Developing Therapeutics for Thyroid Cancer

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Head and Neck Medical Oncology Service
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Disclosures

AstraZeneca (Consultant, Research Funding)
Novartis (Advisory Board)
Pfizer (Research Funding)
Bayer (Research Funding)
Genentech/Roche (Consultant, Research Funding)
Lily (Research Funding)
Eisai (Research Funding, Advisory Board)
Koltan (Research Funding)
Kura (Research Funding)
Merck (Advisory Board)
BMS (Advisory Board)
Sun Pharmaceuticals (Advisory Board)

Off-label use of drugs will be discussed.
Thyroid cancer incidence and mortality is rising (SEER-9 cancer registry)

Avg increase in incidence per year (1974-2013): **3.6%**

Avg increase in incidence-based mortality per year (1994-2013): **1.1%**

Lim, H. *JAMA*, 2017
### Clinical States of Thyroid Cancer: Radioiodine (RAI)

<table>
<thead>
<tr>
<th>PRIMARY TUMOR</th>
<th>RECURRENT/METASTATIC DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroidectomy</td>
<td>RAI-AVID (RAIA)</td>
</tr>
<tr>
<td>Adjuvant RAI ((^{131}\text{I}))</td>
<td>Surgery</td>
</tr>
<tr>
<td>TSH suppression</td>
<td>EBRT</td>
</tr>
<tr>
<td></td>
<td>TSH suppression</td>
</tr>
</tbody>
</table>

#### RAI-AVID (RAIA)
- RAI
- Surgery
- EBRT
- TSH suppression

#### RAI-REFRACTORY (RAIR)
- Chemotherapy
- Surgery
- EBRT
- TSH suppression
RAI-Refractory (RAIR) Thyroid Cancer

• Lack of RAI avidity predicts little to no benefit with RAI and a poor prognosis.

• The subset with indolent/slow-growing disease can be closely followed without therapy.

• Drug therapies for RAIR disease are administered continuously with palliative intent.

Durante, C. J Clin Endocrinol Metab, 91:2892-9, 2006
### RAI-Refractory Differentiated Thyroid Cancers

#### Multi-targeted VEGFR TKIs Phase II Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>#</th>
<th>PR/CR</th>
<th>SD</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>56</td>
<td>11%</td>
<td>63%</td>
<td>Ohio State</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25</td>
<td>23%</td>
<td>53%</td>
<td>Univ. of Pennsylvania</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>29</td>
<td>28%</td>
<td>48%</td>
<td>Univ. of Washington</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>35</td>
<td>17%</td>
<td>74%</td>
<td>Univ. of Chicago</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>37</td>
<td>49%</td>
<td>43%</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Axitinib</td>
<td>45</td>
<td>31%</td>
<td>42%</td>
<td>Multi-Site</td>
</tr>
<tr>
<td>Motesanib</td>
<td>93</td>
<td>14%</td>
<td>67%</td>
<td>Amgen</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>58</td>
<td>59%</td>
<td>36%</td>
<td>Multi-Site</td>
</tr>
<tr>
<td>VEGFtrap</td>
<td>40</td>
<td>0%</td>
<td>83%</td>
<td>MSKCC</td>
</tr>
<tr>
<td>Sorafenib/Everolimus</td>
<td>28</td>
<td>50%</td>
<td>46%</td>
<td>MSKCC</td>
</tr>
</tbody>
</table>
DECISION: Phase III Sorafenib vs. Placebo in RAIR, R/M Differentiated Thyroid Cancer

1:1 randomized, double blind Phase III trial in RAIR, progressive LA/metastatic thyroid cancer

**Median Progression-Free Survival (PFS)**

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Evaluable Patients</strong></td>
<td>196</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>24 (12.2)</td>
<td>1 (0.05)</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 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Stable Disease ≥ 6 months</td>
<td>82 (41.8)</td>
<td>67 (33.2)</td>
<td></td>
</tr>
<tr>
<td><strong>DCR (CR+PR+SD)</strong></td>
<td>106 (54.1)</td>
<td>68 (33.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dose interruption due to AEs, %</td>
<td>66.2</td>
<td>25.8</td>
<td></td>
</tr>
<tr>
<td>Dose reduction due to AEs, %</td>
<td>64.3</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Permanent discontinuation due to AEs, %</td>
<td>18.8</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

