Management of Radio-iodine refractory differentiated thyroid

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Epidemiology of Thyroid Cancer in Asia

### Age-Standardized Rate (ASR) - Incidence /100,000: Men, Women & Both in Asian Countries

<table>
<thead>
<tr>
<th>Region</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>1.5/4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>4.6/15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Africa</td>
<td>0.9/1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.4-10.9/1.6-59.5</td>
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<td></td>
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### Incidence (Y) per 100,000

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>USA</td>
<td>8,931</td>
</tr>
<tr>
<td>China</td>
<td>6,286</td>
</tr>
<tr>
<td>S. Korea</td>
<td>3,214</td>
</tr>
<tr>
<td>India</td>
<td>3,719</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2087</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>20</td>
</tr>
<tr>
<td>Malaysia</td>
<td>186</td>
</tr>
<tr>
<td>Myanmar</td>
<td>214</td>
</tr>
<tr>
<td>Philippines</td>
<td>756</td>
</tr>
<tr>
<td>Singapore</td>
<td>75</td>
</tr>
<tr>
<td>Thailand</td>
<td>1154</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>427</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>153</td>
</tr>
<tr>
<td>India</td>
<td>3926</td>
</tr>
<tr>
<td>Pakistan</td>
<td>482</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>133</td>
</tr>
</tbody>
</table>

GLOBOCAN 2012. at http://globocan.iarc.fr/
Thyroid Cancer: Etiology

- Thyroid cancer is a malignant neoplasm arising from the follicular or parafollicular (C cells) of the thyroid
  - Follicular cells are the cells that derive papillary, follicular, and anaplastic cancers
  - C cells or parafollicular cells derive the medullary subtype of thyroid cancer
- Recent progress shows that many thyroid cancers are due to genetic alterations
  - These alterations lead to aberrant cell signaling
- Specific genetic lesions are associated with each thyroid tumor histotype:
  - **BRAF V600E**: 40–60% of papillary thyroid cancer (PTC)
  - **RET/PTC**: 40% of PTC
  - **RAS**: 40–50% of follicular thyroid cancer (FTC)
  - **Pax8-PPARγ**: 36% of FTC
  - **RET**: 100% hereditary medullary thyroid cancer
  - **p53**: 40–60% sporadic

BRAF=v-Raf (rapidly accelerated fibrosarcoma) murine sarcoma viral oncogene homolog B1; Pax8=paired box gene 8; PPARγ=peroxisome proliferator-activated receptor gamma; RAS=rat sarcoma; RET=proto-oncogene tyrosine-protein kinase receptor Ret

   Last accessed: August 2014
Thyroid Cancer is Divided into Different Types Based on the Histology of the Cancerous Cells

- Three subtypes: differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC)
  - DTC accounts for 90% of all thyroid cancers, 2% of all cancers (180,000 globally*) 1–4

<table>
<thead>
<tr>
<th>DTC</th>
<th>MTC</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary Thyroid Cancer</td>
<td>Follicular Thyroid Cancer</td>
<td>5–8% of all thyroid cancer 1,3</td>
</tr>
<tr>
<td>85–90% of all thyroid cancer 1–4</td>
<td>10–15% of all thyroid cancer 1,3</td>
<td>• Slow progression to metastatic disease</td>
</tr>
<tr>
<td>• 90% have early-stage disease</td>
<td>• Worse prognosis than DTC</td>
<td>• Patients with RET mutations may have an aggressive course</td>
</tr>
<tr>
<td>• 10–20% present/progress to late-stage disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‘Differentiated’ refers to a malignant tumor that has the histologic appearance of cell types normally found in the thyroid

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DTC: Initial Disease Stage Predicts OVERALL SURVIVAL

**Risk of Recurrence in Thyroid Cancer**

- American Thyroid Association (ATA) and European Thyroid Association (ETA)1-3
  - Utilize tumor features (TNM, histologic variant), as well as clinical parameters (eg, postablative thyroglobulin [Tg] level and whole body scan [WBS]) to define 3 risk categories for recurrence1,2

- ATA/ETA system stratifies patients into recurrence risk groups4
  - ATA: low, intermediate, or high recurrence risk based on clinical features and age (<45/>45); despite this, younger patients may be misclassified
  - ETA: very low, low, or high based on completeness of surgery, metastasis, vascular invasion, and histology

