An Update on Novel Therapies for Advanced Differentiated Thyroid Cancer: When to Start and What to Use

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DISCLAIMER:

- My goal is to present information on several agents currently under investigation for the treatment of advanced differentiated thyroid cancer. As none of the agents are FDA approved for this use at this time, all of the data presented will be data collected from clinical trials that have been reported over the past 5 years.
**DISCLOSURE:**

I have financial interest/arrangement or affiliation with:

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer Healthcare</td>
<td>research funding, honorarium</td>
</tr>
<tr>
<td>Onyx</td>
<td>research funding, honorarium</td>
</tr>
<tr>
<td>Novartis</td>
<td>research funding,</td>
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<td></td>
<td>honorarium</td>
</tr>
<tr>
<td>Exelixis</td>
<td>research funding,</td>
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<td></td>
<td>honorarium</td>
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<tr>
<td>Astrazenecca</td>
<td>research funding,</td>
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<tr>
<td></td>
<td>consulting</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>research funding</td>
</tr>
</tbody>
</table>
Objectives:

By the end of this talk it is hoped that you will have a better understanding of:

1. when we consider a patient is a candidate for kinase inhibitor therapy

2. What kinase inhibitors are in the pipeline for treatment of patients with progressive RAI refractory differentiated thyroid cancer
Radioactive-iodine (RAI)-refractory differentiated thyroid cancer (DTC)

• It is estimated\(^1\) that in the USA in 2013 there will be:
  – >60,000 new cases of thyroid cancer, and
  – 1,850 deaths due to thyroid cancer

• In approximately 5–15% of patients with thyroid cancer, the disease becomes refractory to RAI\(^2,3\)

• Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5–3.5 years\(^4,5\)

• Patients often suffer multiple complications associated with disease progression

• There is no standard therapy for patients with RAI-refractory DTC

Differentiated Thyroid Cancer: Treatment Strategy

- High Risk: (Age >45, male, metastasis, extrathyroidal extension, >4cm)
  - Total Thyroidectomy
  - RAI ($^{131}$I) Ablation
  - TSH Suppression Therapy with Thyroid Hormone
  - Follow Serial Thyroglobulin Levels (Tg)
  - XRT for recurrent local disease/positive margins
  - Surveillance: NeckUS, Tg, Neck MRI, Chest CT, RAI Whole body scan, FDG-PET
TSH Suppression Improves Survival for DTC Patients With Metastases

Median

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>&gt; 45 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH suppressed</td>
<td>15 yr</td>
<td>10 yr</td>
</tr>
<tr>
<td>TSH unsuppressed</td>
<td>11 yr</td>
<td>6 yr</td>
</tr>
</tbody>
</table>

$p < 0.01$ $p < 0.005$

$n = 450$

Survival is determined by Response to RAI Treatment

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

- **Group 2**: initial $^{131}$I uptake and persistent disease

- **Group 3**: no initial $^{131}$I uptake

Absence of Detectable Disease As a Function of RAI Cumulative Activity

From a retrospective study of a total of 444 patients treated from 1953–1994 for distant metastases from papillary and follicular thyroid carcinoma in order to estimate the cumulative activity of $^{131}$I.

- Most CRs (96%) are obtained with a cumulative activity of 22 GBq (600 mCi) or less.
- Administration of activities >22 GBq on an individual basis
RAI-refractory disease: consensus criteria used for most Phase II and III trials

- Patients had progressive disease in the 6-14 months prior to enrollment as defined by RECIST criteria (20%).

- RAI refractory means that there are **progressing lesions** that **do not take up RAI** (Note: there may still be some that do)
  - RAI uptake scan is negative and CT scan shows nodules
  - RAI uptake scan has uptake but not in some nodules that are progressing
  - Patient has exceeded total lifetime dose of 600 mCi

Hodak SP, Carty SE. Oncology. 2009;23:775-6.
### Thyroid Cancer is associated with aberrant cell signaling

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>PTC</th>
<th>FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>BRAF copy gain</td>
<td>3%</td>
<td>35%</td>
</tr>
<tr>
<td>RET/PTC (1 and 3)</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>RAS</td>
<td>8-10%</td>
<td>17-45%</td>
</tr>
<tr>
<td>PI3KCA mutations</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>PI3KCA copy gain</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>PTEN</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Pax8/PPARY</td>
<td>0%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>&gt;70%</td>
<td>&gt;65%</td>
</tr>
</tbody>
</table>

Nikiforov, Mod Path, 2008, Xing Endocrine Rel Ca(2005), Wang et al, 2007
Kinase Inhibitors

