Radioiodine-refractory DTC: Targeted Therapies

Giuseppe COSTANTE, MD,
Head, Endocrinology Clinic
Institut Jules Bordet
Université Libre de Bruxelles (U.L.B.)
Thyroid Cancer Incidence

Thyroid (1975-2008)

All cancer sites (1988-2008)

Thyroid Cancer

Incidence

Screening

Ahn, 2014
Differentiated Thyroid Cancer Epidemiology

Stage specific trend (1975-2008)

Enewold, 2009
Screening

Thyroid Cancer Incidence

Ahn, 2014

G. Costante
Differentiated Thyroid Cancer Treatment

Total Thyroidectomy

Suppressive Therapy

$^{131}$I Ablation
Differentiated Thyroid Cancer

Epidemiology

Stage at Diagnosis

SEER summary stage 2000-2007

- Intrathyroidal: 5%
- Regional metastases
- Distant metastases
- Unknown

5% High Risk Patients
Differentiated Thyroid Cancer
Long Term Outcome

High Risk Patients

Jonklaas, 2006
Differentiated Thyroid Cancer

Long Term Outcome

High Risk Patients

Durante, 2013
Differentiated Thyroid Cancer

Distant Metastases

Long Term survival

Jonklaas, 2006
Differentiated Thyroid Cancer

**Distant Metastases**

### $^{131}$I-Treatment

- **Group 1:**
  - $^{131}$I-avid lesions
  - remission

- **Group 2:**
  - no/low $^{131}$I uptake
  - persistent disease

- **Group 3:**
  - $^{131}$I-avid lesions
  - persistent disease

**Survival & $^{131}$I avidity**

- **Survival:**
  - Years after metastasis discovery
  - 127 pts
  - 168 pts
  - 149 pts

**G. Costante**

*Durante, 2006*
Differentiated Thyroid Cancer

**RAI refractory disease**

- Index lesion that did not take up $^{131}$I on a RAI scan

- RAI-avid index lesion that do not respond to RAI treatment within 6-12 months
  - issue of lesion dosimetry

- Cumulative treatment $> 600$ mCi
Differentiated Thyroid Cancer
Response to Chemotherapy

Shimaoka, 1985
Thyroid Cancer Tumorigenesis

Intracellular Signalling Pathways

- PTC: RET/PTC C-MET
- FTC: EGFR

**Endothelial cell**

VEGF-A$_{165}$

- Growth
- Survival
- Proliferation

- HIF1a
- Inhibition of apoptosis
- Migration

- Growth
- Survival
- Proliferation

- Migration
- Angiogenesis

Thyroid Cancer Tumorigenesis

Molecular Events

Giordano, 2014
**Thyroid Cancer Tumorigenesis**

**Targeting Cell Signalling Pathways**

**Tumor Cell**
- RET/PTC
- Axitinib
- Motesanib
- Sorafenib
- Sunitinib
- Vandetanib
- XL184
- Pazopanib
- Lenvatinib
- Sorafenib
- Selumetinib

**Endothelial Cell**
- VEGFR-2
- Axitinib
- Motesanib
- Sorafenib
- Sunitinib
- Vandetanib
- XL184
- Pazopanib
- Lenvatinib
- Everolimus
- Sirolimus
- Pasireotide

**Signalling Pathways**

**Tumor Cell**
- Ras
  - B-Raf
  - MEK
  - ERK
- PI3K
- AKT
- mTOR
- S6K
- Growth
- Survival
- Proliferation
- HIF1α
- Inhibition of apoptosis
- Migration

**Endothelial Cell**
- Ras
  - Raf
  - MEK
  - ERK
- PI3K
- AKT
- mTOR
- S6K
- Growth
- Survival
- Proliferation
- Migration
- Angiogenesis

Approved Drugs for clinical use

- Sorafenib
  - FDA 2013
  - EMA 2014

- Lenvatinib
  - FDA 2015
  - EMA 2015
Differentiated Thyroid Cancer

Targeted Therapies

Outline

- Efficacy
- Safety
- Eligible patients
Differentiated Thyroid Cancer

Sorafenib

Decision Study

Brose, 2014
Differentiated Thyroid Cancer

**Lenvatinib**

Schlumberger, 2015
Differentiated Thyroid Cancer

Targeted Therapies

Outline

- Efficacy
- Safety
- Eligible patients
Differentiated Thyroid Cancer

*Sorafenib*

**Adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Interruption</th>
<th>Reduction</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand–foot skin reaction</td>
<td>55 (26.6%)</td>
<td>70 (33.8%)</td>
<td>11 (5.3%)</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>18 (8.7%)</td>
<td>16 (7.7%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (7.7%)</td>
<td>12 (5.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (3.4%)</td>
<td>28 (13.5%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (7.2%)</td>
<td>7 (3.4%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5 (2.4%)</td>
<td>13 (6.3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4 (1.9%)</td>
<td>6 (2.9%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