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**ATA – Low Risk2**
All of following present:
- Tumor <1 cm
- No local or distant metastases
- All macroscopic tumor has been resected
- No invasion of locoregional tissues
- Tumor does not have aggressive histology (eg, tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer)
- No vascular invasion
- No 131I uptake outside thyroid bed on posttreatment scan, if done
- Age <45 years

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**ATA – Intermediate Risk2**
All of following present:
- Tumor >1 and <2 cm
- No local or distant metastases
- Microscopic invasion into perithyroidal soft tissues
- Cervical lymph node metastases or 131I uptake outside thyroid bed on posttreatment scan done after thyroid remnant ablation
- Tumor with aggressive histology or vascular invasion (eg, tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer)
- Age <45 years

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**ATA – High Risk2**
All of following present:
- Tumor >2 cm
- Nodal involvement
- Macroscopic tumor invasion
- Incomplete tumor resection with gross residual disease
- Locoregional metastases
- Distant metastases
- Age ≥45 years

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## Risk of Recurrence in Thyroid Cancer

<table>
<thead>
<tr>
<th>ETA – Very-Low Risk2</th>
<th>ETA – Low Risk2</th>
<th>ETA – High Risk2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete surgery;</td>
<td>No local or distant</td>
<td>• Less than total</td>
</tr>
<tr>
<td>unifocal &lt;1 cm</td>
<td>metastasis; no</td>
<td>thyroidectomy;</td>
</tr>
<tr>
<td>microcarcinoma; no</td>
<td>locoregional</td>
<td>locoregional</td>
</tr>
<tr>
<td>extension beyond</td>
<td>invasion of tissues or</td>
<td>invasion of tissues</td>
</tr>
<tr>
<td>thyroid capsule; no</td>
<td>structures; absence of</td>
<td>or structures;</td>
</tr>
<tr>
<td>lymph node</td>
<td>aggressive histology or</td>
<td>cervical lymph</td>
</tr>
<tr>
<td>metastases</td>
<td>vascular invasion</td>
<td>node metastases;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vascular invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or aggressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>histology</td>
</tr>
</tbody>
</table>

DTC Disease Progression to Metastatic Disease

- Progression – defined using Response Evaluation Criteria In Solid Tumors (RECIST)1
  - Increase in sum of target lesion diameters >20% over 6 to 14 months

- Overall survival (OS) and disease-specific survival lower for mDTC1
  - OS: 40.7 vs 90.7 ($P<0.001$)
  - Disease-specific survival ($P<0.001$):
    - 5 years:  59.1% vs 98.9%
    - 10 years: 44.3% vs 97.8%
    - 15 years: 38.8% vs 96.5%
    - 20 years: 37.5% vs 95.7%

NCCN and ATA guidelines for the treatment of differentiated thyroid cancer (DTC)

Initial treatment
- Total thyroidectomy, except in patients with unifocal microcarcinoma (individualized to patient and extent of disease)\(^1,2\)

Postoperative treatment
- Radioactive iodine (131I) (RAI) therapy\(^1,2\)

Follow-up treatment
- Levothyroxine to suppress TSH levels to < 0.1mU/L\(^1,2\)

Recurrent or metastatic disease treatment
- Local therapy (re-operation, external radiation)
- Systemic therapy
  - RAI therapy
  - patients with refractory advanced disease
    - chemotherapy (limited efficacy and considerable toxicity)\(^1,2\)
    - participation in clinical trials with small molecule tyrosine kinase inhibitors is recommended\(^1,2\)

\(^1\) NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma V.1.2010.

NCCN = National Comprehensive Cancer Network
ATA = American Thyroid Association
Treatment of Metastatic DTC

- For metastatic disease, initial recommendations include1-4:
  - Further, targeted, surgical resection (if applicable)
  - Further RAI ablation
  - External beam radiation (for non-RAI avid)
  - Levothyroxine at suppressive doses; local treatment modalities; systemic treatment: 131I/others

### Metastatic DTC: Guidelines and Recommendations

#### ESMO Recommendations
- DTC metastases are curable only if small, RAI-avid, and present in lungs
- Chemotherapy not indicated
- Clinical trial participation encouraged

#### ATA Recommendations (in order)
- Surgical excision in potentially curable patients
- 131I therapy for RAI-avid disease
- External beam radiotherapy
- Watchful waiting for slow/asymptomatic disease
- Clinical trial participation for progressive or refractory disease
- For patients with progressive or metastatic disease not wanting to participate in clinical trials, tyrosine kinase inhibitors (TKIs) may be considered [“B Recommendation”]

