Biological and Clinical Insights into Thyroid Cancer

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Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center
Thyroid follicular cell

Parafollicular C cell
A. Thyroid carcinomas

B. Papillary thyroid carcinomas

C. NIFTP – an indolent neoplasm

Overdiagnosis accounts for 70-80% of thyroid cancer diagnosed in US women and 45% in US men.
Papillary Microcarcinoma
Clinical Outcomes

**Active Surveillance**

1,413 patients in 2 independent, prospective Japanese studies

In all cases, deferred therapy was very effective

<table>
<thead>
<tr>
<th></th>
<th>Surgical resection (10-20 yrs)</th>
<th>Active Surveillance (5 yrs)</th>
<th>Active Surveillance (10 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Specific Mortality</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Loco-Regional Recurrence</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>&gt; 3 mm increase in size</td>
<td>-</td>
<td>7%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Mazzaferri. Endocrine Practice. 2007;13(5):498-512
Ito et al. Thyroid. 2013.
Patient Age Is Significantly Related to the Progression of Papillary Microcarcinoma of the Thyroid Under Observation

Yasuhiro Ito, Akira Miyauchi, Minoru Kihara, Takuya Higashiyama, Kaoru Kobayashi, and Akihiro Miya

Genomic Predictors of Disease Progression?

Ito et al. Thyroid 2014
Risk of Persistent/Recurrent Disease

Risk Estimates Using AJCC
Total Thyroidectomy and RRA (n=588)

Death
Persistent/recurrent

<table>
<thead>
<tr>
<th>AJCC I</th>
<th>AJCC II</th>
<th>AJCC III</th>
<th>AJCC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=281)</td>
<td>(n=71)</td>
<td>(n=89)</td>
<td>(n=147)</td>
</tr>
<tr>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Median follow up 7 yrs (1-15yrs)

Tuttle, Shaha, Thyroid 2010
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

Modified 2009 Risks

**High Risk**
Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm

**Intermediate Risk**
Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

**Low Risk**
Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)

- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, >3 LN involved (≈ 40%)
- PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
- pN1, any LN > 3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)
- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈20%)
- pN1, > 5 LN involved (≈20%)
- Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN < 0.2 cm (≈5%)
- pN1, ≤ 5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PMC (≈ 4-6%)
- pN1 with extranodal extension, ≤ 3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)
- Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
- Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
- Unifocal PMC (≈ 1-2%)

*While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available.
What explains the relative indolence of most papillary thyroid cancers?
TERT promoter mutations in thyroid cancers

**Papillary thyroid tumors (TCGA)**

- TERT: 9%
- BRAF: 40%
- NRAS: 73%
- HRAS: 73%
- KRAS: 8%

**Poorly-differentiated thyroid tumors**

- TERT: 40%
- BRAF: 33%
- NRAS: 21%
- HRAS: 5%
- KRAS: 2%

**Anaplastic thyroid tumors**

- TERT: 73%
- BRAF: 45%
- NRAS: 16%
- HRAS: 6%
- KRAS: 0%

**TERT-BRAF/RAS association**

- OR PTC: 3.3
- PDTC+ATC: 3.4
- p-value PTC: 0.03
- PDTC+ATC: 0.004
**TERT** promoter mutations in thyroid cancers

TERT promoter mutations are subclonal events in PTCs, but clonal in PDTCs and ATCs → key transitional event in tumor microevolution

Kaplan-Meier analyses of the impacts of BRAF V600E and TERT C228T mutations on disease-free survival of patients with papillary thyroid cancer (PTC).

Xing M et al. JCO 2014;32:2718-2726
**131I-Therapy**

- Based on selective ability of thyroid cells to concentrate iodine (1% of administered activity/g thyroid tissue; long residence time)

- Maintained to a variable extent by DTC cells (0.5 – 0.001%; shorter residence time)

- First-line treatment after surgery for DTC:
  - Ablation of residual remnant thyroid tissue.
  - Diagnosis of metastases.
  - Treatment of local and metastatic disease.
Side effects

- Nausea, gastric pain
- Sialadenitis
- Loss or change of taste
- Xerostomia, dental decay, gingivitis
- Nasolacrimal duct obstruction
- Infertility (transient)
- Lung fibrosis (patients with pulmonary mets)
- Bone marrow injury (especially elderly)
- Secondary malignancy
Empiric approach – fixed $^{131}$I doses

Non-inferiority of 30 mCi as compared to 100 mCi for ablation after preparation with rhTSH or under hypothyroid conditions.

Study performed in patients with low-risk thyroid cancer: T1 (29%), T2 (47%), T3 (23%); N0 (60%), Nx (25%), N1 (15%).