*Worden, 2015*
Differentiated Thyroid Cancer

**Lenvatinib**

### Adverse events

<table>
<thead>
<tr>
<th>Effect</th>
<th>Lenvatinib (N=261)</th>
<th>Placebo (N=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related adverse effect — no. of patients (%)</td>
<td>254 (97.3)</td>
<td>78 (59.5)</td>
</tr>
<tr>
<td>Adverse effect developing during treatment — no. of patients (%)</td>
<td>198 (75.9)</td>
<td>13 (9.9)</td>
</tr>
<tr>
<td>Serious** Total</td>
<td>130 (49.8)</td>
<td>30 (22.9)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>79 (30.3)</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>Fatal</td>
<td>20 (7.7)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>6 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.8</td>
<td>41.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>59.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>46.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>41.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>35.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysaesthesia syndrome</td>
<td>31.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Headache</td>
<td>27.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18.0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16.9</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>16.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>13.0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Desquamation</td>
<td>10.0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>10.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>6.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.7</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Schlumberger, 2015*
Differentiated Thyroid Cancer

Targeted Therapies

Adverse events

- Accurate patient selection
- Close monitoring
Differentiated Thyroid Cancer

Targeted Therapies

Outline

- Efficacy
- Safety
- Eligible patients
Differentiated Thyroid Cancer

**RAI refractory disease**

- Index lesion that did not take up $^{131}$I on a RAI scan
- RAI-avid index lesion that do not respond to RAI treatment within 6-12 months
  - issue of lesion dosimetry
- Cumulative treatment $> 600$ mCi
- Others?

G. Costante
Differentiated Thyroid Cancer

$^{18}$FDG-PET scan vs survival

<table>
<thead>
<tr>
<th></th>
<th>AND</th>
<th>AWD</th>
<th>DOD</th>
<th>DWD</th>
<th>DND</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 400)</td>
<td>134</td>
<td>173</td>
<td>89</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FDG-PET positive (n = 221)</td>
<td>32</td>
<td>100</td>
<td>87</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FDG-PET negative (n = 179)</td>
<td>102</td>
<td>73</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

AND, Alive no evidence of disease; AWD, alive with disease; DOD, died of disease; DWD, died with disease; DND, died no evidence of disease.

Wang, 2000
Differentiated Thyroid Cancer

18-FDG-PET scan vs RAI response

Survival at 60 months

- **RAI + FDG -**: 95%
- **RAI + FDG +**: 45%
- **RAI - FDG +**: 45%

**RAI**: radioactive iodine

**FDG**: \([^{18}F]\)fluoro-2-deoxy-D-glucose

Robbins, 2006
Differentiated Thyroid Cancer

**RAI refractory disease**

- Index lesion that did not take up $^{131}\text{I}$ on a RAI scan

- RAI-avid index lesion that do not respond to RAI treatment within 6-12 months
  - issue of lesion dosimetry

- Cumulative treatment > 600 mCi

- $^{18}\text{FDG}$ lesions

*G. Costante*
Differentiated Thyroid Cancer

$^{131}I$-Refractory

Management Strategy

- Close monitoring of disease extension
- Consider focal treatment modalities for tumor foci at high risk for complications
  - Cementoplasty
  - Stereotactic RT
  - Thermal ablation
- General strategy planned as early as possible
Male, 46 yrs – Insular Thyroid Carcinoma

April 2013
Thyroidectomy
\( ^{131} \text{I} \) dose 222 mCi

December 2013
\( ^{131} \text{I} \) dose 219 mCi

August 2014
\( ^{131} \text{I} \) dose 217.3 mCi

Stimulated Tg=1049

Stimulated Tg=436

Stimulated Tg=1058

G. Costante
Male, 46 yrs – Insular Thyroid Carcinoma

March 2015

$^{131}$I 218.4 mCi

Stimulated Tg=1423

June 2015

$^{131}$I cumulative dose 877.7 mCi

G. Costante
Recommendation 96

- Kinase inhibitor therapy should be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic and/or imminently threatening disease not otherwise amenable to local control using other approaches. The impact of these agents on overall survival and quality of life remains to be defined.

- (Weak recommendation, Moderate-quality evidence)
**Differentiated Thyroid Cancer**

**Targeted Therapies**

**Initiation of systemic treatment**

<table>
<thead>
<tr>
<th>Tumor burden</th>
<th>Progression (RECIST)</th>
<th>Small (no Target RECIST)</th>
<th>Large &gt;1-2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12-14 months</td>
<td>No</td>
<td>No</td>
<td>? High SUV</td>
</tr>
<tr>
<td>&lt; 12-14 months</td>
<td>No</td>
<td>No</td>
<td>YES</td>
</tr>
</tbody>
</table>

*Schlumberger, 2014*
Male, 46 yrs – Insular Thyroid Carcinoma

March 2015

$^{131}$I 218.4 mCi

Stimulated Tg=1423

June 2015

$^{131}$I cumulative dose 877.7 mCi

pT3N1M1

June 2015

G. Costante
Male, 46 yrs – Insular Thyroid Carcinoma

Basal Thyroglobulin

July 2015

December 2015

G. Costante
Male, 46 yrs – Insular Thyroid Carcinoma

Start Sorafenib

Treatment failure?

