Tyrosine Kinase Inhibition and Thyroid Cancer

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Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
NY, NY
Financial Disclosure

I work with Exelexis in the development of cabozantinib for head and neck squamous cell cancer but receive no financial or other reimbursement for this work.
Outline of the Talk

Overview of Thyroid Cancer Epidemiology, Cancer Genomics, and Tumor Biology

Tyrosine Kinase Inhibitor Development in Thyroid Cancer-Key Studies, Indications, Toxicities

What the Future Holds for Tyrosine Kinase therapy in Thyroid Cancer
# Thyroid Cancer Relative Incidence Rates 2017

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td>161,360</td>
<td></td>
</tr>
<tr>
<td><strong>Lung &amp; bronchus</strong></td>
<td>116,990</td>
<td></td>
</tr>
<tr>
<td><strong>Colon &amp; rectum</strong></td>
<td>71,420</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary bladder</strong></td>
<td>60,490</td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma of the skin</strong></td>
<td>52,170</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney &amp; renal pelvis</strong></td>
<td>40,610</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>40,080</td>
<td></td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>36,290</td>
<td></td>
</tr>
<tr>
<td><strong>Oral cavity &amp; pharynx</strong></td>
<td>35,720</td>
<td></td>
</tr>
<tr>
<td><strong>Liver &amp; intrahepatic bile duct</strong></td>
<td>29,200</td>
<td></td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>836,150</td>
<td>852,630</td>
</tr>
</tbody>
</table>

| **Males**                      | 100%     | 100%      |
| **Females**                    |          |           |

| **Breast**                     | 252,710  | 30%       |
| **Lung & bronchus**            | 105,510  | 12%       |
| **Colon & rectum**             | 64,010   | 8%        |
| **Uterine corpus**             | 61,380   | 7%        |
| **Melanoma of the skin**       | 34,940   | 4%        |
| **Non-Hodgkin lymphoma**       | 32,160   | 4%        |
| **Leukemia**                   | 25,840   | 3%        |
| **Pancreas**                   | 25,700   | 3%        |
| **Kidney & renal pelvis**      | 23,380   | 3%        |

**Thyroid** highlighted with a red circle.
Thyroid Cancer Incidence/Death Rates

Estimated New Cases in 2018: 53,990
% of All New Cancer Cases: 3.1%

Estimated Deaths in 2018: 2,060
% of All Cancer Deaths: 0.3%

Percent Surviving 5 Years: 98.1%
2008-2014

Graph showing the number of new cases per 100,000 persons from 1992 to 2015, increasing over time. The graph also shows the number of deaths in the U.S. over the same period.
Thyroid Cancer

- Papillary: 80%
- Follicular/Hurthle: 13%
- Medullary: 5%
- Anaplastic: 2%
- Lymphoma
# Thyroid Cancer Relative Incidence Rates 2017

## Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>Liver &amp; intrahepatic bile duct</td>
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<td></td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>836,150</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

## Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>84,590</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,150</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>26,730</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,300</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,610</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,300</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,240</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,450</td>
<td></td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td></td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>318,420</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.**

MEMORIAL SLOAN KETTERING CANCER CENTER
Recurrence and Death After Diagnosis of Papillary/Follicular Thyroid Cancer

*N=1355

Thyroid Cancer: Deaths

- Papillary: 50%
- Follicular: 27%
- Hurthle: 12%
- Anaplastic: 11%
THYROID CANCER TREATMENT

Surgery
RAI / TSH suppression
External Beam RT
Chemotherapy/TKI
Post Endocrinologist

When does a medical oncologist get involved? Is it after the disease recurs? Is it after thyroid cancer becomes metastatic?

After radioactive iodine stops working and there no more surgical or radiation based options for local or metastatic treatment.
RAI-REFRACTORY DISEASE

• 25-50% of metastatic thyroid cancers lose iodine concentrating ability and will progress on RAI (~refractory disease)
• Correlates with FDG-PET avidity > 5 SUV
• Attributed to down-regulation of the Na+/I-symporter (NIS)
• This is where the medical oncologist steps in
Thyroid Cancer: Why are Tyrosine Kinase Inhibitors so Important?
Thyroid Cancer and Chemotherapy: A Checkered Past
Doxorubicin +/- Cisplatin

• Randomized Phase II Study thru ECOG, 1985
• 84 patients
• RAI-refractory Thyroid Cancer (no definition)
• Response included use of CXR and bone scans
• Of the patients
  – Differentiated Thyroid Cancer – 35
  – Anaplastic Thyroid Cancer – 37
  – Medullary Thyroid Cancer – 10
  – Mixed DTC and ATC - 2
## Doxorubicin +/- Cisplatin

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Response</th>
<th>Doxorubicin</th>
<th>Dox/Cisplatin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiated</td>
<td>Complete</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>5 (31%)</td>
<td>1 (5%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>11 (69%)</td>
<td>16 (84%)</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>Medullary</td>
<td>Complete</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>1 (25%)</td>
<td>2 (33%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>3 (25%)</td>
<td>4 (67%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>Complete</td>
<td>0 (0%)</td>
<td>3 (17%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>1 (5%)</td>
<td>3 (17%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>20 (95%)</td>
<td>12 (66%)</td>
<td>32 (82%)</td>
</tr>
</tbody>
</table>

Shimaoka K. Cancer **56**:2155-2160, 1985
How Do Tyrosine Kinase Inhibitors Work (or Not)?
Overview of Cancer Genomics: The Central Dogma of Biology

DNA is the instruction book for protein production.