Disadvantages

- Often insufficient dose for adequate treatment
- Often unnecessary exposure for refractory cases
- Often exceed the maximum tolerated dose

<table>
<thead>
<tr>
<th>Age Group</th>
<th>200mCi</th>
<th>250mCi</th>
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<tbody>
<tr>
<td>&lt;70 y</td>
<td>8-15%</td>
<td>22%</td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>22-38%</td>
<td>50%</td>
</tr>
</tbody>
</table>

2. Lesion dose per administered activity (LDpA):
   - Concentration of radioiodine in the lesion (activity/mass).
   - Integrated over time (cumulative activity).
   - Traditionally done with $^{131}$I, using planar imaging.
   - Dosimetry based on planar scintigraphy or SPECT may result in relatively imprecise absorbed dose estimates.
Minimum absorbed dose to kill a DTC metastases:

\(^{131}\text{I} \) lesional dosimetry in 26 patients:

- 85 Gy “almost always successful” (46/47 lesions)
- 35 Gy “almost always unsuccessful”


Probability curve for cure:

- 60 Gy: 50%
- 110 Gy: 90%

# Decision Making for RAI Therapy

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<td>NO</td>
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<td>NO</td>
</tr>
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<td>NO</td>
<td>Conflicting</td>
<td>Selective</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2-4cm, intrathyroidal</td>
<td>NO</td>
<td>Conflicting</td>
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<tr>
<td>T3</td>
<td>&gt;4cm</td>
<td></td>
<td></td>
<td></td>
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<td>YES</td>
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<td>YES</td>
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<tr>
<td></td>
<td>Any age: minimal extrathyroidal</td>
<td>NO</td>
<td>Insufficient data</td>
<td>Selective</td>
</tr>
<tr>
<td></td>
<td>extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Any size: gross extension</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>N0, Nx</td>
<td>No metastatic LNIs</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
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<td>N1</td>
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*Cooper DS* Thyroid 2009;19:1167
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Cooper DS *Thyroid* 2009;19:1167
No effect of radioiodine therapy on overall survival or disease-free survival in patients with low risk thyroid cancer

Retrospective study of 1298 DTC patients at low risk treated between 1975 and 2005 in France.

Logistic regressions were used to identify variables associated to RAI and to calculate the propensity score to receive RAI after surgery.

Overall survival (OS) and disease-free survival (DFS) according to RAI calculated with log-rank tests and univariate and multivariate Cox analyses.

Median follow up of 10.3 years.

Analyses stratified on propensity score were also performed.

Schvartz C et al. JCEM 2012;97:1526-1535
Patients with low risk differentiated thyroid cancer treated with or without radioiodine

<table>
<thead>
<tr>
<th></th>
<th>No RAI (n = 387) n (%)</th>
<th>RAI (n = 911) n (%)</th>
<th>P value</th>
<th>Total (n = 1298) n (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>270 (69.8)</td>
<td>324 (35.6)</td>
<td>&lt;0.0001</td>
<td>594 (45.8)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>117 (30.2)</td>
<td>587 (64.4)</td>
<td></td>
<td>704 (54.2)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (14.0)</td>
<td>161 (17.7)</td>
<td>0.099</td>
<td>215 (16.6)</td>
</tr>
<tr>
<td>Female</td>
<td>333 (86.1)</td>
<td>750 (82.3)</td>
<td></td>
<td>1083 (83.4)</td>
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<tr>
<td><strong>Period of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1998</td>
<td>224 (57.9)</td>
<td>452 (49.6)</td>
<td>0.006</td>
<td>676 (52.1)</td>
</tr>
<tr>
<td>&gt;1998</td>
<td>163 (42.1)</td>
<td>459 (50.4)</td>
<td></td>
<td>622 (47.9)</td>
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<tr>
<td><strong>Thyroid surgery</strong></td>
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<tr>
<td>Lobectomy</td>
<td>237 (61.2)</td>
<td>8 (0.9)</td>
<td>&lt;0.0001</td>
<td>245 (18.9)</td>
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<tr>
<td>Thyroidectomy</td>
<td>147 (38.0)</td>
<td>903 (99.1)</td>
<td></td>
<td>1050 (81.1)</td>
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<tr>
<td>Missing</td>
<td>3 (0.8)</td>
<td>0</td>
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<td>3</td>
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<tr>
<td><strong>pN</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pN0</td>
<td>282 (72.9)</td>
<td>429 (47.1)</td>
<td>&lt;0.0001</td>
<td>711 (54.8)</td>
</tr>
<tr>
<td>Nx</td>
<td>105 (27.1)</td>
<td>482 (52.9)</td>
<td></td>
<td>587 (45.2)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>240 (62.0)</td>
<td>700 (76.8)</td>
<td>&lt;0.0001</td>
<td>940 (72.4)</td>
</tr>
<tr>
<td>Follicular</td>
<td>147 (38.0)</td>
<td>211 (23.2)</td>
<td></td>
<td>358 (27.6)</td>
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<tr>
<td><strong>pT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1 ≤2 cm</td>
<td>262 (67.7)</td>
<td>539 (59.2)</td>
<td>0.004</td>
<td>801 (61.7)</td>
</tr>
<tr>
<td>pT2 (2–4 cm)</td>
<td>125 (32.3)</td>
<td>372 (40.8)</td>
<td></td>
<td>497 (38.3)</td>
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</tbody>
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Schwartz et al. JCEM 2012
A