#### NCCN Recommendations
- Chemotherapy has minimal efficacy in metastatic DTC
- Clinical trial participation encouraged for non-RAI-responsive tumors
- Consider small molecule TKIs
- Best supportive care

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Systemic Therapy

- Chemotherapy is to either by killing the cells or by stopping them from dividing.
- Lists cancer drugs approved by US FDA for thyroid cancer
  - Caprelsa (Vandetanib) - MTC
  - Cometriq (Cabozantinib-S-Malate)- MTC
  - Doxorubicin Hydrochloride
  - Nexavar (Sorafenib Tosylate)-RRDTC
  - Lenvatinib(Lenvima) -RRDTC
Prognostic Factors for Metastatic Disease

- Prognostic factors for metastatic disease
  - Comparison of patients with (n=1291) or without (n=58,518) metastatic differentiated thyroid cancer (DTC) at presentation
  - Metastatic DTC uncommon (2.2% of cohort)

- Multivariable analysis (n=819)
  - Older age (≥65 years), follicular histology, positive lymph nodes, and larger tumor size were among most important variables for metastatic DTC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.45</td>
<td>1.25–1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–64 years</td>
<td>2.58</td>
<td>2.09–3.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥65 years</td>
<td>5.98</td>
<td>4.87–7.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single</td>
<td>1.29</td>
<td>1.11–1.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black race</td>
<td>1.67</td>
<td>1.31–2.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other races</td>
<td>2.11</td>
<td>1.74–2.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FTC</td>
<td>4.19</td>
<td>3.50–5.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCC</td>
<td>1.46</td>
<td>1.10–1.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–40mm</td>
<td>1.46</td>
<td>1.39–2.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;40mm</td>
<td>1.68</td>
<td>2.89–4.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive regional lymph nodes</td>
<td>5.36</td>
<td>4.49–6.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI=confidence interval; FTC=follicular thyroid cancer; HCC=Hürthle cell carcinoma; SEER=Surveillance, Epidemiology and End Results Program
Survival and Response to Treatment

• **Group 1**: initial 131I uptake and CR
  - Age < 40 years
  - Well-differentiated cancer
  - Small size of metastases

• **Group 2**: initial 131I uptake and persistent disease

• **Group 3**: no initial 131I uptake

Treatment of Metastatic and Radioactive Iodine-Refractory Differentiated Thyroid Cancer (RRDTC)
Rationale for Using Tyrosine Kinase Inhibitors in the Treatment of Metastatic Differentiated Thyroid Cancer
RAI-Refractory Disease

- 25-50% of Metastatic Thyroid Cancers lose ability to take up Iodine

- This is attributed to down regulation of the Na+/I- Symporter (NIS) and other genes of NaI metabolism

In other words, the cancer cells “forget” how to take up iodine and so they are immune to the treatment.
Progression to Radioiodine-Refractory Differentiated Thyroid Cancer (RR-DTC)

- Approximately 1/3 of patients with metastatic disease do not show evidence of radioactive iodine (RAI) uptake\(^1\)

- RR-DTC
  - Clinical evidence that RAI is no longer providing benefit suggests patients have become RAI-refractory\(^1\)
  - RR-DTC is rare, representing <5% of patients with clinical DTC\(^1\)–\(^4\)

- RR-DTC patients have poor overall prognosis, with 10-year survival rates of only 10% and median survival from discovery of metastases of only 3–5 years\(^1\)–\(^4\)

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Fig. 2. Survival after the discovery of distant metastases according to the age at discovery and to the extent of disease. 131I uptake was not taken into account, but was closely linked to the two other prognostic factors, and was invariably present in young patients with small metastases (group 1) and rarely present in older patients with large metastases (group 2). Group 1, Patients younger than 40 yr of age with metastases that were not visible on radiographs or that were micronodular (<1 cm in diameter). Group 2, Patients older than 40 yr with macronodular lung metastases or multiple bone metastases. Group 3, Patients older than 40 yr with normal x-rays or micronodular metastases and patients younger than 40 yr with macronodular lung metastases.
Fig. 3. Survival after the discovery of distant metastases. Group 1, Patients with 131I uptake who attained negative imaging studies. Group 2, Patients with 131I uptake who did not attain negative imaging studies. Group 3, Patients with no 131I uptake.
Iodine-Refractory mDTC: diagnostic criteria

Evidence of radiologic progression within 13 months and at least one of the following criteria:

+ 

At least one measurable lesion without iodine uptake on any iodine-131 scan,

At least one measurable lesion that had progressed according to the Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1, criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment,

Or cumulative activity of iodine-131 that was >600 mCi
Definition of Radioiodine (RAI)-Refractory Disease

- Currently, there is no widely accepted definition for RAI-refractory disease
  - Accepted evidence of RAI-refractory disease by most clinicians includes
    - Increasing thyroglobulin (Tg) level after administration of RAI
    - Lack of detectable radioactivity on whole body scan (WBS) after diagnostic or therapeutic administration
  - Most conservative approach is probably progression of lesions after RAI treatment as evaluated by computed tomography, magnetic resonance imaging, or bone scan.