### SELECT: Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid

Targets VEGFR 1-3, RET, PDGFR, KIT, FGFR1-4

2:1 randomized, double blind Phase III trial in RAIR thyroid cancer

**Median Progression-Free Survival (PFS)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo: 3.6 months</th>
<th>Lenvatinib: 18.3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Disease ≥ 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DCR (CR+PR+SD)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo: 3.6 months  
Lenvatinib: 18.3 months  

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Evaluable Patients</td>
<td>261</td>
<td>131</td>
</tr>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>4 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>165 (63.2)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Stable Disease ≥ 6 months</td>
<td>60 (23.0)</td>
<td>71 (54.2)</td>
</tr>
<tr>
<td><strong>DCR (CR+PR+SD)</strong></td>
<td>229 (87.7)</td>
<td>73 (55.7)</td>
</tr>
<tr>
<td>Dose interruption, %</td>
<td>82.4</td>
<td>18.3</td>
</tr>
<tr>
<td>Dose reduction, %</td>
<td>67.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Permanent discontinuation, %</td>
<td>14.2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

TKI-Refractory DTC: Cabozantinib Phase II (ITOG)

Targets RET, c-MET, VEGFR (cabozantinib dose: 60 mg daily)
RAIR thyroid cancer (papillary, follicular, Hurthle, poorly differentiated) with RECIST progression on prior VEGFR-targeted therapy (up to two previous lines)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Evaluable Patients</td>
<td>25</td>
</tr>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10 (40%)*</td>
</tr>
<tr>
<td>Stable Disease &gt; 6 months</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Inevaluable</td>
<td>2 (8%)</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>12.7 mos (95% CI 10.9 to 34.7 mos)</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>34.7 mos (95% CI 18.3 to NR)</td>
</tr>
<tr>
<td>Dose escalation to 80 mg/day, %</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Dose reduction to 40 mg/day, %</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Dose reduction to 20 mg/day, %</td>
<td>8 (32%)</td>
</tr>
</tbody>
</table>

Cabanillas ME, et. al., JCO, 2017
TKIs in RAIR Thyroid: When to Treat?

- Systemic therapy is palliative not curative.
- Spectrum of clinical aggressiveness exists for RAIR thyroid cancers (indolent → aggressive).
- TKI impact upon overall survival has not been demonstrated.
- Therapy requires continuous management of drug toxicities.
- Common AEs: Hand-foot syndrome, hypertension, fatigue, diarrhea, asthenia, anorexia, proteinuria, alopecia.
- Mortality: (lenvatinib) 6 drug-related deaths; (sorafenib) 1 drug-related death

**BASIC PARADIGM**

Treat when risk of *progressive disease* and/or *tumor-related symptoms* outweigh risks of systemic therapy.

“Tumor Volume Doubling Time of Pulmonary Metastases Predicts Overall Survival and Can Guide the Initiation of Multikinase Inhibitor Therapy in Patients with Metastatic Follicular Cell-Derived Thyroid Carcinoma”  
(Sabra MM et. al., Cancer, 123:2955-2964, 2017)
TKI plus mTORC1 Inhibitor: Sorafenib plus Everolimus

**Study rationale:**
- PI3K/Akt/mTOR pathway alterations in thyroid cancer
- PI3K/Akt/mTOR pathway mediates resistance to TKIs?

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>PR</th>
<th>*PR</th>
<th>SD</th>
<th>POD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>5 (56%)</td>
<td>0</td>
<td>3 (33%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Follicular</td>
<td>1 (50%)</td>
<td>0</td>
<td>1 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>Hurthle Cell</td>
<td>6 (67%)</td>
<td>1 (11%)</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>4 (50%)</td>
<td>0</td>
<td>4 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>Medullary¹</td>
<td>4 (40%)</td>
<td>0</td>
<td>4 (40%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20 (52%)</td>
<td>1 (3%)</td>
<td>14 (37%)</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

¹ Six of 10 patients with medullary thyroid cancer had been on ≥ 1 prior regimens

Eric Sherman
Hurthle Cell Carcinoma: Alliance Cooperative Group Trial

Hurthle Cell
1:1 Randomization
No Prior Sorafenib or mTOR inhibitor

Sorafenib

Cross over to Everolimus at POD (exploratory)