Disease Free Survival

Survival (%)

Logrank p-value = 0.0013

Years

N at risk

No RAI

RAI

387 382 380 376 354 318 208 274 248 231 215 201 165 167 148 128

911 902 892 879 830 785 794 623 533 476 421 382 322 271 241 208

B

Overall Survival

Survival (%)

Logrank p-value = 0.0059

Years

N at risk

No RAI

RAI

387 382 380 376 354 318 208 274 248 231 215 201 165 167 148 128

911 902 892 879 830 785 794 623 533 476 421 382 322 271 241 208

Schwartz C et al. JCEM 20
97:1526-1535
No Effect of RAI Rx on Overall and Disease-Free Survival in Low Risk Thyroid Cancer Patients After Adjustment for Propensity Score.
Many very low risk patients are receiving RAI ablation

Iyer et al, Cancer 2011
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Cooper DS *Thyroid* 2009;19:1167
Clinical Outcomes Following Empiric Radioiodine Therapy in Patients with Structurally Identifiable Metastatic DTC with Negative Diagnostic but Positive Post-Therapy Whole Body Scans.

Negative diagnostic but positive post-therapy $^{131}$I scan

Diagnostic WBS (1.5 mCi I-131)

Negative

Positive

Iodine avidity

Negative

Positive

Post therapeutic WBS (30-300 mCi)

Sabra MM et al. Thyroid 2012
27 patients, retrospective assessment of response to RAI therapy

- Complete Response 0%; Partial Response 0%; Stable Disease 12/27 (44%); Progressive Disease 15 (56%).

- Additional RAI therapies in patients with PD and 5 patients with SD failed to change the course of the disease.
Clinical Outcomes Following Empiric Radioiodine Therapy in Patients with Structurally Identifiable Metastatic DTC with Negative Diagnostic but Positive Post-Therapy Whole Body Scans.

Negative diagnostic but positive post-therapy $^{131}$I scan

Diagnostic WBS (1.5 mCi I-131)

Negative

Positive

Iodine avidity

RAI Rx ineffective

Negative

Post therapeutic WBS (30-300 mCi)

Positive

Sabra MM et al. Thyroid 2012
Papillary thyroid cancer: A genetically simple disease

Thyroid = 0.41 non-silent mutations per Mb

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs.

Lawrence et al. Nature 2013:499;214-218
Thyroid Analysis Working Group

**Broad Institute**
- Gad Getz (co-chair)
- Chip Stewart
- Juok Cho
- Jaegil Kim
- Mike Lawrence
- Mike Noble
- Carrie Sougnez
- Kristian Cibulskis

**MDACC**
- Samir Amin
- Sahil Seth
- Da Yang
- Jianhua Zhang

**JHU**
- Leslie Cope
- Luda Danilova
- Justin Bishop

**UCSD**
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- Trey Ideker

**BSGSC**
- Andy Chu
- Elizabeth Chun
- Steve Jones
- Katayoon Kasaian
- Andy Mungall
- Gordon Robertson
- Payal Sipahimalani
- Dominik Stoll

**ISB**
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- Sheila Reynolds
- Ilya Shmulevich
- Wei Zhang

**USC**
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- Dan Weisenberger

**Disease experts**
- Tom Giordano (co-chair)
- Sylvia Asa
- Jim Fagin
- Ian Ganly
- Rony Ghossein
- David McFadden
- Yuri Nikiforov
- Matt Ringel
- Bob Smallridge
- Chris Umbricht
- Martha Zieger