Colevas D, Shah MH. Evaluation of Patients With Disseminated or Locoregionally Advanced Thyroid Cancer: A Primer for Medical Oncologists. ASCO Workbook on Thyroid Cancer, 2012
Management of Refractory Differentiated Thyroid Cancer

- Levothyroxine treatment: serum thyroid stimulating hormone <0.1mU/L
- Local treatments when needed: surgery, external radiation, radiofrequency-, or cryo-ablation
- Imaging follow up every 6 months
- Stable disease: follow up

Progression
- >20% (Response Evaluation Criteria in Solid Tumors) in 6–15 months
- Inclusion in a trial
- Chemotherapy: low efficacy, significant toxicity (e.g., doxorubicin: <5% partial response, median progression-free survival: 7 months)

Targeted therapy as first line
- Lenvatinib was recently approved for the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment

ATA, Cooper. Thyroid. 2009;19:1167
Limited Role for Chemotherapy

- Biology of differentiated thyroid cancer (DTC) may limit the utility of chemotherapy for DTC1
  - More effective on rapidly dividing cells, whilst thyroid tumors are slower growing
- Guidelines (ESMO, ETA, ATA, NCCN) do not recommend chemotherapeutic agents for metastatic DTC2,3
- Available chemotherapeutic agents include: anthracyclines (doxorubicin), alkylating agents (cisplatin), antitumor antibiotics (bleomycin), and early antiangiogenics (e.g., thalidomide, lenalidomide), but have limited therapeutic benefit1,5–8
- In advanced disease, mono- or poly-chemotherapy has not shown substantial clinical benefit (<20% response rate)3
  - For patients with metastatic disease, doxorubicin alone or in combination is the most effective cytotoxic therapy but complete response is rare and there is a notable toxicity profile1,4

ATA=American Thyroid Association; ESMO=European Society for Medical Oncology; ETA=European Thyroid Association; NCCN=National Comprehensive Cancer Network
8. Colevas D, Shah MH. ASCO Workbook on Thyroid Cancer; 2012
Who is appropriate for kinase inhibitor therapy?

1. Patients whose tumors no longer take up radioactive iodine or who have exceeded their lifetime dose
2. Patients with disease measurable by exam or CT scan
3. Patients with >1 lesion which is >1 cm in size and who are symptomatic
4. Patients with progressive disease
Rationale for TKIs for the Treatment of DTC

- Chemotherapeutic agents (i.e., doxorubicin or cisplatin) have shown limited benefit in DTC1–4
- In patients with metastatic DTC treated with chemotherapy, only 3% had an objective response5,6
- TKIs target proangiogenic and oncogenic signaling pathways on both endothelial (pericyte) and tumor cells7–14
  - Inhibition of proangiogenic growth factors (e.g., VEGF, FGF, PDGF1–3)
  - Regulation of aberrant signaling (e.g., RET, RAS, BRAF)
- Several TKIs have demonstrated antitumor activity in clinical trials in patients with advanced DTC15

<table>
<thead>
<tr>
<th>Factor</th>
<th>Critical Oncogenic Pathways1–8</th>
</tr>
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<tbody>
<tr>
<td>VEGF</td>
<td>Angiogenesis, survival, proliferation</td>
</tr>
<tr>
<td>FGF</td>
<td>Angiogenesis, survival, proliferation, migration, invasion</td>
</tr>
<tr>
<td>PDGF</td>
<td>Angiogenesis, proliferation, differentiation, survival, migration, metastasis</td>
</tr>
<tr>
<td>RET</td>
<td>Survival, differentiation, proliferation, migration</td>
</tr>
<tr>
<td>BRAF</td>
<td>Differentiation, metastasis</td>
</tr>
<tr>
<td>RAS</td>
<td>Proliferation, differentiation, survival</td>
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</tbody>
</table>