Primary Endpoint: PFS

Secondary Endpoints: Response Rate, Overall Survival, Adverse Events

Eric Sherman
MAPK Pathway Alterations in Differentiated Thyroid Cancers

Papillary Carcinoma

5-15% RET

10-15% RAS

45% BRAF

Follicular Carcinoma

5-15% TRK

10-15% 40-50% RAS

45% BRAF

1/2 MEK

1/2 Erk

PAX8/PPARgamma
## BRAF Inhibitor Combinations

<table>
<thead>
<tr>
<th>RAIR-DTC</th>
<th>Vemurafenib No Prior RXN</th>
<th>Vemurafenib Prior RXN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PR + CR</strong></td>
<td>10/26 (38%)</td>
<td>6/22 (27%)</td>
</tr>
</tbody>
</table>

Shah, MH 2017 ASCO Annual Meeting
Sherman, ES 2017 ASCO Annual Meeting
# BRAF Targeting in ATC

<table>
<thead>
<tr>
<th>RAIR-DTC</th>
<th>Dabrafenib</th>
<th>Dabrafenib + Trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PR + CR</strong></td>
<td>10/26 (38%)**</td>
<td>9/27 (33%)**</td>
</tr>
</tbody>
</table>

*Hyman, DM, NEJM, 2015  
**Shah, MH, 2017 ASCO Annual Meeting  
***Subbiah, V., 2017 ASCO Annual Meeting  
Sherman, ES, 2017 ASCO Annual Meeting
Model of HER3 Mediated Intrinsic, Adaptive Resistance to BRAF Inhibition

Phase I of Dabrafenib plus Lapatinib in $BRAF^{V600E}$ Thyroid Cancer

**BRAF MUT**
RAIR thyroid cancer

**Biopsy #1**

Dabrafenib 150 mg bid
x 1 week

**Biopsy #2**

Lapatinib added as per dose level

**Biopsy #3**

Treat until POD

**Lapatinib Dose Levels**
- Level 1 (L 750 mg) – 1/6 DLTs (3 serial bxs)
- Level 2 (L 1250 mg) – 0/3 DLTs (1 serial bx)
- Level 3 (L 1500 mg) – 0/6 DLTS (3 serial bxs)

Eric Sherman, MSKCC and NCI/CTEP
# Dabrafenib/Lapatinib: Efficacy Outcomes

<table>
<thead>
<tr>
<th>Cohort</th>
<th>#</th>
<th>All Patients</th>
<th>#</th>
<th>DTC only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Response Rate</td>
<td>Median PFS</td>
<td>Response Rate</td>
</tr>
<tr>
<td>1 – Lapatinib 750mg</td>
<td>6*</td>
<td>50% (3)</td>
<td>10.1m</td>
<td>5</td>
</tr>
<tr>
<td>2 – Lapatinib 1250mg</td>
<td>3*</td>
<td>33% (1)</td>
<td>15.1m</td>
<td>2</td>
</tr>
<tr>
<td>3 – Lapatinib 1500mg</td>
<td>6</td>
<td>83% (5)</td>
<td>Undefined</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>60%</td>
<td>15.1m</td>
<td>13</td>
</tr>
</tbody>
</table>

* 2 ATC patients treated
MAPK Pathway Alterations in Differentiated Thyroid Cancers

**Papillary Carcinoma**
- RET: 5-15%
- TRK
- RAS: 10-15%
- BRAF: 45%
- MEK 1/2
- Erk 1/2

**Follicular Carcinoma**
- RET
- TRK
- RAS: 40-50%
- BRAF
- MEK 1/2
- Erk 1/2
- PAX8/PPARgamma
Targeting RAS with Farnesyltransferase Inhibitors (FTIs)

FTase + FPP → FTI

H-Ras

K-, N-

Ras

CAAX

GGTase-I

RAF, RaLGD, PI3K....
Tipifarnib (R11577; Zarnestra) for HRAS Mutant Solid Tumors

- Imidazole-containing heterocyclic nonpeptidomimetic
- *In vitro* FTase IC50s:
  - 0.86 nM (lamin B)
  - 7.9 nM (K-rasB)

