NEW TREATMENTS FOR Advanced Thyroid Cancer

SATURDAY, SEPTEMBER 12, 2015
11:15 AM – 12:15 PM
Intercontinental Miami Hotel, Grand Ballroom

FACULTY
Lori J. Wirth, MD
Massachusetts General Hospital

LEARNING OBJECTIVES:
• Summarize the mechanism of action of recent MKIs in the treatment of RAI-refractory DTC
• Recognize MKI indications and contra-indications in the application of therapy
• Identify patients with thyroid cancer most likely to benefit from MKI therapy
• Discuss recent updates in clinical data on efficacy of recently approved MKIs

AGENDA TOPICS
• Multi-targeted Kinase Inhibition
• Update on Clinical Trials
• Identifying Patients that are Most Likely to Benefit
• Optimizing Patient Outcomes

This activity is supported by an educational grant from Bayer Healthcare Pharmaceuticals Inc. and Eisai Inc.

Sponsored by ENDOCRINE SOCIETY

CME Credits: 1.0 AMA PRA Category 1 Credit™
SYMPOSIUM AGENDA

11:15 – 11:20 AM  Registration & Meal Service

11:20 – 11:25 AM  Welcome and Introduction
   Lori J. Wirth, MD

11:25 AM – 12:05 PM  Symposium
   • Multi-targeted Kinase Inhibition
   • Update on Clinical Trials
   • Identifying Patients that are Most Likely to Benefit
   • Optimizing Patient Outcomes
   Lori J. Wirth, MD

12:05 – 12:15 PM  Audience Q&A and Closing Remarks

FACULTY

Lori J. Wirth, MD
Assistant Professor of Medicine, Harvard Medical School
Medical Director, Center for Head and Neck Cancers
Massachusetts General Hospital
Boston, Massachusetts
ACCREDITATION STATEMENT

The Endocrine Society is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Endocrine Society has achieved Accreditation with Commendation.

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LEARNING OBJECTIVES

Upon completion of this educational activity, learners will be better able to:

- Summarize the mechanism of action of recent MKIs in the treatment of RAI-refractory DTC
- Recognize MKI indications and contra-indications in the application of therapy
- Identify patients with thyroid cancer most likely to benefit from MKI therapy
- Discuss recent updates in clinical data on efficacy of recently approved MKIs

TARGET AUDIENCE

This continuing medical education activity should be of substantial interest to endocrinologists, endocrine fellows, and healthcare professionals who treat patients with thyroid disorders

STATEMENT OF INDEPENDENCE

As a provider of continuing medical education (CME) accredited by the Accreditation Council for Continuing Medical Education, the Endocrine Society has a policy of ensuring that the content and quality of this educational activity are balanced, independent, objective, and scientifically rigorous. The scientific content of this activity was developed under the supervision of the Endocrine Society’s Special Programs Committee (SPC). The commercial supporter(s) of this activity have no influence over the planning of this CME activity.

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**Lori J. Wirth, MD**: Speaker, Ashion, Eisai, Loxo
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The following SPC members reported no relevant financial relationships: John Carmichael, MD; Natalie Cusano, MD; Michael S Irwig, MD; Connie B Newman, MD

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When prescribing medications, the physician is advised to check the product information sheet accompanying each drug to verify conditions of use and to identify any changes in drug dosage schedule or contraindications.

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ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

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To receive a maximum of 1.0 AMA PRA Category 1 Credits™ participants must complete the activity evaluation online at education.endocrine.org/ThyroidCEU15 by October 30, 2015. After completing the evaluation, you will be able to save or print a CME certificate.

