Thyroid nodule
  – 50% have cervical lymph node involvement
  – 15% have symptoms—dysphagia, hoarseness
  – 5% have distant metastases

– Systemic symptoms:
  • Secretes calcitonin: diarrhea, facial flushing
  • Can secrete corticotrophin (ACTH): Cushing’s syndrome
# Inherited MTC
Autosomal Dominant Syndromes

<table>
<thead>
<tr>
<th>MEN 2A</th>
<th>MEN 2B</th>
<th>FMTC (Familial Medullary Thyroid Cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC (100%)</td>
<td>MTC (100%)</td>
<td>MTC</td>
</tr>
<tr>
<td>pheochromocytoma</td>
<td>pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Primary parathyroid hyperplasia (hyperparathyroidism)</td>
<td>Mucosal neuromas</td>
<td></td>
</tr>
<tr>
<td>RET C634A</td>
<td>RET M918T</td>
<td>RET exon 11</td>
</tr>
</tbody>
</table>
Did he have a pheochromocytoma when assassinated?
- Thinner, he fainted while getting up quickly from a chair, he had periodic severe headaches and cold hands and feet.

Did 2 of his sons, Willie and Tad, also have MEN 2B?
- Photographs of them show somewhat irregular lips.
- Willie died at 11, probably of typhoid fever
- Tad at 18, reportedly of tuberculosis

His mother died at 34

Doubtful... he had already lived to 56
Inherited MTC

• Kindred can be screened for medullary thyroid cancer with calcitonin levels
  – Screening of MEN 2A families found 80% of cases—most had no thyroid abnormalities on exam

• Kindred are now screened for point mutations in the RET proto-oncogene
  – Allows for earlier diagnosis and prophylactic thyroidectomies
Clinical Evaluation

- CTs of neck, chest, abdomen, pelvis
- Bone scan
- PET/CT imaging controversial—can often miss metastases
- Serum calcium level
- 24 hour excretion of metanephrines, norepinephrine, and epinephrine
- RET mutation
- Calcitonin level
Prognosis

• Postoperative calcitonin doubling time:
  – < 6 months: 10 yr survival = 8%
  – 6-24 months: 10 yr survival = 37%
  – > 2 yrs: 10 yr survival = 100%

• Age at diagnosis:
  – < 40: 10 yr survival = 65%
  – > 40: 10 yr survival = 50%

• RET M918T mutation
Treatment of Medullary Thyroid Cancer

- Cured only by complete resection of tumor and lymph node mets
- Total thyroidectomy
  - Up to 30% have bilateral or multifocal disease
- Start thyroxine (T4) immediately post-op
  - Maintain euthyroid state
  - C-cells are not TSH responsive
  - No role for radioiodine
- Measure serum calcitonin and CEA 6 months after surgery
  - Detect residual disease
  - If undetectable, 5% 5-yr recurrence rate
Residual/Recurrent MTC

- Surgical resection
- Radiation?
  - No prospective data
  - May prolong disease progression interval
- Chemotherapy
  - Not effective
- Clinical trials with targeted agents
- Vandetanib approved for advanced, progressive or symptomatic disease on 4/6/11
Vandetanib in locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind Phase III trial (ZETA)

SA Wells,1 BG Robinson,2 RF Gagel,3 H Dralle,4 JA Fagin,5 M Santoro,6 E Baudin,7 J Vasselli,8 J Read9 and M Schlumberger7

1Medical Oncology Branch, National Cancer Institute, NIH, Bethesda, MD
2Kolling Institute of Medical Research, University of Sydney, Australia
3University of Texas MD Anderson Cancer Center, Houston, TX
4Martin Luther University Halle-Wittenberg, Halle, Germany
5Memorial Sloan-Kettering Cancer Center, New York,
6Universita' di Napoli Federico II, Naples, Italy
7Institut Gustave Roussy, Villejuif, France
8AstraZeneca, Wilmington, DE
9AstraZeneca, Macclesfield, UK
Study design