**Tumors with mutant HRAS**

**COHORT 1**
Thyroid Ca

**COHORT 2**
Solid Tumors

**Primary Objective**
Objective Response Rate

**Secondary Objectives:**
PFS and DOR
Safety/tolerability
Thyroid Cancer Clinical Trial Portfolio (2017)

**DTC**
- pII Lenvatinib plus Pembrolizumab (ITOG)
- Pilot of Durvalumab plus RAI

**BRAF MUT**
- pI Dabrafenib/Lapatanib (CTEP)
- Next generation BRAFi (Plexxicon)

**Anaplastic**
- pII Pazopanib/Taxol plus RT (NRG)
  - Trametinib plus taxol
  - SBRT + anti-CTLA4/PD-L1 inh

**Hurthle Cell**
- pII Sorafenib vs Sorafenib/Everolimus (Alliance)

**Medullary**
- Next Generation RET inhibitors (LOXO, Blueprint)

**R/M Thyroid Cancer**

**HRAS MUT**
- Tipifarnib (Kura)

Eric Sherman
Alan Ho
Thyroid Hormone Biosynthesis

Follicular Cell

Basolateral surface

Apical surface

NIS

2 Na⁺

I⁻

2 Na⁺

TSH

TSHR

T4

T3

TPO

H₂O₂

I

TG

Lysosomal compartment

Follicular Cell

Thyroid Follciles

Colloid

Thyroid Follicles

Follicular Cell

Colloid
Basic Principles of RAI Therapy

• Tumor RAI avidity is heterogeneous:
  – Clinicopathologic features: age, histology, tumor size, site of metastasis, FDG avidity
  – Genetic and biologic features: tumor genotype, expression of thyroid-specific gene

• RAI efficacy ~ Lesional $^{131}$I activity delivered

• RAI is dosed to toxicity, not lesionsal activity

• 1st line $^{131}$I therapy for RAI-avid disease: 19% RR

Mitogen-Activated Protein Kinase (MAPK) pathway activation suppresses expression of NIS in thyroid cancer

Expression of Thyroid Specific Genes

NIS: Na/I⁻ Symporter

Pharmacologic inhibition of oncogenic BRAF signaling increases RAI incorporation in an inducible *BRAF*<sup>V600E</sup> mouse model.

Hypothesis

Inhibiting MAPK pathway activity in RAIR thyroid cancers will enhance RAI incorporation and efficacy.
Clinical Research Toolbox circa 2009 to Address RAI Resistance

selumetinib (AZD6244 Hyd-Sulfate, ARRY-142886)
- Highly selective, allosteric inhibitor of MEK 1/2
- Inhibits MEK1 \textit{in vitro} with an IC$_{50}$ of 14.1 +/- 0.79 nM

\textbf{124}I –\textbf{Positron Emission Tomography (PET)/CT}

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

Primary Objective: To determine whether RAI incorporation increases in RAI-refractory thyroid cancer metastases after 4 weeks of treatment with a MAPK pathway inhibitor.

\textit{Ho, A.L. et. al., NEJM, 368:623-632, 2013}
Protocol Schema

Definitions of RAIR Disease

1. Index lesion that did not take up RAI on a diagnostic RAI scan (up to 2 years prior to enrolment)

2. RAI-avid index lesion that did not respond to therapeutic RAI treatment 6 months or more prior to entry in the study.

3. $^{18}$F-fluoro-deoxy glucose (FDG) avid PET lesions

Ho, A.L. et. al., NEJM, 368:623-632, 2013
¹²⁴I PET: Selumetinib induces iodine incorporation in a BRAF MUT patient

Baseline

Post-selumetinib

Selumetinib increases iodine incorporation in an NRAS MUT patient with $^{124}$I negative and positive tumors at baseline.