ATP → KI → P → Activated pathway → Cancer

Activated Pathway Cancer

RET, BRAF..... inhibition

Tumor growth

VEGFR inhibition

Tumor angiogenesis

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Marcia Brose)
Targeting cell signaling in thyroid cancer

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

**Endothelial Cell**
- VEGFR-2
  - Ras
  - Raf
  - PI3K
  - AKT
  - mTOR
  - ERK
  - S6K
  - Growth
  - Survival
  - Proliferation
  - Migration
  - Angiogenesis

**Drugs**
- Motesanib
- Sorafenib
- Sunitinib
- Vandetanib
- Cabozantinib
- Lenvatinib
- Everolimus
- Sirolimus

# Targets of 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>
</tr>
</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>FLT-3</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>
## Targeted Agents: Phase II Clinical Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Key Baseline Characteristics</th>
<th>n</th>
<th>PFS</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%</td>
<td>74%</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 (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>Vemurafenib (Brose)</td>
<td>• BRAF V600E DTC first line</td>
<td>26</td>
<td>15.6</td>
<td>35%</td>
<td>23%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Background and rationale for sorafenib in DTC

• Sorafenib is a multikinase inhibitor targeting VEGFRs1-3 and PDGFRs, BRAF, RET and c-Kit

• Sorafenib is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma

• Sorafenib has been shown to have activity as monotherapy in Phase 2 trials in patients with advanced refractory thyroid cancer

• DECISION is a randomized, double-blinded, placebo-controlled Phase 3 trial designed to explore the efficacy and safety of sorafenib in patients with RAI-refractory DTC


PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
## Investigator-Sponsored Studies (Phase 2)

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Study Population</th>
<th>Subjects</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Subjects with progressive metastatic or locally advanced RAI-refractory DTC</td>
<td>Total: 32</td>
<td>No reinduction of RAI uptake at metastatic sites PR: 25% (n = 8); SD: 34% (n = 11); PD: 22% (n = 7) DCR: 59% (n = 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treated: 31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single center, pilot study</td>
<td>34</td>
<td>RR (6 months): 15% RR (12 months): 21% mPFS and mOS not reached at 19 months OS (1 year): 88% PFS (1 year): 79%</td>
</tr>
<tr>
<td></td>
<td>Subjects with metastatic advanced DTC and MTC considered unsuitable for treatment with RAI</td>
<td>19 with DTC (15 with MTC)</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Subjects with metastatic, iodine-refractory thyroid carcinoma</td>
<td>55</td>
<td>mPFS: 84 weeks Median time on study: 39 weeks</td>
</tr>
<tr>
<td></td>
<td>47 with DTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Subjects with iodine-refractory metastatic PTC</td>
<td>56</td>
<td>ORR: 15% mPFS: 16 months mOS: 23 months SD: 57%</td>
</tr>
<tr>
<td></td>
<td>41 with DTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; DCR, disease control rate; DTC, differentiated thyroid cancer; mOS, median OS; mPFS, median PFS; MTC, medullary thyroid carcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RR, response rate; SD, stable disease.

DECISION study design

417 patients
- Locally advanced or metastatic RAI-refractory DTC
- Progression (RECIST) within the previous 14 months
- No prior chemotherapy targeted therapy, or thalidomide

Sorafenib
400 mg orally twice-daily

Placebo
orally twice-daily

Randomization 1:1

Primary endpoint
- Progression-free survival

Secondary endpoints
- Overall survival
- Response rate
- Safety
- Time to progression
- Disease control rate
- Duration of response
- Sorafenib exposure (AUC_{\text{0-12}})

• Stratified by:
  - geographical region (North America or Europe or Asia)
  - age (<60 or ≥60 years)
• Progression assessed every 8 weeks (independent central review)
• Patients were allowed to receive open-label sorafenib after progression

Brose MS et al. BMC Cancer 2011;11:349; www.clinicaltrials.gov. NCT00984282
Progression-free survival
(by independent central review)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, days (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>329 (10.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>175 (5.8)</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.587 (0.454-0.758)

p < 0.0001

Full analysis set; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
## PFS in predefined subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>≥60 years</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td><strong>Histology (central review)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Hürthle cell</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td><strong>Lung metastases only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>347</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td><strong>Bone metastases only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>304</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td><strong>FDG uptake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td><strong>No. target or non-target lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; median</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>≥ median</td>
<td>254</td>
<td></td>
</tr>
<tr>
<td><strong>Target lesion size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; median</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>≥ median</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative RAI ≥600 mCi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>133</td>
<td></td>
</tr>
</tbody>
</table>

FDG, fluorodeoxyglucose
Overall survival

A total of 150 placebo patients (71%) and 55 sorafenib patients (27%) received open-label sorafenib after progression.