BRAF=serine/threonine-protein kinase B-Raf; DTC=differentiated thyroid cancer; FGF=fibroblast growth factor; PDGF=platelet-derived growth factor; RET=proto-oncogene tyrosine-protein kinase receptor Ret; VEGF=vascular endothelial growth factor

# Targets of Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>VEGFR</th>
<th>BRAF</th>
<th>PDGFR</th>
<th>KIT</th>
<th>RET</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>FLT-3</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>FLT-3</td>
</tr>
<tr>
<td>Axitinib (AG-013736)</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>
</tr>
<tr>
<td>Pazopanib (GW786034)</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vandetanib (Zactima)</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>EGFR</td>
</tr>
<tr>
<td>Cabozotanib (XL184)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>C-MET</td>
</tr>
<tr>
<td>Lenvatinib (E7080)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FGFR</td>
</tr>
</tbody>
</table>
Molecular Signaling Pathways and Drug Targets in DTC

- EGFR = epidermal growth factor receptor
- VEGFR = vascular endothelial growth factor receptor
- MAPK = mitogen-activated protein kinases
- MEK = MAPK kinase
- ERK = extracellular signal-regulated kinase
- PI3K = phosphatidylinositol 3-kinase
- mTOR = mammalian target of rapamycin.

Minerva Endocrinol. 2012 December; 37(4): 335
## Profile of TKIs in Clinical Trials for Radioiodine-Refractory Differentiated Thyroid Cancer (RR-DTC)

### Summary of Some TKIs in Clinical Trials, Their Targets, and Observed Adverse Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Targeted Tyrosine Kinase</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib1</td>
<td>VEGFR1-3, PDGFR, c-Kit</td>
<td>Fatigue, diarrhea, nausea, anorexia, hypertension, stomatitis, weight loss, headache</td>
</tr>
<tr>
<td>Cabozantinib (XL184) 1</td>
<td>HGFR, VEGFR2, RET</td>
<td>Hand–foot syndrome (palmar–plantar erythrodysesthesia), mucositis, elevations in aspartate aminotransferase, alanine aminotransferase, and lipase levels</td>
</tr>
<tr>
<td>Lenvatinib (E7080) 1</td>
<td>VEGFR1-3, FGFR1-4, RET, c-Kit, PDGFR</td>
<td>Hypertension, fatigue, diarrhea, weight loss, anorexia, proteinuria</td>
</tr>
<tr>
<td>Motesanib1</td>
<td>VEGFR1-3, PDGFR, c-Kit, RET</td>
<td>Diarrhea, fatigue, hypertension, anorexia, hypothyroidism</td>
</tr>
<tr>
<td>Pazopanib1</td>
<td>VEGFR, PDGFR, c-Kit</td>
<td>Fatigue, skin and hair pigmentation, diarrhea, nausea</td>
</tr>
<tr>
<td>Ponatinib2</td>
<td>FLT3, RET, KIT, FGFR1-4, PDGFR</td>
<td>Thrombosis, venous thromboembolism, congestive heart failure, hypertension, pancreatitis, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression tumor lysis syndrome, poor wound healing</td>
</tr>
<tr>
<td>Sorafenib1</td>
<td>VEGFR1-3, PDGFR, RET, RAF, c-Kit</td>
<td>Diarrhea, oral cavity pain, hand–foot syndrome, alopecia, hypertension, muscle pain or cramping, cytopenia</td>
</tr>
<tr>
<td>Sunitinib1</td>
<td>PDGFR, VEGFR1-3, c-Kit, RET, CSF1R, FLT3</td>
<td>Fatigue, neutropenia, hand–foot syndrome, diarrhea, leukopenia</td>
</tr>
<tr>
<td>Vandetanib (ZD6474) 1</td>
<td>VEGFR2-3, RET, EGFR</td>
<td>Photosensitive skin rash, prolonged QT interval, diarrhea, nausea, hypertension, headache, leukopenia</td>
</tr>
</tbody>
</table>

CSF1R=macrophage colony-stimulating factor 1 receptor; EGFR=epidermal growth factor receptor; FGFR=fibroblast growth factor receptor; FLT3=FL cytokine receptor; HGFR=hepatocyte growth factor receptor; PDGFR=platelet-derived growth factor receptor; RAF=RAF proto-oncogene serine–threonine-protein kinase; RET=proto-oncogene tyrosine-protein kinase receptor Ret; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor

## Targeted Agents: Phase II Clinical Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Key Baseline Characteristics</th>
<th>n</th>
<th>PFS Months</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (Brose)</td>
<td>• DTC+ PDTC (90%),</td>
<td>47</td>
<td>20</td>
<td>38%</td>
<td>47%</td>
<td>2%</td>
</tr>
<tr>
<td>Sunitinib (Cohen)</td>
<td>• DTC (74%); MTC (26%)</td>
<td>51</td>
<td>-</td>
<td>17% DTC</td>
<td>74% DTC</td>
<td>9% DTC</td>
</tr>
<tr>
<td>Axitinib (Cohen)</td>
<td>• Papillary (50%); Medullary (18%); Follicular/Hurthle (25%/18%); Anaplastic (3%)</td>
<td>60</td>
<td>18.1</td>
<td>30%</td>
<td>48%</td>
<td>7%</td>
</tr>
<tr>
<td>Motesanib (Sherman)</td>
<td>• Papillary (61%); Follicular/Hurthle (34%)</td>
<td>93</td>
<td>10</td>
<td>14%</td>
<td>67%</td>
<td>8%</td>
</tr>
<tr>
<td>Pazopanib (Bible)</td>
<td>PD and DTC (Progression &lt;6months)</td>
<td>37</td>
<td>12</td>
<td>49%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lenvatinib (E7080, Sherman)</td>
<td>• DTC 100%</td>
<td>58</td>
<td>13.3</td>
<td>45%</td>
<td>46%</td>
<td>5%</td>
</tr>
<tr>
<td>Compound Name</td>
<td>DTC/MTC</td>
<td>Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>DTC</td>
<td>First Line – International Phase III – Positive. Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lenvatinib (E7080)</td>
<td>DTC</td>
<td>First and Second Line – Phase III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib (BRAF V600E inhibitor)</td>
<td>DTC (PTC)</td>
<td>First and Second Line Phase II – (Phase III?)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Everolimus+Sorafenib</td>
<td>DTC</td>
<td>Second Line – Phase II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>DTC</td>
<td>First Line – Phase I complete First Line and Second Line Phase II– Pending Approved for MTC (also Vandetanib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (PPARγ)</td>
<td>DTC (FTC*)</td>
<td>First and Second Line -  Phase II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pazopanib (GW786034)</td>
<td>DTC</td>
<td>First and Second line – Phase II Done</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>DTC</td>
<td>First line Phase II – Done.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Phase III Trials in RRDTC

Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial

Marcia S Brose, Christopher M Nutting, Barbara Jarzab, Rossella Elisei, Salvatore Siena, Lars Bastholt, Christelle de la Fouchardiere, Furio Pacini, Ralf Paschke, Young KeeShong, Steven I Sherman, Johannes WA Smit, John Chung, Christian Kappeler, Carol Pena, István Molnár, Martin J Schlumberger, and on behalf of the DECISION Investigators

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

Martin Schlumberger, M.D., Makoto Tahara, M.D., Ph.D., Lori J. Wirth, M.D., Bruce Robinson, M.D., Marcia S. Brose, M.D., Ph.D., Rossella Elisei, M.D., Mouhammed Amir Habra, M.D., Kate Newbold, M.D., Manisha H. Shah, M.D., Ana O. Hoff, M.D., Andrew G. Gianoukakis, M.D., Naomi Kiyota, M.D., Ph.D., Matthew H. Taylor, M.D., Sung-Bae Kim, M.D., Ph.D., Monika K. Krzyzanowska, M.D., M.P.H., Corina E. Dutcus, M.D., Begoña de las Heras, M.D., Junming Zhu, Ph.D., and Steven I. Sherman, M.D.
Sorafenib

DECICION Trial
Brose M et al. NEJM 2014
Sorafenib. DECISION
Brose M et al. Lancet 2014
Sorafenib. DECISION
Brose M et al. Lancet 2014

- PFS
- Sorafenib -10.8 months
### Sorafenib. DECISION
Brose M et al. Lancet 2014
Adverse Events

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Sorafenib (n=207)</th>
<th>Placebo (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>158 (76.3)</td>
<td>42 (20.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>142 (68.6)</td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>139 (67.1)</td>
<td>–</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>104 (50.2)</td>
<td>10 (4.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>103 (49.8)</td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>97 (46.9)</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84 (40.6)</td>
<td>20 (9.7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>66 (31.9)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Oral mucositis (functional/symptomatic)</td>
<td>48 (23.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>44 (21.3)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (20.8)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>37 (17.9)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>32 (15.5)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>31 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30 (14.5)</td>
<td>10 (4.8)</td>
</tr>
<tr>
<td>Neuropathy: sensory</td>
<td>30 (14.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Abdominal pain - not otherwise specified</td>
<td>29 (14.0)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Pain, extremity – limb</td>
<td>28 (13.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Dermatology - Other</td>
<td>27 (13.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Voice changes</td>
<td>25 (12.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Fever</td>
<td>23 (11.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (11.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>22 (10.6)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pain, other</td>
<td>22 (10.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pain, throat/pharynx/larynx</td>
<td>21 (10.1)</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic/laboratory – other</td>
<td>74 (35.7)</td>
<td>0</td>
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</tbody>
</table>
Lenvatinib
SELECT TRIAL
A phase 3, multicenter, double-blind, placebo-controlled trial of Lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer.