Ho, A.L. et. al., NEJM, 368:623-632, 2013
$^{124}$I PET: Selumetinib increases iodine incorporation in bone metastases (NRAS MUT patient)

Ho, A.L. et. al., NEJM, 368:623-632, 2013
Impact of selumetinib upon $^{124}$I incorporation

Patients with new/increased $^{124}$I incorporation after selumetinib: 12/20

Patients who went on to receive therapeutic RAI: 8/12

Ho, A.L. et. al., NEJM, 368:623-632, 2013
Responses for RAI-Treated Patients

Ho, A.L. et. al., NEJM, 368:623-632, 2013
Pilot Study Summary

• The MEK inhibitor selumetinib can significantly enhance RAI incorporation/efficacy in a subset of RAIR thyroid tumors.
• RAS mutant patients may be particularly susceptible to this strategy.
• The impact of MEK inhibition upon RAI avidity in the BRAF MUT and BRAF/RAS WT cohorts was heterogeneous.
## 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>RAI remnant ablation/adjuvant therapy</td>
<td>RAI (Curative or Palliative Intent)</td>
</tr>
</tbody>
</table>
Risk Stratification for Advanced Thyroid Cancers

- Primary tumor > 4 cm
- Primary tumor with gross extrathyroidal extension (T4 disease)
- Metastatic disease in central neck, lateral neck or mediastinal lymph nodes that:
  1) Measure ≥ 1 cm
  2) Involve ≥ 5 lymph nodes

70% of patients with any of these tumor characteristics will fail to achieve complete remission with initial therapy

R.M Tuttle
Selumetinib Registration Study: Impact upon Complete Remission When Administered with Post-Operative RAI

**Primary Objectives:** To compare the complete remission rate at 18 month between patients treated with selumetinib versus placebo in combination with RAI.

**Secondary Objectives:** 1) Complete remission in *BRAF* or *NRAS* mutant subgroup, 2) Clinical remission rate, 3) Clinical remission rate in *BRAF* and *NRAS* mutant subgroup, 4) Safety/Tolerability, 5) PKs

ASTRA
Adjuvant
Selumetinib
For differentiated Thyroid cancer,
Remission
After radioiodine

Higher risk thyroid cancer patients s/p thyroidectomy N=228

2:1

Selumetinib x 5 weeks + 100 mCi RAI

Placebo x 5 weeks + 100 mCi RAI

AstraZeneca
International Thyroid Oncology Group (ITOG): Randomized Phase II RAI plus Selumetinib vs. Placebo in RAIA Patients

Patients with r/m thyroid cancer:
- Avid lesion on RAI scan (dx, post-therapy, post-ablation) ≤ 24 mos prior to registration.
- Radiographically evident disease
- No therapeutic RAI ≤ 6 mos prior to registration.
- Cumulative therapeutic 131-I received ≤ 600 mCi.
- No previous exposure to MEK/RAS/RAF inhibitors (previous sorafenib is allowed).
- Systemic therapy completed ≤ 28 days prior to registration.

Primary endpoint: Response rate at 6 months

Secondary endpoints: Best overall response, progression-free survival, thyroglobulin response, safety/tolerability.

Exploratory endpoint: Correlate genomic/transcriptomic analysis of RAI-avid tumors to clinical outcomes.

ITOG/ACCRU/AstraZeneca
MEK Inhibition in RAIR Thyroid Cancer: *RAS MUT*

<table>
<thead>
<tr>
<th>Tumor Genotype</th>
<th>Patients with increased lesional iodine incorporation after selumetinib (fraction of total)</th>
<th>Patients who received RAI (fraction of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF (9 patients)</td>
<td>4 (4/9)</td>
<td>1 (1/9)</td>
</tr>
<tr>
<td>NRAS (5 patients)</td>
<td>5 (5/5)</td>
<td>5 (5/5)</td>
</tr>
<tr>
<td>RET/PTC (3 patients)</td>
<td>2 (2/3)</td>
<td>1 (1/3)</td>
</tr>
<tr>
<td>Wild-type (3 patients)</td>
<td>1 (1/3)</td>
<td>1 (1/3)</td>
</tr>
<tr>
<td>Total (20 patients)</td>
<td>12 (12/20)</td>
<td>8 (8/20)</td>
</tr>
</tbody>
</table>

- Promising activity with selumetinib was observed in the *RAS MUT* group.
- Approaches for directly targeting RAS activity are lacking (e.g. farnesyl-transferase inhibitors).
- True efficacy/applicability of this approach (ORR, PFS) was not addressed by the pilot study (n=5 patients).
Not All MEK Inhibitors Are Created Equal

Phase II of MEK Inhibition (Trametinib) plus RAI in RAIR, Thyroid Cancers (RAS Mutant)