Protein is the “stuff” of our physical body...hands, tongue, eyes. etc.

If the DNA is altered, protein production will be altered.
Overview of Cancer Genomics: The Process of Tumorigenesis

Alterations in DNA Lie at the Heart of Cancer Development

Causes of DNA Damage
- Viruses (HPV)
- Smoking
- Chemicals
- Sunlight
- Life (ageing)
- Inflammation
- Radiation
- Nutritional Deficiency

Healthy cell:
- Normal DNA-black
- Normal Proteins-purple

Cancer cell:
- Damaged DNA-black
- Abnormal Proteins-red
Overview of Cancer Genomics:
Abnormal DNA Can Result in Three Major Types of Protein Alterations

Gain-of-function mutations: Oncogene activation (Driver mutations)- B-raf is the prototype for thyroid cancer

Loss-of-function mutations: Tumor suppressor inactivation P53 is the prototype for thyroid cancer

Epigenetic Activation/Suppression: Non-mutated proteins which are either over-expressed or underexpressed

Causes of DNA Damage
Viruses (HPV)
Smoking
Chemicals
Sunlight
Life (ageing)
Inflammation
RADIATION
NUTRITIONAL DEFICIENCY

Memorial Sloan Kettering Cancer Center
Overview of Cancer Genomics: Abnormal Proteins Can Result in Unrestrained Cellular Growth Causing Tumor Formation

Gain-of-function mutations: Oncogene activation (Driver mutations)-B-raf is the prototype for thyroid cancer

Loss-of-function mutations: Tumor suppressor inactivation P53 is the prototype for thyroid cancer

Epigenetic Activation/Suppression: Non-mutated proteins which are either over-expressed or underexpressed

Causes of DNA Damage
Viruses (HPV)
Smoking
Chemicals
Sunlight
Life (ageing)
Inflammation
RADIATION
NUTRITIONAL DEFICIENCY
Overview of Cancer Genomics: 
What Types of Proteins/Functions are Altered by these Collective Changes in DNA?
Tyrosine Kinase Signaling is Immensely Complicated
Overview of Cancer Genomics: Alterations in DNA/Proteins Drive the Hallmarks of Cancer (Hanahan and Weinberg, 2011)-10 Distinct Functions Acquired by Tumor Cells

http://goo.gl/Yhbsj
Overview of Cancer Genomics: Alterations in DNA/Proteins Drive the Hallmarks of Cancer (Hanahan and Weinberg, 2011)

Epigenetic Activation/Suppression: Non-mutated proteins which are either over-expressed or underexpressed

Gain-of-function mutations: Oncogenes

Loss-of-function mutations: Tumor Suppressors

http://goo.gl/Yhbsj

Memorial Sloan Kettering Cancer Center
Overview of Cancer Genomics: Abnormal DNA and Proteins in Cancer Cells Render Tumor Cells Vulnerable to the Four Classes of Cancer Therapy

Healthy cell:
Normal DNA-black
Normal Proteins-purples

Cancer cell:
Damaged DNA-black
Abnormal Proteins-red

Radiation
Chemotherapy
Immunotherapy
Targeted Therapy (TKI)
Overview of Cancer Genomics: Why Tumor Cells are More Susceptible to Chemotherapy and Radiation Than Normal Cells

Normal Cells with Normal DNA

Normal Cells Can Repair the DNA Damage Caused by Chemotherapy and Radiation

Cancer Cells with Damaged DNA

Cancer Cells with Excessive DNA Damage Caused by Chemotherapy and Radiation Die

Chemo/XRT
Overview of Cancer Genomics: How Targeted Therapies Work to Kill Cancer Cells

Targeted therapies inhibit the abnormal cancer proteins on which the cancers cells are more reliant than normal cells.

- Normal Cell - Normal Proteins
- Cancer Cell - Abnormal Proteins
Overview of Cancer Genomics: What are Tyrosine Kinases?

- Approximately 90 in the human genome
- Can be receptor or non-receptor tyrosine kinases
- Are frequently mutated and oncogenic themselves (meaning can induce tumors in experimental models)
Overview of Cancer Genomics: What are Tyrosine Kinases?