For questions about content or obtaining CME credit, please contact the Endocrine Society at education.endocrine.org/contact.
Lori J. Wirth, MD

Lori Wirth, MD is an Assistant Professor in Medicine at Harvard Medical School, and joined Massachusetts General Hospital in 2008 to become the Medical Director of the Center for Head and Neck Cancers. Dr. Wirth attended Brown University as an undergraduate, then obtained her MD from Columbia University College of Physicians and Surgeons, where she had the distinction of being nominated to Alpha Omega Alpha Honor Medical Society. Dr. Wirth was a fellow in Hematology/Oncology at Harvard’s Dana-Farber/Partners CancerCare Fellowship Program. Dr. Wirth was on staff in Head and Neck Oncology at the Dana-Farber Cancer Institute in Boston. Dr. Wirth is a leading authority in head and neck oncology, with special expertise in combined modality therapy for cancers of the head and neck, and new treatments for advanced thyroid cancers. She sits on national and international committees that guide cancer treatment and research efforts.
Radioiodine-Refractory Differentiated Thyroid Cancer

Recent Advances and New Challenges

Lori J. Wirth, MD
Massachusetts General Hospital
My Disclosures

Have received consulting fees as speaker for:

• Eisai
• Loxo
• Ashion
Advanced Thyroid Cancer

- Patients with advanced, progressive thyroid carcinoma that is refractory to radioactive iodine (RAIR-DTC) have few treatment options, until recently
- Cytotoxic chemotherapy offers little to no benefit RAIR-DTC
- New targeted agents are now approved and more are under investigation in this patient population
RAIR-DTC

In the US in 2015 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

Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5–3.5 years

Patients often suffer multiple complications associated with disease progression

Sorafenib approved in USA in 2013 based on DECISION trial and lenvatinib in 2015 based on SELECT trial

Thyroid Cancer Incidence & Mortality 1974-2014 (USA)

Overall Incidence: 56460
Women: 43210
Men: 13250
Mortality: 1780
Thyroid Cancer Classification
Genotype-Phenotype Correlation

Follicular origin, 96%
- Well-differentiated
  - Papillary thyroid carcinoma, 82%
  - Follicular thyroid carcinoma, 13%
    - NRAS mutations common, HRAS, PAX8/PPAR rearrangements, germline PTEN
  - Hürthle cell carcinoma, 5% Lacking BRAF & RAS, PI3K-Akt pathway alterations

Poorly-differentiated, 5%
- Heterogeneity NRAS, HRAS, BRAF, PIK3CA, RET/PTC

Anaplastic, 2%
- ↑↑ Genomic instability NRAS, BRAF mutations common
  - PIK3CA, p53, β-catenin mutations

C-cell origin, 4%
- Medullary thyroid carcinoma (MTC)
  - Sporadic (75%) – 50% sporadic RET mutations, M918T most common, poor prognosis
  - Familial
    - MEN2A – codon 634
    - MEN2B - M918T
    - Familial MTC – codon 768, V804M

↑ R/O iodine-refractoriness, ETE, LN mets, LR recurrence, DM, death
- Tall cell variant (10% PTCs) – BRAF V600E mutation common
- Diffuse sclerosing variant (6% PTCs) – RET/PTC rearrangements common (radiation-induced)
- Hobnail – (<1% PTCs) BRAF V600E mutation common

More aggressive variants often harbor concomitant TERT promoter mutations
Survival in Advanced DTC

- 10-15% of patients with DTC will develop advanced disease
- 444 patients with metastatic DTC treated with $^{131}$I
  - 68% of pts $^{131}$I responsive
    - 10-yr survival 92%
  - 32% $^{131}$I refractory
    - 10-yr survival 10%
    - Variability in natural history even within this subset of advanced DTC

Durante, J Clin Endocrinol Metab, 2006
Spectrum of Oncogenic Mutations in PTC

Adapted from Giordano, Cell 2014
BRAF & RAS Mutations → Distinct Biology in PTC

Giordano, Cell 2014
Signaling Pathways in DTC
Angiogenesis
A Hallmark of Cancer

Hanahan & Weinberg, Cell, 2000
VEGF and Angiogenesis in PTC

BRAF+ tumors 2.6x more likely to have high intensity staining for VEGF than BRAF- tumors

Vieira, et al., Eur J Endocrinol, 2005
Jo, et al., J Clin Endocrinol Metab, 2006
FGFs in Resistance to Anti-VEGFR Therapy

Bergers & Hanahan, Nat Rev Cancer, 2008
Radio-iodine halts one type of cancer

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein’s tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York’s Montefiore Hospital seven years ago he appeared to be suffering from an overactive thyroid gland rather than from cancer. He had a very fast heart and quivering hands, and he was weak and emaciated. But examination revealed that he had no thyroid gland: it had been removed by surgery for cancerous. Apparently some of the cancer had spread beyond his body: eight cancerous tumors were found in his ribs, femur, spine, pelvis and sternum, and in his thyroid tissue, were secreting hormones.