**MSKCC**
- Giovanni Ciriello

**Brown**
- Ben Raphael
- Fabio Vandin
- Jonathon Eldridge

**Harvard**
- Raju Kucherlapati
- Angela Hadjipanayis
- Semin Lee

**MD Anderson**
- Rehan Akbani
- Gordon Mills
- Wenbin Liu

**TCGA and BCRs**
- Kenna Shaw
- Brad Ozenberger
- Entire TCGA Network
Putting it all together

Chip Stewart, Broad

Genomic landscape of papillary thyroid cancer

- **BRAF**
- **RAS (N>H>K)**

RTK fusions:
- RET, NTRK
- ALK, others.
Plasma membrane

RTK

RAS

RAF

MEK

ERK

Signaling output

RTK

RAS

RAF

MEK

ERK

Signaling output

RTK

RAS

RAF

MEK

ERK

BRAF^V600E

Signaling output
Thyroid hormone biosynthesis

From Nancy Carrasco
Association of Genotype and Differentiated Gene Expression

Iodine metabolism

BRAF

RAS RTK fusions
Iodine metabolism

BRAF tumor cluster retaining differentiation properties
Pharmacologic inhibition of oncogenic BRAF signaling increases RAI incorporation in mice with thyroid-specific inducible expression of $BRAF^{V600E}$.  


Uninduced 1 wk ON 1 wk OFF

1 wk ON +1 wk vehicle

1 wk ON  +6d PD901

1 wk ON +1 wk PLX4720

Pax8, Nkx2.1  
↓ Tg, TPO, TSHR, NIS  
↓ Iodine incorporation  
↓ Response to RAI therapy

Knauf J Oncogene 2003,  
Mitsutake N Cancer Res 2005

Survival after the discovery of metastases according to the presence or absence of $^{131}$I uptake

*Durante C et al. J Clin Endocrinol Metab 2006*
Alan L. Ho MD, PhD

Ravi Grewal MD
Keith Pentlow
Desiree D’Andreis MD
Steve Larson MD

Rebecca Leboeuf MD
R. Mike Tuttle MD
Primary Objective

To determine whether RAI incorporation increases in RAI-refractory thyroid cancer metastases after 4 weeks of treatment with selumetinib.

Selumetinib (AZD6244, ARRY-142886)
- Highly selective, allosteric inhibitor of MEK 1/2
- Inhibits MEK1 \textit{in vitro} with an IC$_{50}$ of 14 nM

124I –Positron Emission Tomography

Advantages of 124I –PET
Quantitative, allows lesional dosimetry
Structural correlates for iodine incorporation

Normal Biodistribution of 124I

Thyrogen

124I PET

Weeks 2-4

Week 5

Response on 124I PET

(+) Response on 124I PET

Inadequate Response on 124I PET

Discontinue selumetinib

Continue selumetinib and receive RAI

Serial radiologic scans/serum thyroglobulin


selumetinib 75 mg po bid x 4 weeks

Week 1
Lesions with $^{124}\text{I}$ incorporation at baseline

Lesions without $^{124}\text{I}$ incorporation at baseline

A

Before selumetinib

After selumetinib

B

$\text{SUV}_{\text{max}}$

Individual Tumors

$\text{SUV}_{\text{max}}$

Pre-selumetinib $\text{SUV}_{\text{max}}$

Post-selumetinib $\text{SUV}_{\text{max}}$

(100 %)

(+50%)

(+25%)

(+0%)

(-25%)

(-50%)

(-75%)
### Serum Thyroglobulin Values (ng/ml)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Preselumetinib (Week 1)</th>
<th>Postselumetinib (Week 5)</th>
<th>1 month Post-RAI</th>
<th>2 months Post-RAI</th>
<th>6 months Post-RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>650</td>
<td>780</td>
<td>240</td>
<td>200</td>
<td>740</td>
</tr>
<tr>
<td>2</td>
<td>360</td>
<td>880</td>
<td>270</td>
<td>210</td>
<td>194</td>
</tr>
<tr>
<td>3</td>
<td>2700</td>
<td>3200</td>
<td>3700</td>
<td>740</td>
<td>480</td>
</tr>
<tr>
<td>4</td>
<td>510</td>
<td>1300</td>
<td>N/A</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>220</td>
<td>530</td>
<td>11.3</td>
<td>0.4</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>6</td>
<td>840</td>
<td>570</td>
<td>46</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>6500</td>
<td>1070</td>
<td>170</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>650</td>
<td>N/A</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Tumor Genotype</td>
<td>Patients with increased lesional iodine incorporation after selumetinib (fraction of total)</td>
<td>Patients who received RAI (fraction of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>BRAF</em> (9 patients)</td>
<td>4 (4/9)</td>
<td>1 (1/9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>NRAS</em> (5 patients)</td>
<td>5 (5/5)</td>
<td>5 (5/5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>RET/PTC</em> (3 patients)</td>
<td>2 (2/3)</td>
<td>1 (1/3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type (3 patients)</td>
<td>1 (1/3)</td>
<td>1 (1/3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (20 patients)</strong></td>
<td><strong>12 (12/20)</strong></td>
<td><strong>8 (8/20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Role for RAI in Different Clinical States of Thyroid Cancer