Patients with unresectable locally advanced or metastatic MTC
N=331

2:1 randomization

Vandetanib 300 mg/day
n=231
Follow for progression

Placebo
n=100
Follow for progression

Discontinue blinded treatment at progression

Optional open-label vandetanib 300 mg/day

Follow for survival
Progression-free survival

Time (months)

Vandetanib 300 mg
Placebo

Hazard ratio = 0.46 (0.31–0.69); P<0.0001
Median (months): not reached (vandetanib); 19.3 (placebo)

At risk (n)
Vandetanib  231  198  171  141  42  1  0
Placebo   100  72  57  45  13  0  0

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>ITT analysis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response rate</td>
<td>45% (104)</td>
<td>13% (13)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>5.48 (2.99–10.79), P&lt;0.0001</td>
<td></td>
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</tbody>
</table>

Excluding open-label scans

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>44% (101)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>76.91 (16.68–1366), P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- 24 patients randomized to placebo received open-label therapy before progression according to central read
  - 12 (50%) had an objective tumor response
- 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
# Phase I study of XL184

<table>
<thead>
<tr>
<th>RECIST RESPONSE</th>
<th>N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>Stable Disease (&gt; 6 months)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>?</td>
</tr>
</tbody>
</table>

Median response duration not yet reached
Phase I study of XL184

Best Tumor Response: MTC Patients

*Indicates prior TKI therapy

- Available scan for 17 patients with measurable disease (RECIST)
- 3 MTC subjects had non-measurable disease; as of 5/22/08, 2 are TEE
Sorafenib in metastatic MTC

<table>
<thead>
<tr>
<th>Response</th>
<th>Hereditary N=3 (%)</th>
<th>Sporadic N=16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>1 (33)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2 (67)</td>
<td>14 (87)</td>
</tr>
<tr>
<td>&gt; 20-29% decrease</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10-20% decrease</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>&gt;0-10% decrease</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Stable Disease &gt; 6 months</td>
<td>1 (33)</td>
<td>10 (62)</td>
</tr>
<tr>
<td>Median Duration Stable Disease months</td>
<td>5 (4-6+)</td>
<td>12 (2-22+)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>0</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>
AEE After 6 Weeks of Sorafenib
## NCI Clinical Trials in Advanced Thyroid Cancer

<table>
<thead>
<tr>
<th>STATUS</th>
<th>MALIGNANCY</th>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPEN</td>
<td>Medullary Thyroid Cancer</td>
<td>A Targeted Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA)plus the proteasome inhibitor, Bortezomib (Velcade), in advance or metastatic Medullary Thyroid Cancer (MTC)</td>
</tr>
<tr>
<td>OPEN</td>
<td>Anaplastic Thyroid Cancer</td>
<td>Phase 1/2 Trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)</td>
</tr>
</tbody>
</table>
Phase I/II trial of ZD6474 (Vandetanib; ZACTIMA) plus the Bortezomib (Velcade), in Medullary Thyroid Cancer (MTC)

• Phase I
  – Study Design:
    • assess the safety, tolerance and activity of daily oral Vandetanib and Bortezomib on days 1, 4, 8 and 11 every 28 days in adults.
  – Eligibility for phase I:
    • diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

• Phase II:
  – Study Design:
    • Compare the activity of the combination of bortezomib plus vandetanib or vandetanib alone using a 2:1 randomization
  – Eligibility for phase II:
    • Previously untreated recurrent or metastatic medullary thyroid cancer
Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Crolibulin (EPC2407):
• microtubule inhibitor that has been shown to have direct antitumor effects in vivo and in vitro
• disruption of endothelial cells with disruption of blood flow to the tumor
Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Eligibility:
• Adults ≥18 with diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

Phase II Eligibility:
• Adults ≥18 with a diagnosis of recurrent, metastatic or primary unresectable ATC
Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Study Design:
• Dose escalation of Cisplatin Day 1 + Crolibulin Days 1,2,3 q 21 days

Phase II Study Design:
• Randomization 2:1 of patients receiving MTD of Cisplatin/Crolibulin vs. Cisplatin alone.
QUESTIONS?