Radio-iodine was given to Brunstein because like tumors would absorb the chemical. Ordinary iodine. If they did, he would die. He lived. Last May a section of Brunstein’s skull was removed for a microscopic examination of the site of one of his tumors. Only scar tissue and dead cells remained, and not a single living cancer cell was found.

iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether.

Bernard Brunstein in 1942 (left); as he looks today.

“...the first person known to be cured...of metastatic cancer: by drinking 4 doses of radioactive iodine.”

Life, Oct 31 1949
Treatment Modalities for RAIR DTC

- TSH suppression
- Active Surveillance
- Localized treatments
  - Surgery
  - External beam radiation
  - Cryoablation/RFA
  - Embolization
- Bone modulating drugs
- Multikinase inhibitor therapy

- Zoledronic acid
- RANK-ligand inhibitors

FAILURE?
DECISION Trial

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, 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 Kee Shong, Steven I Sherman, Johannes WA Smit, John Chung, Christian Kappeler, Carol Peña, István Molnár, Martin J Schlumberger, on behalf of the DECISION investigators*

417 patients randomized from Oct 2009 to July 2011

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

Randomization 1:1

Sorafenib 400 mg orally twice daily

Primary Endpoint
Progression-free survival

Placebo orally twice daily

Secondary Endpoints
Overall survival
Response rate
Safety

► Progression assessed by independent central review every 8 wks
► At progression pts on placebo allowed to cross
DECISION

Progression-Free Survival

Median PFS, n days (months)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>207</td>
<td>329 (10.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>210</td>
<td>175 (5.8)</td>
</tr>
</tbody>
</table>

HR: 0.587; 95% CI: 0.454–0.758; p<0.0001

DECISION
Overall Survival

<table>
<thead>
<tr>
<th>Days from randomization</th>
<th>Survival probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td>90</td>
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<tr>
<td>200</td>
<td>80</td>
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<td>300</td>
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<tr>
<td>900</td>
<td>10</td>
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<tr>
<td>1000</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS
- Sorafenib: Not reached
- Placebo: Not reached

HR: 0.802; 95% CI: 0.539–1.194
p=0.138, one-sided

At progression:
- 150 patients on placebo (71%) received open-label sorafenib
- 55 patients on sorafenib (27%) received open-label sorafenib

### DECISION: Other Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoints</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 (PRs) months (range)</td>
<td>10.2 (7.4–16.6)</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Lenvatinib
*Phase I Experience*

Recommended phase II dose: 24 mg daily

AEs: HTN, proteinuria, fatigue, GI symptoms

PR in 3/5 patients with thyroid cancer (both DTC & MTC)

Hong, et al., ASCO 2010
SELECT Trial

Global, randomized, double-blind, phase 3 trial

Pts w RAIR-DTC (N = 392)

- Progressive disease by RECIST 1.1 in previous 13 months (confirmed by IRR)
- $^{131}$I-refractory disease
- Measurable disease
- Up to 1 prior VEGF or VEGFR-targeted therapy

Lenvatinib (n = 261)
24 mg daily PO

Treatment until disease progression confirmed by IRR (RECIST v1.1)

Placebo (n = 131)
24 mg daily PO

Primary endpoint
PFS
2^o endpoints
ORR
OS
Safety

Lenvatinib
(Optional, open-label)

Schlumberger, NEJM, 2015
SELECT
Primary Endpoint

Median PFS, months (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib</td>
<td>18.3</td>
<td>(15.1–NR)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.6</td>
<td>(2.2–3.7)</td>
</tr>
</tbody>
</table>

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

Progression events, 41%
Progression events, 86%

Number of subjects at risk:

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>261</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>198</td>
<td>43</td>
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<td>3</td>
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</tr>
</tbody>
</table>

Cl, confidence interval; HR, hazard ratio; NR, not reached.