<table>
<thead>
<tr>
<th>PRIMARY TUMOR</th>
<th>RECURRENT/METASTATIC DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>POST-THYROIDECTOMY</td>
<td>RAIA</td>
</tr>
<tr>
<td></td>
<td>(Curative or Palliative Intent)</td>
</tr>
<tr>
<td>RAI remnant ablation/adjuvant therapy</td>
<td>RAI</td>
</tr>
<tr>
<td>(Curative Intent)</td>
<td>No role for RAI</td>
</tr>
</tbody>
</table>

![Image](MSKCC)
ASTRA

Adjuvant Selumetinib for differentiated Thyroid cancer, Remission After radioiodine

An International Randomised, Double Blind Study to Compare the Complete Remission Rate Following Selumetinib or Placebo and Adjuvant Radioactive Iodine Therapy in Patients with High Risk Differentiated Thyroid Cancer

Primary endpoint: Comparison of post-RAI rate of complete remission at 18 months

High-risk thyroid cancer patients s/p thyroidectomy N=228

Selumetinib x 5 weeks + 100 mCi RAI

Placebo x 5 weeks + 100 mCi RAI

2:1 Randomize
Are BRAF-mutant thyroid cancers refractory to MAP kinase pathway inhibitors?
Lineage-dependent responses in clinical trials with vemurafenib.

1) Vemurafenib induces dramatic responses in patients with metastatic \(BRAF\)-mutant melanoma (ORR \(\sim\) 60\%) and increases overall survival.

2) Only 1/20 (5\%) patients with \(BRAF\)-mutant metastatic colorectal cancer responded to vemurafenib.

3) Results from a phase 2 trial in metastatic thyroid cancer showed ORR of 38\%.

Lito P et al. Cancer Cell 2012
MEK and RAF inhibitory activities of CH5126766.

A

B

RAF family

IC$_{50}$(CRAF): 0.056 ± 0.016 μmol/L
IC$_{50}$(BRAF): 0.019 ± 0.0030 μmol/L
IC$_{50}$(BRAF V600E): 0.0082 ± 0.0015 μmol/L

Papillary thyroid cancer in *TPO-Cre/LSL-Braf\textsuperscript{V600E}* mice

Aime Franco. PNAS 2011.

Normal Papillary Thyroid Cancer

Aime Franco. PNAS 2011.
Uptake of 18F-tetrafluoroborate peaks 14 days after daily administration of CKI in LSL-Braf^{V600E} mice

CONCLUSIONS

The expression of genes required for iodide incorporation is downregulated by oncoproteins that activate MAPK signaling.

Short term treatment of patients with RAI-refractory metastatic thyroid cancer with selumetinib restored iodide incorporation and prompted responses to RAI therapy, particularly in RAS-mutant disease, whereas tumors harboring BRAF mutations had an attenuated response.

BRAF-mutant thyroid cancer cells adapt to MAPK inhibitors by derepressing a NRG1-HER3/HER2 signaling program. Relief of other feedback pathways that suppress inputs upstream of oncogenic BRAF also contribute to primary resistance.

More robust responses to radioiodine will likely ensue with strategies to block MAPK signaling in a more profound and sustained manner. Short term treatments may allow this to be done while minimizing toxicity.
RAI-MAPK Continuum: Potency of MAPK Inhibition

RAI Avidity

MAPK Activity

Minimum Lesional Dose Threshold
RAI-MAPK Continuum: Tumor Factors

- RAI Avidity
- MAPK Activity

Minimum Lesional Dose Threshold

Tumor RAI-MAPK Continuum
Nanostring RAI response predictor: Thyroid Differentiation Classifier (TDC)

Nanostring work flow.

Enhancing the thyroid differentiation score

16 genes used by TCGA for TDS score

TDS correlated genes (29 pos + 20 Neg + 15 mIRs)

Enhanced TDS

Pathway/Cell Purity Gene Sets | Source
--- | ---
BRAF/RAS classifier | TCGA, Cell 2014
ERK output | Pratilas et al, PNAS 2009
Tumor purity score | TCGA, Cell 2014
Housekeeping controls | Nanostring + TCGA

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