BCOP Clinical Sessions
Welcome!

The BCOP Clinical Sessions are part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by the American College of Clinical Pharmacy and the American Society of Health-System Pharmacists (ASHP).
Earning BCOP Recert Credit

To earn BCOP Recertification Credit for this session you must attend the session or view the full recording of the session (available at www.accp.com) and then successfully submit and pass the post-test for the session no later than March 1, 2017.
Access to the Recertification Posttest

- Participants who pre-paid the post-test fee for the BCOP Clinical Sessions will have access to the posttest immediately following the session at www.accp.com/myaccount.

- Participants who paid the posttest fee in Las Vegas will receive access no later than December 20.
Reminders:

– Post-tests must be submitted by March 1, 2017
– Participants may only submit the posttest one time.
BCOP Clinical Sessions: Lung Cancer Therapy and Molecular Targets

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Assistant Professor
Texas Tech University Health Sciences Center School of Pharmacy
Clinical Coordinator, Hematology/Oncology
Clements University Hospital
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Personalized Medicine Specialist
DeBartolo Family Personalized Medicine Institute
Moffitt Cancer Center,
Tampa, Florida
Disclosures

• Christine M. Walko:
  • BMS- Honorarium for ICLIO Melanoma Subcommittee
  • Merck-Honorarium for ICLIO Melanoma Subcommittee
Objectives

• Review the common mutations present in Non-Small Cell Lung Cancer
• Review the history of targeted therapy in advanced Non-Small Cell Lung Cancer
• Discuss the common targeted treatment modalities in advanced Non-Small Cell Lung Cancer
• Identify the current barriers to targeted therapy in the management of advanced Non-Small Cell Lung Cancer
Objectives

- Discuss less common genetic alterations in NSCLC and their associated treatments and outcomes
- Explain the purpose and value of a molecular tumor board in terms of treatment recommendations
- Outline the support and process for obtaining off label genetic-guided therapy when clinical trials are not available
- Identify future challenges to the implementation of genetic-guided therapy into standard oncology clinical practice
Back to the Future: Advances in Lung Cancer Targeted Therapy

Gary Jean, Pharm.D., BCOP
Assistant Professor
Texas Tech University Health Sciences Center School of Pharmacy
Clinical Coordinator, Hematology/Oncology
Clements University Hospital
UT Southwestern Medical Center
Dallas, Texas
Patient Case

- JW is a 40 year old non smoking female recently diagnosed with metastatic adenocarcinoma non-small cell lung cancer.

- Her path is significant for an EGFR mutation with exon 19 deletion.
Time for a Poll
How to vote via the web or text messaging
How to vote via text message

How's my presentation so far?

- Respond at PollEv.com/ashp
- Text a **KEYWORD** to 22333

<table>
<thead>
<tr>
<th>Comment</th>
<th>Votes</th>
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</thead>
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<td>152964</td>
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<tr>
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</tr>
</tbody>
</table>
Patient Case: Question 1

What is the most appropriate treatment for JW?

A. Cisplatin + Pemetrexed
B. Carboplatin + Paclitaxel + Bevacizumab
C. Erolitnib
D. Alectinib
Patient Case: Question 1

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Non-Small Cell Lung Cancer

• New Cases: 224,390
  – 2\textsuperscript{nd} most common among men and women
• Deaths: 158,080
  – Leading cause of cancer related death among men and women
• > 50% of patients present with metastatic disease
  – Treatment is histology driven
  – Starts with testing for driver mutations
    – Especially with adenocarcinoma

Accessed [July 22, 2016].
Driver Mutations

- 2009-2012 at 14 US sites
- 1007 metastatic adenocarcinoma lung cancer patients were tested for 10 oncogenic drivers
- An oncogenic driver was identified in 64% of patients
- Results were used to select a targeted therapy or clinical trial in 28%
  - Median survival was 3.5 years in patients with a mutation directed therapy compared to 2.4 years in those who didn’t

Progression of Targeted Therapy in Lung Cancer

- **1980s**: Cytotoxic Chemotherapy
- **1990s**: 2003: Gefitinib*
- **2000s**: 2004: Erlotinib
- **2010s**: 2011: Crizotinib
- **2020s**: 2015: Gefitinib*
- **2010s**: 2014: Ceritinib
- **2010s**: Ramucirumab
- **2010s**: 2015: Gefitinib*

Key Therapies:
- 2006: Bevacizumab
- 2013: Afatinib
- 2015: Alectinib
- Nivolumab
- Pembrolizumab
- Necitumumab
- Osimertinib