Lenvatinib is a Multi-Targeted Kinase Inhibitor

- Lenvatinib targets the TKI receptors VEGFR1-3, FGFR1-4, PDGFRα*, RET, and c-Kit1–6
- In preclinical models, lenvatinib
  - Shows potent antiangiogenic and antilymphogenic activity
  - Inhibits tumor cell proliferation
  - Induces tumor regression
  - Inhibits cell migration and invasion1,2,7–10
- Lenvatinib inhibits tumor angiogenesis, survival, proliferation, differentiation, invasion, migration, and metastasis1,2,7–10

*Lenvatinib also inhibits PDGFRβ but the assay cut-off value is 100nm

Lenvatinib is a Selective Multi-Targeted TKI 1–9

Survival, differentiation, proliferation, invasion, migration, and metastasis

Tumor cell

Lenvatinib

Angiogenesis, survival, proliferation

Survival, differentiation, proliferation, migration

Angiogenesis, survival, proliferation, migration, invasion

Angiogenesis, survival, proliferation, differentiation, invasion, migration, metastasis

Endothelial cell

* Lenvatinib also inhibits PDGFRβ but the assay cut-off value is 100nm

Lenvatinib Inhibits Multiple Oncogenic Signaling Pathways

- For tumor cells, while VEGF, FGF, and PDGF regulate important oncogenic pathways, RET and aberrant signaling of downstream effectors like RAS and BRAF are also purported to be involved in driving tumor pathogenesis and proliferation1–6

- Key DTC oncogenic pathways1–8
  - Mitogen-activated protein kinase (MAPK) pathway
  - BRAF and RAS
  - Vascular endothelial growth factors receptors 1–3 (VEGFR)
  - Fibroblast growth factor receptor 1–4 (FGFR)
  - RET (rearranged during transfection)/PTC

- Lenvatinib targets multiple antiangiogenic and oncogenic signaling pathways, ensuring simultaneous inhibition of both the primary angiogenic target and evasive signaling networks

Patients with DTC (n=392)

- ≥18 years old
- IRR evidence of progression within previous 13 months
- 131I-refractory disease
- Blood pressure ≤150/90 mmHg
- Up to 1 prior VEGF or VEGFR-targeted therapy

Stratification

- Geographic region (Europe, N. America, Other)
- Prior VEGF/VEGFR targeted therapy (0,1)
- Age (≤65 years, >65 years)

Lenvatinib (n=261)
24 mg daily PO

Placebo (n=131)
Daily PO

Primary endpoint
- PFS

Secondary endpoints
- ORR
- OS
- Safety

Treatment until IRR-verified disease progression by RECIST 1.1

Global, randomized, double-blind Phase III trial

DTC, differentiated thyroid cancer; 131I, radioiodine; IRR, independent radiologic review, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor
Figure 1. Enrollment, Randomization, and Treatment.
RESULTS

• Median PFS was

  Lenvatinib: 18.3 mo (95% CI 15.1–not evaluable)
  Placebo : 3.6 mo (95% CI 2.2–3.7).

  (Hazard ratio 0.21, 95% confidence interval [CI] 0.14–0.31; \( P < .0001 \));

• PFS benefit with lenvatinib was observed in all predefined subgroups

  Median PFS with lenvatinib for patients

  • with prior VEGF-therapy was 15.1 mo (n=66)
  • without prior VEGF-therapy was 18.7 mo (n=195)
Lenvatinib. SELECT
Schlumberger et al. NEJM 2015

Primary Endpoint: Kaplan-Meier Estimate of PFS

Median PFS, months (95% CI)
- Lenvatinib: 18.3 (15.1-NR)
- Placebo: 3.6 (2.2-3.7)