Schlumberger, NEJM, 2015
SELECT
PFS by Previous VEGF-Targeted Therapy

No Previous VEGF-Targeted Therapy (n = 299)

- Lenvatinib: Median 18.7 (95% CI: 16.4–NR)
- Placebo: Median 3.6 (95% CI: 2.1–5.3)

HR (95% CI): 0.20 (0.14–0.27)
Log-rank Test: \( P < 0.0001 \)

Previous VEGF-Targeted Therapy: 1 line (n = 93)

- Lenvatinib: Median 15.1 (95% CI: 8.8–NR)
- Placebo: Median 3.6 (95% CI: 1.9–3.7)

HR (95% CI): 0.22 (0.12–0.41)
Log-rank Test: \( P < 0.0001 \)
SELECT Trial: Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib (n = 261)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>169 (65%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>59.0–70.5</td>
<td>0.0–3.6</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>165 (63%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Stable disease ≥ 23 weeks</td>
<td>40 (15%)</td>
<td>39 (30%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>18 (7%)</td>
<td>52 (40%)</td>
</tr>
<tr>
<td>Median time to objective response, months (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0 (1.9–3.5)</td>
<td>–</td>
</tr>
<tr>
<td>Duration of response, months, median (95% CI)</td>
<td>NR (16.8–NR)</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Non-responders were not included in the median time to response assessment.
SELECT
Most Frequent Treatment-Related Adverse Events (> 20%)

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Lenvatinib (n = 261)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68</td>
<td>42</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue / asthenia</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>
# SELECT
## Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Lenvatinib (n = 261)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>260 (&gt;99%)</td>
<td>118 (90%)</td>
</tr>
<tr>
<td>TEAE reported as treatment-related</td>
<td>254 (97%)</td>
<td>78 (60%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>133 (51%)</td>
<td>31 (24%)</td>
</tr>
<tr>
<td>TEAE resulting in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>177 (68%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>215 (82%)</td>
<td>24 (18%)</td>
</tr>
<tr>
<td>Discontinuation of treatment</td>
<td>37 (14%)</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Fatal TEAE</td>
<td>20 (8%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Fatal TEAE reported by investigator as treatment-related</td>
<td>6 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

6/20 lenvatinib treatment-emergent deaths were considered by investigator as treatment-related:

- Pulmonary embolism (n = 1)
- Hemorrhagic stroke (n = 1)
- General health deterioration (n = 4)
SELECT

Conclusions

► In patients with RAIR-DTC, lenvatinib prolonged median PFS by 14.7 months compared with placebo:
  ● Lenvatinib median PFS: 18.3 months (95% CI 15.1–NR)
  ● Placebo median PFS: 3.6 months (95% CI 2.2–3.7)
    • HR 0.21 (99% CI, 0.14–0.31)

► Response rates for lenvatinib:
  ● ORR: 65% (with CR: 2%)
  ● The median time to objective response for lenvatinib was 2.0 months (95% CI, 1.9–3.5 months)
  ● The median duration of response for lenvatinib has not been reached
    • 75% of responders had an objective response >9.4 months

► Main toxicities: hypertension, proteinuria, diarrhea, fatigue and weight loss

► No OS benefit yet (data not mature)

► Effective new therapeutic – how do we take the best advantage of it?
Which FDA-Approved TKI for RAIR-DTC Should be Used?

Clear PFS benefit across VEGFR-MKIs investigated

**Sorafenib: DECISION**

- **Med PFS = 10.8 vs 5.8 mos**
- **ORR=12%**

**Lenvatinib: SELECT**

- **Med PFS = 18.3 vs 3.6 mos**
- **ORR=65%**

Who Should be Treated?

PFS Benefit Across Subgroups

PFS benefit across subgroups: PTC, FTC, HCC, PDTC; Genotype; Site of mets; Disease burden; 2nd line (lenvatinib)
Reasons to Treat
Does Response Matter?