Can potently promote signaling that will lead to activation of multiple functions characterized as a “hallmark of cancer”
Mechanism of Action of Tyrosine Kinase Inhibitors

- BCR-Abl was the first tyrosine kinase effectively targeted by a small molecule
- Causes chronic myelogenous leukemia
- Imatinib mesylate (Gleevec) was approved to treat CML in 2001
Chronic Myelogenous Leukemia Was the First Major Application of Tyrosine Kinase Inhibition

- Gleevec can cure this disease, approved in 2001
- The oncogene BCR-ABL is solely responsible for CML
- This experience resulted in the development of a term referred to as “oncogene addiction”
- 2001—this experience ushered in the era of “Precision Medicine”
Chronic Myelogenous Leukemia Was the First Major Application of Tyrosine Kinase Inhibition

Opinion

Are We Being Misled About Precision Medicine?

Doctors and hospitals love to talk about the cancer patients they’ve saved, and reporters love to write about them. But deaths still vastly outnumber the rare successes.

By Liz Szabo
Ms. Szabo is a health reporter for Kaiser Health News.

NY Times 2018
BUT:

- CML is a unigenic disease
- Thyroid cancer (like most cancers) is a polygenic disease
- Thyroid cancer is a fully transformed neoplasm whereas CML is pre-leukemic
- Exposure to tyrosine kinase inhibitors results in either new mutations or hyper-activation of bypass pathways
- Therefore tyrosine kinase inhibitors are not curative in most fully cancerous tumors
Overview of Cancer Genomics: There are Many Ways to Skin a Cat!

Gain-of-function mutations: Oncogenes

http://goo.gl/Yhbsj
Overview of Cancer Genomics: There are Many Ways to Skin a Cat!

Gain-of-function mutations: Oncogenes

Epigenetic Activation/Suppression: Non-mutated proteins which are either overexpressed or underexpressed

http://goo.gl/Yhbsj
Overview of Cancer Genomics: What are the Genes/Proteins Commonly Altered in Thyroid Cancer Targeted by Tyrosine Kinase Inhibitors

Papillary thyroid cancers:
- **B-Raf** ~55%
- N-Ras ~9%
- H-Ras ~3%
- VEGF-epigenetic activation
- FGF-epigenetic activation

Medullary thyroid cancer
- **Ret**-40-50% of sporadic cases, ~100% of familial thyroid cancer

Anaplastic thyroid cancer
- **B-Raf** ~45%
- **PI3K** ~39%
- N-Ras ~18%

P53-~73%-a tumor suppressor that hyperactivates numerous tyrosine kinases
Overview of Cancer Genomics:
Papillary Thyroid Cancer: B-Raf and Ras
Overview of Cancer Genomics:
Vascular Endothelial Growth Factor is a Major Non-Mutant Driver of Thyroid Cancer

↑ VEGF levels epigenetically
- ↑ Recurrence
- ↓ DFS
-Malignant thyroid tissue


Relative fold of VEGF-C protein expression

p<0.001
p=0.004
p=0.002

Benign
PTC LN(-)
PTC LN(+)

Memorial Sloan Kettering Cancer Center
Cancer Clinical Trial Endpoints

Phase I: toxicity measurements and dose finding

Phase II: Response rate-a surrogate for survival
   Complete response-disappearance of all lesions
   Partial response-at least a 30% decrease in the sum of target lesions
   Stable disease-neither CR, PR, or progressive disease
   Progressive disease-at least a 20% increase in lesions

Phase III: overall survival
   progression-free survival-the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse
Differentiated Thyroid Cancers
Phase II studies – Multitargeted TKIs

<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>Vandetanib</td>
<td>72</td>
<td>8%</td>
<td>57%</td>
<td>RII (5% RR in placebo)</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>
Sorafenib

- Tyrosine Kinase Inhibitor
- Target VEGF-R 1 to 3, PDGF receptor, RET
- RAF kinase inhibitor
## Response Rates – Phase II

Ohio State versus Penn

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Ohio State (56 pts)</th>
<th>University of Penn (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>6 (11%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>35 (63%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>9 (16%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Cell Types with responses</td>
<td>Papillary</td>
<td>Papillary, Follicular, Hurthle</td>
</tr>
</tbody>
</table>
DECISION Study  
Randomized Phase III, 2014

• Progression-free Survival, median
  – Sorafenib (207) 10.8 months
  – Placebo (210) 5.8 months
    • P<0.0001; HR 0.587; 95% CI 0.454-0.758

• Overall Survival not significant (median not reached and crossover made this analysis difficult)

• 150 patients (71%) on placebo crossed over to receive sorafenib
DECIISION Study
Progression-Free Survival

A

### Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median PFS, days (months)</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 0.59, 95% CI 0.45–0.76
p<0.0001