HR (99% CI): 0.21 (0.14-0.31)
Log-rank test: P < 0.0001

Number of subjects at risk:
<table>
<thead>
<tr>
<th>Group</th>
<th>At Risk</th>
<th>261</th>
<th>225</th>
<th>198</th>
<th>176</th>
<th>159</th>
<th>148</th>
<th>136</th>
<th>92</th>
<th>44</th>
<th>24</th>
<th>11</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Lenvatinib</td>
<td></td>
<td>261</td>
<td>225</td>
<td>198</td>
<td>176</td>
<td>159</td>
<td>148</td>
<td>136</td>
<td>92</td>
<td>44</td>
<td>24</td>
<td>11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>131</td>
<td>71</td>
<td>43</td>
<td>29</td>
<td>19</td>
<td>13</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.
RESULTS

- Median OS has not been reached; Deaths per arm were
  - Lenvatinib: 71 (27.2%)
  - Placebo: 47 (35.9%).

- The 5 most common Lenvatinib treatment-related adverse events (TRAEs; any grade) were hypertension (68%), diarrhea (59%), appetite decreased (50%), weight loss (46%), nausea (41%).
## Sorafenib versus Lenvatinib

<table>
<thead>
<tr>
<th></th>
<th>DECISION</th>
<th>SELECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>417</td>
<td>360</td>
</tr>
<tr>
<td>Study period</td>
<td>21 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Primary objective</td>
<td>PFS</td>
<td>PFS</td>
</tr>
<tr>
<td>Secondary objectives</td>
<td>ORR, OS</td>
<td>ORR, OS</td>
</tr>
<tr>
<td>Prior anti-VEGFR therapy</td>
<td>No</td>
<td>Yes (maximum one)</td>
</tr>
<tr>
<td>Evidence of disease progression</td>
<td>Prior 14 months</td>
<td>Prior 12 months</td>
</tr>
<tr>
<td>Centrally confirmed</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>radiologic progression</td>
<td></td>
<td></td>
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<tr>
<td>prior to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor evaluation</td>
<td>RECIST 1.0</td>
<td>RECIST 1.1</td>
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<tr>
<td>Response evaluation by</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>independent central review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossover for placebo patients</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Conclusion

- DTC accounts for 94% of all thyroid cancers
- RAI refractory means that there are progressing lesions that do not take up RAI
- 25–50% of metastatic thyroid cancers lose ability to take up iodine
- Role of TKIs is in RR-DTC after surgery, RAI ablation and EBRT
- Lenvatinib has properties distinct from other TKIs
- Lenvatinib significantly improved PFS compared with Placebo in pts with progressive RR-DTC. (SELECT trial)
- Appears to be offering greater benefits than sorafenib (SELECT versus DECISION) in the management of RR-DTC
## Metastatic Differentiated Thyroid Cancer (DTC): Guidelines and Recommendations

### ESMO Recommendations1
- DTC metastases are curable only if small, radioiodine (RAI)-avid, and present in lungs
- Chemotherapy not indicated
- Clinical trial participation encouraged

### ATA Recommendations (in order)2
- Surgical excision in potentially curable patients
- 131I therapy for RAI-avid disease
- External beam radiotherapy
- Watchful waiting for slow/asymptomatic disease
- Clinical trial participation for progressive or refractory disease

### NCCN Recommendations3
- Vandetanib
- Cabozantinib
- Clinical trial
- Consider other small-molecule kinase inhibitors if above not available/appropriate
- If patient progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered, using dacarbazine or combinations including dacarbazine

### Note:
Lenvatinib was recently approved for the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.

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ATA=American Thyroid Association; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network

LENVATINIB Preferred in Papillary DTC

NCCN Guidelines Version 2.2017
Thyroid Carcinoma – Papillary Carcinoma

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

- For progressive and/or symptomatic disease, consider levetrazinib (preferred) or sorafenib.aa
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate. bb,cc,dd
- Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapiesee when available to metastatic lesions if progressive and/or symptomatic.
- Active surveillance is often appropriate in asymptomatic patients with indolent disease assuming no brain metastases. bb (See PAP-7)

- Consider surgical palliation and/or EBRT/SBRT/other local therapies when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage.
- Consider embolization or other interventional procedures as alternatives to surgical resection/EBRT/IMRT in select cases.
- Consider intravenous bisphosphonate or denosumab.z
- Active surveillance may be appropriate in asymptomatic patients with indolent disease. bb (See PAP-7)
- For progressive and/or symptomatic disease, consider levetrazinib (preferred) or sorafenib.bb While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate. bb,cc,dd
- While not FDA approved for the treatment of differentiated thyroid cancer.