*Denotes alternatives to standard chemotherapy.
But First...
Where targeted therapy started

• Late 1990’s-2000
  – Imatinib
    – Originally approved in 2001
    – Oral TKI that targets the fusion protein
    – Game Changer → Replaced transplant based approach
      – Major Cytogenetic Response: 87.1%
      – Complete Cytogenetic Response: 76.2%
  – Trastuzumab
    – Originally approved in 1998 in metastatic breast cancer

2000’s
Gefitinib

- Originally approved in 2003
  - Accelerated approval on phase II data
  - 216 patients
    - 75% Adenocarcinoma
    - 2/3 Never smokers
    - 142 Evaluable patients
      - 15 partial responses ~ RR 10.6%
  - Marginal survival
- Limited Access in 2005
  - Based lack of efficacy demonstrated in follow up trials
- Fully approved for the first line treatment 2015
  - Median overall survival was 19.2 months in the Phase IV follow up

Cohen MH et al. Oncologist 2003;8:303-6
Erlotinib

• Got lucky...
  – Approved over best supportive care in 2004
    – 2 month survival benefit → No longer recommended
  – Added a switch maintenance indication in 2010
    – 12.3 weeks vs 11.1 weeks → No longer recommended
  – Added First line treatment in EGFR mutation 2013
    (exon 19 deletions, or exon 21 substitutions)
    – PFS 13.1 vs 4.6 HR 0.16, 95% CI 0.10 – 0.26; p<0.0001

Bevacizumab

• A different target therapy
  – 2 month overall survival benefit when used as first line
  – Maintenance therapy
    – Alone vs. combo (pemetrexed)

• Work horse

Then there’s Cetuximab

- “Ground Breaking” – FLEX Trial
- Cetuximab plus Cisplatin/Vinorelbine
  - EGFR(+) – Expression... not mutation
  - Median OS: 11.3 vs. 10.1, HR 0.87 95% CI 0.762 – 0.996, p=0.044
  - PFS: 4.8 vs 4.4, HR 0.94 95% CI 0.825 – 1.077, p=0.39
- Targeting the receptor – Marginal benefit
  - Category 2B recommendation

2010’s
Crizotinib/Ceritinib/Alectinib

• The ALK inhibitor boom
• Approved based on early clinical trials
  – Crizotinib RR in first line: ~ 60%
  – Ceritinib RR in crizotinib refractory patients: 56%
    – 20x more potent than Crizotinib
  – Alectinib RR in crizotinib refractory patients: 50%
• Limitation: Prevalence and Resistance
  – 5-10% of all NSCLC diagnoses
  – Duration of response ~12 months

Crizotinib

• Phase I data

• N=143 (evaluable)
  – 60.8% Objective Response
    – 3 complete responses
    – 84 partial responses
  – Duration of Response: 49 weeks
  – PFS: 9.7 Months

Ceritinib

- Phase I data → Second line
- N=130
  - 68% had received crizotinib in the past
- Overall Response Rate: 58%
  - 56% in crizotinib refractory
  - 62% in crizotinib naïve
- PFS: 7 months
  - 6.9 months in crizotinib refractory
  - 10.4 months in crizotinib naïve

Afatinib

- Another EGFR
- Afatinib vs. Cisplatin/Pemetrexed in EGFR Mut
  - 49.1% Exon 19 deletion; 39.6% Exon 21 substitution
  - PFS 11.9 vs 6.9 HR, 0.58; 95% CI, 0.43 to 0.78; p=.001

Where do we go now?
- Afatinib + Cetuximab?

Ramucirumab

- **REVEL**
  - N=1253
  - Ramucirumab 10mg/kg and docetaxel 75 mg/m2 Q 21 days vs. placebo and docetaxel
  - Median OS: 10.5 vs 9.1 months (HR 0.86, 95% CI 0.75-0.98; p=0.023)
  - Median PFS: 4.5 months compared with 3.0 months for the control group (0.76, 0.68-0.86; p<0.0001).

- *Included patients with squamous cell histology*

Patient Case

• JW presents to clinic for his 9 month follow
  – Staging scans reveal disease progression with new liver lesion and increased size in lung mass
  – Biopsy of new liver lesion reveals:
    – EGFR – T790M Mutation

• What is the next step in his treatment
Patient Case: Question 2

• What is the next step in JW treatment
  A. Cisplatin/Vinorelbine + Cetuximab
  B. Osimertinib
  C. Ceritinib
  D. Pembrolizumab
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T790M

• Only present in 5% of all EGFR mutations
  – Increases the affinity of the kinase to ATP → Decreasing affinity to erlotinib/gefitinib
  – Most common resistance mechanism (50-60%)
    ─ Can be present on diagnosis
    ─ Or develop during treatment

• Was dreaded EGFR mutation until...