Cohort A (25 pts)

N, K, H-RAS MUT RAIR, progressive thyroid cancer

Serial $^{124}$I PET/CT lesional dosimetry to evaluate trametinib impact upon RAI incorporation

Insufficient $^{124}$I PET/CT response
Continue trametinib on Cohort C

Sufficient $^{124}$I PET/CT response
Continue trametinib and treat with RAI

Cohort C

Patients with insufficient $^{124}$I PET responses (from Cohort A or Cohort B)

Continue trametinib single agent therapy and tumor assessments

Discontinue until POD or toxicity

Primary Objectives (Cohort A): Evaluate PFS at 6 months and overall response at 6 months

Exploratory Objective (Cohort C): BOR, 6-month PFS

NCI/CTEP; GlaxoSmith Kline; NIH R01
<table>
<thead>
<tr>
<th>Tumor Genotype</th>
<th>Patients with increased lesional iodine incorporation after selumetinib (fraction of total)</th>
<th>Patients who received RAI (fraction of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF (9 patients)</td>
<td>4 (4/9)</td>
<td>1 (1/9)</td>
</tr>
<tr>
<td>NRAS (5 patients)</td>
<td>5 (5/5)</td>
<td>5 (5/5)</td>
</tr>
<tr>
<td>RET/PTC (3 patients)</td>
<td>2 (2/3)</td>
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<tr>
<td>Wild-type (3 patients)</td>
<td>1 (1/3)</td>
<td>1 (1/3)</td>
</tr>
<tr>
<td>Total (20 patients)</td>
<td>12 (12/20)</td>
<td>8 (8/20)</td>
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</table>

Can more potent MEK inhibition with trametinib enhance impact on RAI avidity for \textit{BRAF/RAS WT} tumors?
### BRAF MUT Tumors: Beyond MEK Inhibition

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**Vemurafenib (Zelboraf; Genentech/Daiichi Sankyo)**

Potent, selective ATP-competitive inhibitor of BRAF (V600E)

FDA approved for unresectable/metastatic, **BRAF**\(^{V600E}\) mutant melanoma

<table>
<thead>
<tr>
<th>IC50 in vitro (nM) (purified kinases)</th>
<th></th>
</tr>
</thead>
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<tr>
<td><strong>BRAF</strong>(^{V600E})</td>
<td>35</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>110</td>
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<tr>
<td><strong>CRAF</strong></td>
<td>48</td>
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<tr>
<td><strong>Brk</strong></td>
<td>240</td>
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<tr>
<td><strong>Kit</strong></td>
<td>610</td>
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<tr>
<td><strong>KDR</strong></td>
<td>5300</td>
</tr>
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</table>
BRAF MUT Tumors: Alternatives to MEK Inhibition

**BRAF Mutant Cell (Tumor)**
- MUT BRAF
- Inhibitor
- MEK 1/2

**BRAF WT Cells (Normal Tissues)**
- RAS
- RAF
- RAF
- Inhibitor
- MEK 1/2

**Graph:***
- **Drug Exposure**
- **MTD**
- Therapeutic Window
- Effective Tumoral Target Inhibition

**References:**
- Poulikakos, Cancer Cell, 19: 11-15, 2011
Model of HER3 Mediated Intrinsic, Adaptive Resistance to BRAF Inhibition

Montero-Conde C. et al., Cancer Discover, 3: 520-533, 2013
Future Program Goals

• Continue to develop and optimize this therapeutic strategy
  – Optimizing pathway inhibition
  – Clinically validating the biologic hypothesis
  – Minimizing toxicities.

• Define the appropriate clinical settings in which this approach may be incorporated into standard therapy.

• Explore predictive markers of thyroid “differentiation status” beyond tumor genotype that may predict for susceptibility.
Conclusions

• Sorafenib and Lenvatinib are both FDA-approved for treatment of RAIR thyroid cancers.

• When to initiate therapy needs to balance risks/benefits of drug therapy with the risk posed by the disease.

• New therapeutic approaches being tested involve matching individual molecular profiling with selective molecular inhibitors.

• Several different approaches utilizing selective MAPK pathway inhibitors to enhance RAI avidity/efficacy in a variety of clinical studies are under investigation.
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