Treatment Group: Lenvatinib

Median tumor shrinkage (range): -52% (-100%, -30%)

Treatment Group: Placebo

J Clin Oncol 32:5s, 2014 (suppl; abstr LBA6008)
Reasons to (or Not to) Treat OS Benefit?

Will we see an OS benefit with VEGFR-MKIs?
- Med OS not yet reached (2 ½ - 3 ½ Y)
- Cross-over design confounds potential OS benefit
Reasons to (or Not to) Treat Side Effects of VEGR MKIs

- Side effects with sorafenib may add up, may impact on QoL
  - Hand–foot skin reaction (76%)
  - Diarrhea (69%)
  - Alopecia (67%)
  - Rash/desquamation (50%)
  - Fatigue
  - Weight loss
  - Hypertension

- 64% of patients had dose reductions in DECISION
- 19% permanent discontinuation due to side effects

Similar for lenvatinib
- More HTN, less HFS
Rare Life-Threatening AEs w VEGFR-MKIs

• 6 deaths on lenvatinib considered treatment-related
  – PE, hemorrhagic stroke, general deterioration, 3 sudden death NOS

• Cardiac ischemia and/or myocardial infarction
  – Sorafenib vs. placebo-treated patients: 1.9-2.7% vs. 0-1.9%

• Bleeding
  – Sorafenib vs. placebo-treated patients: 2.4-17.4% vs. 0.2-4%
  – 1 death attributed to hemorrhagic stroke on lenvatinib

• Venous Thromboembolism

• Gastrointestinal perforation
  – Sorafenib: < 1%

• Aerodigestive fistula formation
  – Seen in patients with h/o radiation and tumor abutting trachea
Who Needs Treatment, Who Doesn’t?

Why not treat everyone with iodine-refractory DTC?
- Treatment has side effects that may impact QoL.
- CRs rarely seen.
- Treatment ≠ cure.
- Improvement in OS?
- Is earlier treatment more effective?

Watchful waiting for as long as possible
Time to Reconsider Long Watchful Wtg?
Open Label Lenvatinib PFS Shorter

Median PFS, months (95% CI)

Lenvatinib 24 mg 12.4 (8.3, NE)

Outcome

ORR 45 (55)
95% CI (44, 66)

Number of subjects at risk:
Lenvatinib 24 mg 82 67 57 48 43 27

Time (months)
16 11 11 2 1 1 1 0

Parameter
Rates, % (95% CI)
Lenvatinib 24 mg (n = 82)
6 months 71 (59, 80)
12 months 51 (38, 62)
18 months 48 (34, 60)
Factors When Considering Therapy

• Nature of the disease
  – Rate of progression
    • Progression over the prior 12-14 months now standard criterion for clinical trial eligibility
  – Burden of disease
  – Symptoms from disease
  – Comorbid conditions
  – Patient preference
Formula for Treatment

Any patient with symptoms

- 65-year-old male high school principal
  - I-131-refractory metastatic PTC
  - Tall cell variant, *BRAF V600E*-mutation
  - Chest pain, SOB
Formula for Treatment

Impending symptoms

- 64-year-old female teacher
  - Metastatic PTC, I-131-refractory, tall cell
  - Too numerous to count lung nodules, several new subcm nodules & several increased by 2-3 mm over 4 mos
Formula for Treatment

Location, location, location

- 58-year-old male lawyer with locally recurrent and metastatic FTC
  - Local recurrence unresectable without laryngectomy
  - Voice and swallowing fine now
Formula for Treatment

Rapidly progressive disease

- Fit 75-year-old male retiree

Oct, 2013: XRT

Mar, 2014: New pathologic compression fracture at T6

May, 2014: New FDG+ lytic lesion R lesser trochanter

SRS to T6 and T11, XRT to R femur now underway
Formula for Treatment

Asymptomatic progressive disease, moderate pace, moderate disease burden

- 49-year-old mom, metastatic HCC
  - Anxiety, somatization
  - Paralyzed VC, neck XRT, dyspnea

May, 2013

April, 2014
Asymptomatic slowly progressive disease

- 62 y/o woman metastatic PTC, radiation exposure in North Dakota as a child?
- TKIs may not appropriate for most patients like this
Getting the Dose Right

• Toxicity frequent, dose interruption and/or reduction not uncommon.