<table>
<thead>
<tr>
<th>Date</th>
<th>Number at risk</th>
<th>Days from randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td>0–30 days</td>
<td>157</td>
<td>110</td>
</tr>
<tr>
<td>31–60 days</td>
<td>81</td>
<td>49</td>
</tr>
<tr>
<td>61–90 days</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>91–120 days</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>121–150 days</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>151–180 days</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
## DECISION Study: Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib n (%)</th>
<th>Placebo n (%)</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>Response rate</strong></td>
<td>24 (12.2)</td>
<td>1 (0.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Complete Response</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>24 (12.2)</td>
<td>1 (0.05)</td>
<td></td>
</tr>
<tr>
<td><strong>Stable Disease ≥ 6 months</strong></td>
<td>82 (41.8)</td>
<td>67 (33.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Control Rate (CR+PR+SD)</strong></td>
<td>106 (54.1)</td>
<td>68 (33.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Dose modification due to AEs, %</strong></td>
<td>77.8</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td><strong>Permanent discontinuation due to AEs, %</strong></td>
<td>18.8</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>
Lenvatinib (E7080) Background

• Lenvatinib (E7080):
  – Small molecule, tyrosine kinase inhibitor administered orally by once daily continuous dosing

• Targets
  – VEGFR1-3, FGFR 1-4, RET, PDGFR and KIT
Phase III Study: Lenvatinib vs Placebo

- Phase 3 Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid
  - SELECT (2015)

- 2:1 randomization Lenvatinib vs Placebo
  - Required POD within 13 months by independent reviewer
  - RAI refractory
  - Prior VEGF-TKI allowed (up to 1)
  - Crossover at POD
  - Primary outcome: PFS
## Response Rates: SELECT Study

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib (n=261)</th>
<th>Placebo (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>169 (65%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>95%, CI</td>
<td>59.0-70.5</td>
<td>0-3.6</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Complete Response</strong></td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>165 (63%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td><strong>Stable Disease ≥23 weeks</strong></td>
<td>40 (15%)</td>
<td>39 (30%)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>18 (7%)</td>
<td>52 (40%)</td>
</tr>
<tr>
<td><strong>Median time to objective response, months (95% CI)</strong></td>
<td>2.0 (1.9-3.5)</td>
<td>-</td>
</tr>
</tbody>
</table>
## Response Rate: TKI Exposed vs. Unexposed

<table>
<thead>
<tr>
<th></th>
<th>Prior VEGFR-targeted therapy N=17 (%)</th>
<th>No prior VEGFR-targeted therapy N=41 (%)</th>
<th>Overall N=58 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>8 (47%)</td>
<td>26 (63%)</td>
<td>34 (59%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>(45-71%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>8 (47%)</td>
<td>13 (32%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Durable SD</td>
<td>4 (24%)</td>
<td>10 (24%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (6%)</td>
<td>2 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD)</td>
<td>16 (94%)</td>
<td>39 (95%)</td>
<td>55 (95%)</td>
</tr>
</tbody>
</table>

Sherman, S; ASCO 2011
Primary Endpoint:
Kaplan-Meier Estimate of PFS

Median (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (95% CI)</th>
<th>Hazard Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib</td>
<td>18.3 mo (15.1–NE)</td>
<td>0.21 (0.14–0.31)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.6 mo (2.2–3.7)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio for progression or death, P<0.001

No. at Risk

<table>
<thead>
<tr>
<th>Group</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>66</th>
<th>44</th>
<th>24</th>
<th>11</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</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>
<td>0</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NR, not reached.
PFS by Previous VEGF-Targeted Therapy

**TKI Naïve (n = 299)**

- Median (months) (95% CI)
  - Lenvatinib: 16.7 (13.4–NE)
  - Placebo: 3.6 (2.1–6.3)
- HR (95% CI): 0.20 (0.14–0.27)
- Log-rank Test: $P < 0.0001$

**One Prior TKI Treatment Regimen (n = 93)**

- Median (months) (95% CI)
  - Lenvatinib: 15.1 (8.8–NE)
  - Placebo: 3.6 (1.9–3.7)
- HR (95% CI): 0.22 (0.12–0.41)
- Log-rank Test: $P < 0.0001$
Overall Survival, ITT population

HR (95% CI): 0.73 (0.50–1.07)
Log-rank test: \( P = 0.1032 \)

No significant difference was observed in the RPSFT-adjusted OS (secondary endpoint; \( P = 0.051 \)), which was used to correct for a potential cross-over effect in the placebo arm.