G. Costante
Differentiated Thyroid Cancer

Treatment with MKIs

When to withdraw?

- At structural progression after the nadir (RECIST +20%)?
- More pronounced progression?

No general consensus
Lesion snapshots

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Baseline (07/26/2016)</th>
<th>Follow-up 1 (09/16/2016)</th>
<th>Follow-up 2 (11/10/2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T01 Lymph node</td>
<td>SA: 47.7 mm</td>
<td>SA: 47.4 mm (-0.6%)</td>
<td>SA: 51.8 mm (+9.2%)</td>
</tr>
<tr>
<td>T02 Lymph node</td>
<td>SA: 35.8 mm</td>
<td>SA: 35.7 mm (-0.4%)</td>
<td>SA: 43.2 mm (+21.2%)</td>
</tr>
<tr>
<td>T03 Lung</td>
<td>LA: 15.8 mm</td>
<td>LA: 14.0 mm (-11.4%)</td>
<td>LA: 17.2 mm (+23.1%)</td>
</tr>
</tbody>
</table>

G. Costante
Differentiated Thyroid Cancer
Withdrawal of MKIs

What to do next?

• Second line treatment
  » Lenvatinib
Male, 46 yrs – Insular Thyroid Carcinoma

Start Lenvatinib

Sorafenib

Basal Thyroglobulin

G. Costante
Differentiated Thyroid Cancer
Withdrawal of MKIs

What to do next?

- Clinical protocols
  - New drugs
    - Nintedanib
    - Immunotherapy
  - Sequential treatment
  - Association of drugs
    - UPCC 19309
  - Redifferentiation
## Differentiated Thyroid Cancer

**Retinoic Acid Redifferentiation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Histology</th>
<th>Tg</th>
<th>$^{131}$I uptake</th>
<th>Tumor size</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PTC/FTC</td>
<td>↓</td>
<td>↑</td>
<td>?</td>
<td>Responder</td>
</tr>
<tr>
<td>2</td>
<td>FTC</td>
<td>↓</td>
<td>↑</td>
<td>n.d.</td>
<td>Responder</td>
</tr>
<tr>
<td>3</td>
<td>PTC</td>
<td>↓</td>
<td>⇔</td>
<td>?</td>
<td>Responder</td>
</tr>
<tr>
<td>4</td>
<td>PTC</td>
<td>⇔</td>
<td>↑</td>
<td>⇔</td>
<td>Responder</td>
</tr>
<tr>
<td>5</td>
<td>PTC</td>
<td>⇔</td>
<td>↑</td>
<td>⇔</td>
<td>Stable disease</td>
</tr>
<tr>
<td>6</td>
<td>FTC</td>
<td>⇔</td>
<td>↑</td>
<td>⇔</td>
<td>Stable disease</td>
</tr>
<tr>
<td>7</td>
<td>PTC</td>
<td>⇔</td>
<td>↑</td>
<td>n.d.</td>
<td>Stable disease</td>
</tr>
<tr>
<td>8</td>
<td>PTC</td>
<td>⇔</td>
<td>⇔</td>
<td>⇔</td>
<td>Stable disease</td>
</tr>
<tr>
<td>9</td>
<td>FTC</td>
<td>↑</td>
<td>↑</td>
<td>n.d.</td>
<td>?</td>
</tr>
<tr>
<td>10</td>
<td>PTC/FTC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>11</td>
<td>PTC</td>
<td>↑</td>
<td>⇔</td>
<td>?</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>12</td>
<td>FTC</td>
<td>↑</td>
<td>↑</td>
<td>n.d.</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>13</td>
<td>PTC</td>
<td>↑</td>
<td>↑</td>
<td>n.d.</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>14</td>
<td>PTC/FTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>15</td>
<td>PTC/OTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>16</td>
<td>PTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>17</td>
<td>FTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>18</td>
<td>PTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>19</td>
<td>PTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
<tr>
<td>20</td>
<td>PTC</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
<td>Nonresponder</td>
</tr>
</tbody>
</table>

Prof. Pierre Bourgeois

G. Costante
Differentiated Thyroid Cancer

Selumetinib Redifferentiation

DTC refractory N=20

124-I / rhTSH

Selumetinib 4 weeks

131-I

Patients with Increased Iodine Uptake in a Lesion after Selumetinib

<table>
<thead>
<tr>
<th>Tumor Genotype</th>
<th>no./total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>4/9</td>
</tr>
<tr>
<td>NRAS</td>
<td>5/5</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>2/3</td>
</tr>
<tr>
<td>Wild-type</td>
<td>1/3</td>
</tr>
<tr>
<td>Total</td>
<td>12/20</td>
</tr>
</tbody>
</table>

Patients Who Received Radioiodine

Ho, 2013