• Lower the dose from the beginning for better tolerability?
  – No!
  – Clinical approach to lowering dose may be easier than raising dose
  – Lenvatinib starting dose = 24 mg daily
  – Median time to first dose reduction = 3 months
  – Median time to first response = 2 months
Optimal SE Management is Key

- It’s a team sport
- 97% patients on lenvatinib had treatment-related SE
- Intensive management is needed
- Example: hypertension
  - On-target class effect VEGFR TKIs
  - 69% patients on lenvatinib experienced HTN
  - Onset of HTN early after lenvatinib initiation
    - 2.3 weeks
  - HTN correlated with PFS benefit
    - 19 months vs 13 months (p=0.0085)
    - OS: Not reached vs 22 mos (p=0.0003)
HTN Management Plan

• BP control prior to initiation, <140/90 mmHg
• BP measured at home & in clinic on days 1 and 15 of Cycles 1 and 2, and day 1 of every treatment cycle thereafter
  – Patients with confirmed BP ≥ 140/90 started antihypertensive and monitored every 2 weeks
  – If already on antiHTN med, increased; or 2nd drug added
  – Patients with persistent BP ≥ 160/100 mmHg despite optimal management held, then dose reduced
• Requires good communication with patient and amongst team
Monitoring the Patient On Treatment

• Response determination per RECIST standard
  – Imaging every 2-3 cycles (1 cycle = 28 days)
  – Follow TG in measurable patients along with restaging
  – Rx continued until disease progression per RECIST or unacceptable toxicity

• Follow-up every 2 weeks for first 2 months, including PE (√ BP), heme, renal, liver toxicity labs & urinalysis

• Special notes:
  – TSH must be followed!
  – Attention to QTc interval with EKG monitoring!
Advanced Iodine-Refractory DTC
Final Thoughts

• VEGR-MKIs have significant clinical efficacy for patient population previously without any good therapeutic options

• New generation has robust activity

• Not every patient needs treatment now
  – But pendulum may be swinging back towards earlier treatment

• When treatment is initiated, toxicity is common
  – Intensive monitoring & aggressive management helps keep patients on therapy – team approach is key!
  – Need to get the dose right to balance efficacy and tolerability

• Major unmet needs include correlation of PFS with OS benefit & QoL studies

• More to come soon on targeting RAS/RAF/MAPK pathway
  – Primary therapy
  – RAI sensitization
Cases, Consultation, and Clinical Decision-Making

Deploying Novel, MKI-Based Therapies In Practice
Case 1

- 54-year-old male with widely metastatic papillary thyroid cancer (liver and lungs). He has a performance status of 0 and takes no medications.

- He has mild shortness of breath. LFTs are normal. CT scan C/A/P performed shows mets that have increased in size and number compared to 12 months earlier.

- RAI 4 mCi scan 11 mos earlier showed no uptake.
Case 2

- 44-year-old woman from Maine
- First surgery aborted, tumor invading esophagus.
- Redo L thyroidectomy Sept 2010: PTC invasive into soft tissues, 1/5 LNs +
- 150 mCi 131-I, uptake in neck only
- April 2011: Revision neck surgery: PTC replacing LN, invasion into subQ tissues
- EBRT to neck, 6000 cGy
Case 2

- 131-I WBS Dec, 2013: Negative.
- PET/CT Dec, 2013: FDG-avid L parapharyngeal mass, several lung nodules with endobronchial involvement, R hilar mass.
- TG = N/A
- Endobronchial biopsy of level VII node Feb, 2014: PTC.
Case 2

- Occasional scant hemoptysis and back pain, impacting on comfort
- Neck & chest CT: Multiple lung nodules (largest 2.5 cm), mediastinal nodes (largest 3.5 cm), L node of Rouviere (1.7 cm), moth-eaten T11 with kyphosis, no epidural component.
  Measurable lesions ↑ by 1-3 mm each compared to Jan, 2014
- TG > 3000, TSH = 0.09
- Genotyping: BRAF V600E +