ITT, intent-to-treat; RPSFT, rank-preserving structural failure time.
## Toxicity: Select Study

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Levnatinib (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>73</td>
<td>44</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Venous TEs</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Arterial TEs</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic Failure</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>PRES</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

|                        | Any Grade          | Grade ≥ 3       |
| Hypertension           | 15                 | 4               |
| Proteinuria            | 3                  | 0               |
| Venous TEs             | 5                  | 2               |
| Arterial TEs           | 2                  | 1               |
| Renal Failure          | 1                  | 1               |
| Hepatic Failure        | 0                  | 0               |
| PRES                   | 0                  | 0               |
Conclusion-Decision and Select Studies

Excellent Results both in terms of PFS, response rate, and time to response for lenvatinib
  -Sorafenib underperforms compared to lenvatinib
Definite toxicity with lenvatinib
  -No QOL measures. Unsure how this relates to other drugs in the class
  -Grade V events: 20 vs 6
Question: What line do you each drug?
  -Excellent results for lenvatinib as a second line agent
  -But efficacy is so high that lenvatinib is commonly the first-line agent
Overview of Cancer Genomics: What are the Genes/Proteins Commonly Altered in Thyroid Cancer Targeted by Tyrosine Kinase Inhibitors

Papillary thyroid cancers:
- B-Raf ~55%
- N-Ras ~9%
- H-Ras ~3%
- VEGF-epigenetic activation
- FGF-epigenetic activation

Medullary thyroid cancer
- Ret ~40-50% of sporadic cases, ~100% of familial thyroid cancer

Anaplastic thyroid cancer
- B-Raf ~45%
- PI3K ~39%
- N-Ras ~18%

P53 ~73%—a tumor suppressor that hyperactivates numerous tyrosine kinases
BRAF

- BRAF most common mutation in papillary thyroid cancer
- May portend to a worse prognosis
- Increase risk of radioactive iodine refractoriness
- Classical or tall cell variant PTC
- Presentation at more advanced stage
- More frequently invasive
- Higher risk of progression to UTC
Vemurafenib-B-Raf inhibitor

• In Phase I Study
  – 1/3 thyroid cancer with response; other 2 with stable disease

• Phase II study in thyroid cancer completed 2016

  • Recurrent, unresectable or metastatic papillary thyroid cancer
  • BRAF V600 mutation+ by cobas
  • Radioactive iodine refractory
  • Evidence of progression within 14 months

  VEGFR2i-naïve (n=26)

  VEGFR2i-pretreated (n=25)

  Vemurafenib 960 mg BID until disease progression or unacceptable toxicity
## Response Rate: Vemurafenib

<table>
<thead>
<tr>
<th></th>
<th>VEGFR2i-naïve</th>
<th>VEGFR2i-pretreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable Patients</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10 (39%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>15 (58%)</td>
<td>14 (63%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Median duration of treatment</td>
<td>63.6 weeks</td>
<td>27.6 weeks</td>
</tr>
</tbody>
</table>

The Lancet Oncology, Volume 17, Issue 9, 1272 – 1282, 2016
• BRAF mutant thyroid cancer response to vemurafenib significantly less than in melanoma
Differentiated Thyroid Cancer Treatment: Timing of Treatment

- We do not automatically treat asymptomatic RAI-refractory patients with TKIs.

- Advise to wait until patient has
  1. Rapid doubling time (less than 6 months)
  2. Potential for symptomatic disease in the case of indolent tumors
  3. When we need disease control in a dangerous area like the neck or supraclavicular region.
Patient MZ, 30 year old female with metastatic papillary thyroid cancer x 6 years

-Started on lenvatinib 2018 due to hypoxia

-Now normoxic and leading a normal life
Overview of Cancer Genomics: What are the Genes/Proteins Commonly Altered in Thyroid Cancer Targeted by Tyrosine Kinase Inhibitors

Papillary thyroid cancers:
- B-Raf - ~55%
- N-Ras - ~9%
- H-Ras - ~3%
- VEGF
- FGFR

Medullary thyroid cancer:
- Ret activating mutations - 40-50% of sporadic cases, ~100% of familial thyroid cancer
- VEGF

Anaplastic thyroid cancer
- B-Raf - ~45%
- PI3K - ~39%
- N-Ras - ~18%

P53 - ~73% - a tumor suppressor that hyperactivates numerous tyrosine kinases
Overview of Cancer Genomics: Medullary Thyroid Cancer: Ret
Vandetanib
Vandetanib (ZD6474)

- Potent inhibitor of wild-type and mutated (activated) RET
  - IC\textsubscript{50} 100 nM
- Also inhibits:
  - VEGFR – Vascular inhibitor

Carlomagno et al., Cancer Research 62:7284-7290, 2002
Randomized Phase III

Patients with unresectable locally advanced or metastatic MTC (N=331)

2:1 randomization

Vandetanib 300 mg/day
n=231
Follow for progression

Placebo
n=100
Follow for progression

Discontinue blinded treatment at progression

Optional open-label vandetanib 300 mg/day

Follow for survival

Wells, SA Journal of Clinical Oncology 2012
## Objective tumor assessments

<table>
<thead>
<tr>
<th></th>
<th>Vandetanib 300 mg (n=231)</th>
<th>Placebo (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat analysis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response rate</td>
<td>45% (104)</td>
<td>13% (13)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>5.48 (2.99–10.79), (P&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