Median OS

- **Sorafenib**: NR
- **Placebo**: NR

HR (95% CI): 0.802 (0.539–1.194)

\( p = 0.138 \), one-sided

Full analysis set. NR, not reached.
### Other secondary efficacy endpoints

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib n (%)</th>
<th>Placebo n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total evaluable patients</td>
<td>196</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td>24 (12.2)</td>
<td>1 (0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (12.2)</td>
<td>1 (0.5)</td>
<td>–</td>
</tr>
<tr>
<td>Stable disease for ≥6 months</td>
<td>82 (41.8)</td>
<td>67 (33.2)</td>
<td>–</td>
</tr>
<tr>
<td>Disease control rate (CR + PR +SD ≥6 months)</td>
<td>106 (54.1)</td>
<td>68 (33.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>10.2 (7.4-16.6)</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Complete response (CR); partial response (PR); stable disease (SD)
–, p value not determined; NA, not assessed
Summary: Phase III trials for RAI refractory DTC

• DECISION is the first phase 3 study completed of a targeted agent in Progressing RAI-refractory DTC, a rare condition with a poor prognosis and no effective standard treatment

• Sorafenib significantly improved PFS and extended median PFS by 5 months vs placebo
  – 10.8 vs 5.8 months (HR, 0.587; 95% CI, 0.454-0.758; \( P < 0.0001 \))
  – FDA submission in progress

• Two additional Phase III trials in this population are ongoing
  – Lenvatinib: Enrollment complete, results expected soon
  – Vandetanib: Enrollment open

AE, adverse event; DTC, differentiated thyroid cancer; HR, hazard ratio; PFS, progression-free survival; RAI, radioactive iodine.
Multi-Institutional Study Selumetinib in High-Risk DTC Patients: Phase III ASTRA Study Design

**Patient population**
- Newly-diagnosed DTC post surgery
- Complete gross resection
- Genetic all-comers
- No distant mets
- Eligibility criteria defines a population at 70% risk of primary treatment failure with surgery and RAI alone

 Selumetinib
75 mg bid
5 weeks duration
RAI 100 mCi
n = 152

Placebo bid
5 weeks duration
RAI 100 mCi
n = 76

**Primary endpoint**
Complete remission (CR) rate at 18 months post-RAI

**Other endpoints**
- Clinical remission rate at 18 months post RAI (per SoC)
- Safety/tolerability
- Re-treatment

228 Patients randomized (2:1 ratio)

**Longer-term follow up**
- Safety findings related to drug (selumetinib, RAI)
- Follow-up at 3 years post-RAI for
  - Remission (Y/N)
  - Re-treatment (Y/N)
  - Recurrence (Y/N)
  - Alive (Y/N)

DTC, differentiated thyroid cancer; RAI, radioactive iodine; SoC, standard of care.
Questions

1. For which of the following kinase inhibitors currently have Phase III evidence of activity in DTC?
   a) Cabozantinib
   b) Pazopanib
   c) Solumetanib
   d) Sorafenib
   e) Sunitinib
   f) All of the above
Questions

2. Which of the following agents are actively under evaluation in Phase III studies for DTC?
   a) Lenvatinib
   b) Solumetanib
   c) Sorafenib
   d) Vandetanib
   e) All of the above
University of Pennsylvania
Thyroid Cancer Therapeutics Program

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  – Raya Terry MD
  – Tatyana Kuznetsova, PhD
  – Waixing Tang MD
  – Stephen Stopenski

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  – Carolyn Grande RN, CRNP
  – Thelma McCloskey
  – Parna Prajapati
  – Ramkrishna Makani
  – Jillian Stanley

• Pathology/Imaging/Stats
  – Michael Feldman MD PhD
  – Laurie Loevner MD
  – Andrea Troxel PhD

• Thyroid Cancer Interest Group
  – Susan Mandel MD
  – Ara Chalian MD
  – Douglas Fraker MD
  – Robert Lustig MD
  – Virginia LiVolsi MD
  – Zubair Baloch MD

• MSB is a Damon Runyon-Siemens Clinical Investigator

• We gratefully extend our thanks to the many community endocrinologists that have referred their patients, and the patients that have agreed to participate in our trials.