- 12 of 13 responses on the placebo arm occurred while patients were receiving vandetanib in the open-label phase
- Objective responses were durable; median duration of response not reached at 24 months of follow-up
**PFS (primary endpoint)**

Hazard ratio = 0.46 (0.31–0.69); \( P<0.0001 \)

Median: not reached (vandetanib); 19.3 months (placebo)

<table>
<thead>
<tr>
<th>At risk (n)</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib 231</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>171</td>
</tr>
<tr>
<td></td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Placebo 100</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Hazard ratio <1 favors vandetanib
Cabozantinib

• A potent oral targeted therapy that inhibits MET, VEGFR2, and RET

• Clinical activity observed in MTC patients in Phase 1\(^2\)
  – 29% confirmed response rate per RECIST
  – 68% disease control
    • Stable disease for > 6 months or confirmed partial response

\(^1\)Yakes et al. (2011) Mol Cancer Ther, v10(12); \(^2\)Kurzrock et al. (2011) J Clin Oncol, v29(19)
Phase 3 Study Design (EXAM)

Treatment until progression or unacceptable toxicity

Locally advanced or metastatic MTC with documented RECIST progression

Cabozantinib 140 mg

Placebo

2:1 Randomization

PROGRESSION

No Cross-Over
No Unblinding

Survival follow-up

Schöffski P et al., ASCO Annual Meeting, Chicago, 04 June 2012
From: Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma
Ann Oncol | © The Author 2017. Published by Oxford University Press on behalf of the European Society for Medical Oncology. any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Conclusion

• There are 2 FDA approved drugs now for MTC
  – Primary objective met (PFS)
  – Currently there is trend to improved OS with cabozantinib
• Still unclear which is the important target
• Still unclear order to use drugs and what to do afterwards
• Still unclear when to start medications
• May not work without either a RET or RAS mutation present
  – Analysis of cabozantinib study
Anaplastic Thyroid Cancer
Anaplastic Thyroid Cancer

• 2-3% of all thyroid cancers are Anaplastic
• 19% 1-year survival
  – Rarely resectable at diagnosis. Attaches to vital structures
  – **Asphyxiation** a significant concern. Half of patients will die from asphyxiation or upper airway problems
Overview of Cancer Genomics: What are the Genes/Proteins Commonly Altered in Thyroid Cancer Targeted by Tyrosine Kinase Inhibitors

Papillary thyroid cancers:
B-Raf-~55%
N-Ras-~9%
H-Ras ~3%

Medullary thyroid cancer
Ret-40-50% of sporadic cases, ~100% of familial thyroid cancer

Anaplastic thyroid cancer
B-Raf ~45%
PI3K ~ 39%
N-Ras ~ 18%

P53-~73%-a tumor suppressor that hyperactivates numerous tyrosine kinases
Anaplastic Thyroid Cancer: ECOG Study

- Randomized study of cisplatin/doxorubicin versus doxorubicin alone
  - p=0.03
- 2 of 3 CR’s had duration of response for > 34 months

<table>
<thead>
<tr>
<th></th>
<th>Doxo.</th>
<th>CDDP/Doxo.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0 (0%)</td>
<td>3 (17%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>1 (5%)</td>
<td>3 (17%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>No Response</td>
<td>20 (95%)</td>
<td>12 (66%)</td>
<td>32 (82%)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>18</td>
<td>39</td>
</tr>
</tbody>
</table>

Shimaoka K, et al.; Cancer 1985
Anaplastic Thyroid Cancer

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAFV600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria, ...

• Dabrafenib is a B-Raf inhibitor

• Trametinib is a MEK inhibitor

• Clinical studies in melanoma have revealed that when B-Raf is inhibited MEK is upregulated as a compensatory mechanism

January 2018, Journal of Clinical Oncology
Overview of Cancer Genomics: Ras-Raf Signaling

- **RAS**
  - **RAF**
  - **MEK1**
  - **ERK1/2**
  - **CREB**
  - **ELK-1**
- **SOS**
- **GRB2**
- **SHC**
- **SHP2**
- **AKT**
- **RAC**
- **RHO**
- **Lamellipodia**
- **FAK**
- **Focal Adhesion Stress Fiber**
- **Cell Survival**
- **Cell Proliferation**

**Memorial Sloan Kettering Cancer Center**
## Table 1. Baseline Patient Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Patient Demographic and Disease Characteristic</th>
<th>Anaplastic Thyroid Cancer (n = 16)</th>
<th>All Tumor Cohorts* (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>72.0 (56-85)</td>
<td>59.5 (18-85)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (38)</td>
<td>62 (62)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American/African heritage</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Central/South Asian heritage</td>
<td>1 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>East Asian heritage</td>
<td>7 (44)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Southeast Asian heritage</td>
<td>2 (12.5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>White/European heritage</td>
<td>6 (37.5)</td>
<td>85 (85)</td>
</tr>
<tr>
<td>ECOG performance status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (12.5)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>1</td>
<td>14 (87.5)</td>
<td>59 (59)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>10 (10)</td>
</tr>
<tr>
<td>BRAF V600E central confirmation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF V600E mutation confirmed</td>
<td>15 (94)</td>
<td>90 (90)</td>
</tr>
<tr>
<td>No BRAF V600E or V600K mutation†</td>
<td>1 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Insufficient tumor quantity for testing</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Invalid</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No tumor indicated</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

NOTE: Data are given as No. (%) unless otherwise noted.
Abbreviations: BRAF, B-Raf kinase; ECOG, Eastern Cooperative Oncology Group.
*Seven of nine tumor-specific patient cohorts had enrolled patients at the time of this analysis (Data Supplement).
†BRAF V600 mutation status was determined with the THxID-BRAF kit (bioMérieux, Durham, NC) by Hematogenix Laboratory Services.
‡One patient with anaplastic thyroid cancer, two with hairy cell leukemia, and two with grade 1 or 2 glioma did not have central confirmation of BRAFV600E or V600K mutation.
Fig 1. Maximum percent change from baseline in the sum of target lesion diameters in the anaplastic thyroid cancer intent-to-treat population. (A) Change from baseline in target lesion diameter was determined according to RECIST v1.1. The gray horizontal line indicates a 30% decrease, which is the minimum change needed to qualify for partial response according to RECIST. Best confirmed response (bar color) and best unconfirmed response (bar height) are as indicated. One patient experienced progression of disease in the brain at week 1 and, thus, a percent change could not be calculated. (*) An anaplastic thyroid cancer B-Raf kinase (BRAF) V600E mutation identified locally was not centrally confirmed in this patient. (B) Computed tomography scans of a representative patient with anaplastic thyroid cancer collected at baseline and after 8 weeks of treatment with dabrafenib plus trametinib. (Top) A patient presented with anaplastic thyroid cancer and symptomatic metastasis to the lung (grade 2 cough). The patient also had grade 2 dysphagia caused by a paratracheal mass and grade 2 dyspnea secondary to pericardial effusion (arrows indicate lesion locations). Cough and dyspnea both resolved after receiving dabrafenib plus trametinib combination therapy for 2 weeks. (Bottom) The size of all lesions was visibly reduced after 8 weeks of treatment.

Published in: Vivek Subbiah; Robert J. Kreitman; Zev A. Wainberg; Jae Yong Cho; Jan H.M. Schellens; Jean Charles Soria; Patrick Y. Wen; Christoph Zielinski; Maria E. Cabanillas; Gladys Urbanowicz; Bijoyesh Mookerjee; Dazhe Wang; Fatima Rangwala; Bhumsuk Keam; JCO 2018, 36, 7-13.
DOI: 10.1200/JCO.2017.73.6785
Copyright © 2017 American Society of Clinical Oncology
Fig 2. Treatment duration and time to events in individual patients with B-Raf kinase (BRAF) V600E–mutated anaplastic thyroid cancer. Data presented are the best investigator-assessed responses in the intent-to-treat population. Each bar denotes an individual patient, with bar length representing the duration of treatment and bar color denoting the best confirmed response. The blue arrowhead is positioned at the time of first radiologic response. The dagger denotes a patient in whom an anaplastic thyroid cancer BRAF V600E mutation that was identified locally was not centrally confirmed. The gray vertical line indicates the 12-month (52-week) time point. AE, adverse event.

Published in: Vivek Subbiah; Robert J. Kreitman; Zev A. Wainberg; Jae Yong Cho; Jan H.M. Schellens; Jean Charles Soria; Patrick Y. Wen; Christoph Zielinski; Maria E. Cabanillas; Gladys Urbanowit; Bijoyesh Mookerjee; Dazhe Wang; Fatima Rangwala; Bhumsuk Keam; JCO 2018, 36, 7-13.
DOI: 10.1200/JCO.2017.73.6785
Copyright © 2017 American Society of Clinical Oncology
Anaplastic Thyroid Cancer: Dabrafenib Trametinib Study

Table 2. Best Overall Response to Therapy in Anaplastic Thyroid Cancer

<table>
<thead>
<tr>
<th>Radiology Review Type</th>
<th>Intent-to-Treat (n = 16)</th>
<th>BRAF V600E Centrally Confirmed Patient Population (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Investigator</td>
<td>Investigator</td>
</tr>
<tr>
<td></td>
<td>Independent</td>
<td>Independent</td>
</tr>
<tr>
<td>Best response*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (6)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (63)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (13)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (19)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>11 (69)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>[41.3 to 89.0]</td>
<td>[35.4 to 84.8]</td>
<td>[44.9 to 92.2]</td>
</tr>
</tbody>
</table>

NOTE. Data are given as No. (%) unless otherwise noted.

Abbreviation: BRAF, B-Raf kinase.

*Investigator and independent assessment per RECIST v1.1.

†Complete response plus partial response. CIs were estimated by using the exact Clopper-Pearson method.

- 69% is best overall response
- 12 month duration of response 90%
- 12 month progression free survival 79%
- 12 month overall survival 80%

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DOI: 10.1200/JCO.2017.73.6785
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Where is Tyrosine Kinase Inhibition Headed?

The same place the rest of cancer treatment is headed: IMMUNOTHERAPY!

New Methods for Cancer May Benefit Jimmy Carter’s Fight

By Pam Belluck

Aug. 20, 2015

President Jimmy Carter, who disclosed Thursday that he has metastatic melanoma, is in a position to benefit from promising new approaches to attacking cancer, including a drug approved less than a year ago.
Where is the Tyrosine Kinase Inhibition Headed?

How the Promise of Immunotherapy Is Transforming Oncology
Immune Evasion: A Hallmark of Cancer
Overview of Cancer Genomics:
What Types of Proteins/Functions are Altered by these Collective Changes in DNA?

-Damaged proteins are frequently immunogenic

-Immune cells can (but do not always) recognize abnormal proteins and kill the cancer cells

-Tumor cells can inhibit attack by T cells and evade immune destruction
The Immunologic Concept of Cancer is not Novel

- The concept that our immune system can fight cancer is not new

- Dr. W. Coley found that injecting bacteria into sarcoma patients could occasionally cause tumor regression as a sequela of infection

- The molecular basis of this would not be understood for another 100 years or so

- We know now that revving up the immune system can have anti-cancer effects—a principle that is not the basis for modern immunotherapy
The Immunologic Concept of Cancer is not Novel

- Paul Ehrlich proposed that the immune system can restrain neoplastic growth.

- He proposed a process referred to as “immunosurveillance” which involves active involvement of the immune system in keeping cancer growth in check.

- This theory has now been proven and is part of what is referred to now as the “Cancer Immunity Cycle.”

The Cancer-Immunity Cycle
- Immunoediting/Surveillance: 1.) Elimination -

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (DCs / APCs)
3. Priming and activation (APCs and T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs and endothelial cells)
6. Recognition of cancer cells by T cells (CTLs and cancer cells)
7. Killing of cancer cells

Chen and Mellman, Immunity, 2013, 39:1-10
The Cancer-Immunity Cycle

2.) Equilibrium
The Cancer-Immunity Cycle
3.) Escape

Phan et al., 2015

- CTL anti-CTLA-4
- anti-PD-1 / anti-PD-L1
- Treg
- TAM
- Loss of neoantigen
- Tumour escape

- PD-1
- CD28
- CD80/CD86
- CTLA4
- PD-L1
- Stimulatory cytokines
- Inhibitory cytokines
The immune system has breaks (or checkpoints) to minimize autoimmunity, and PD-1 ligation inhibits T cell killing. Tumor cells know to express the PD-1 ligand (PD-L1) and can suppress T cell killing. Antibodies to PD-1 and PD-L1 can turn off the T cell inhibitory signal and result in immune-mediated T cell killing.
The Cancer-Immunity Cycle: Overcoming Escape

- CTL
- anti-CTLA-4
- anti-PD-1 / anti-PD-L1
- Treg
- TAM
- Loss of neoantigen
- Tumour escape
- Checkpoint inhibitors
- Alternative neoantigen
- Tumour killing

PD-1, CD28, CD80, CD86, CTLA4, PD-L1, Stimulatory cytokines, Inhibitory cytokines

Memorial Sloan Kettering Cancer Center...
Multiple Mechanisms Exist to Enhance the Cancer Immunity Cycle

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonist

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Chen and Mellman Immunity, 2013, 39:1-10
How Do Tyrosine Kinase Inhibitors Fit into the Picture?

Tyrosine kinase signaling is indispensable to T cell function and activation.

Tyrosine kinase signaling can promote an “immunosuppressive environment” (meaning allowing tumor cells to evade immune detection).

ERK, AKT, and VEGF are tyrosine kinases that can contribute to immunosuppression and tumors escaping T cell attack and immunogenic death.
Overview of Cancer Genomics: How Immunotherapy Engenders Cancer Cell Death

-Immunotherapy Unleashes the Immune System to Attack Abnormal Proteins in Cancer Cells

Tyrosine kinase inhibitors may further hyperactivate T cells
Optimizing Immunotherapy is the Major Focus of Oncology Research (Basic and Clinical)

Combination Targeted Therapy with Pembrolizumab and Lenvatinib in Progressive, Radioiodine-Refractory Differentiated Thyroid Cancers: A Phase II Study

ClinicalTrials.gov Identifier: NCT02973997
Innovation in Oncology May (Hopefully) be Accelerating

Chemotherapy: ~ 1950s

Tyrosine kinase inhibition: imatinib (Gleevec)-2001

Immunotherapy: ipilimumab (Yervoy)-2011
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