Osimertinib

• Rapid approval
• Potent irreversible inhibitor of EGFR TKI – T790M
  – N=253 patients → 138 confirmed T790M mutations
  – PFS 9.6months vs 2.8months

Osimertinib

• Disease Control Rate: 84%

• 6 month response rate – 85%
  – Not fully mature at publication

• Lack of efficacy in non-T790M mutants

Patient Case

• JW presents to clinic for his 6 month follow up and staging scans reveal disease progression and new lesions on his liver.
• Path is sent of for further mutational analysis
• In the mean time JW want to pursue further treatment
Patient Case: Question 3

- Which of the following is the most appropriate treatment for JW
  A. Carboplatin+Paclitaxel
  B. Carboplatin+Pemetrexed+Bevacizumab
  C. Cisplatin+Vinorelbine+Cetuximab
  D. Nivolumab
Patient Case: Question 3

Your poll will show here

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Nivolumab

• Rocky Start
  – Approved in March 2015 in squamous – only
  – Approved in October 2015 in non-squamous as well

• ~3 month *overall survival* benefit
  – No difference in PFS 2-4 months vs docetaxel
    – 1 year PFS rate was higher: 19% vs 8%

• ~20% response rate

Nivolumab

- Only approved in as 2nd line
- Delayed response
- Toxicity management

Pembrolizumab

- Approved off of phase I data – KEYNOTE – 001
  - Must PD-L1 expression
  - Response Rate 19%
  - Overall Survival: 12 months
  - Progression Free: ~3.7 months

Pembrolizumab

Response Rate

Pembrolizumab

• PD-L1 Status
  – > 1%
  – Catch 22?

• Dose?
  – 2mg vs 10mg
  – Q2week vs Q3Week

• Delayed Response

• Data Immature

Patient Case

• Pathology Results
  – New C797S mutation

• What is the best course of treatment now?
What has the past shown us

• Strengths
  – Driver mutations provide a target for therapy
  – Profound Responses
  – Multiple new agents

• Weakness
  – Specific mutations not very prevalent
  – Responses are not very durable
  – Limited use
  – Re-biopsy
  – Duration of response
  – Onset of response (PD-1)
“Typical Patient”*

EGFR • Erlotinib

T790M • Osimertinib

Disease Progression • Traditional Chemotherapy + VEGF

Disease Progression • PD-1 based therapy

Disease Progression • ?
Patient Summary

- EGFR – Exon 19 Del
- T790M
- C797S Mutation
Back to the Future
Beyond the Standard of Care in Lung Cancer: Focus on Translation of Molecular Targets

Christine M. Walko, Pharm.D., BCOP, FCCP
Personalized Medicine Specialist
DeBartolo Family Personalized Medicine Institute
Moffitt Cancer Center
Tampa, Florida
Guidelines are backward looking.

With cancer, things change too rapidly for doctors to be able to rely on yesterday’s guidelines for long.

Vincent T. DeVita, Jr, MD
The Death of Cancer
Goal of Precision Medicine

• Determine the optimal treatment or *sequence* of treatments for a patient
  – Which therapy will yield the best response?
  – How do we optimize the response?
  – How do we minimize toxicity?
Mutation Landscape Changes over Time

- 40 yo non-smoking female diagnosed with Stage IV NSCLC, adenocarcinoma
EGFR C797S and Resistance

- We are familiar with resistance mutations:
  - Erlotinib $\rightarrow$ T790M
  - Osimertinib $\rightarrow$ C797S

- EGFR C797S – acquired resistance mutation
  - Covalent binding site for 2\textsuperscript{nd} and 3\textsuperscript{rd} generation EGFR-inhibitors like afatinib and osimertinib

\[ \text{C797S mutation in CIS with T790M} \]

\[ \text{C797S mutation in TRANS with T790M} \]

\begin{itemize}
  \item Resistant to EGFR-inhibitors, use alternate therapy
  \item Combination of first- and third-line EGFR inhibitors
\end{itemize}

Clin Cancer Res. 2015;21:3924-33
Evolution of NSCLC Treatment

Non-small cell lung cancer

Adenocarcinoma

Squamous Cell Carcinoma

Large Cell Carcinoma

- BRAF
- PIK3CA
- EML4-ALK
- KRAS
- EGFR
- HER2
- BRAF
- MET
- DDR2
- PIK3CA

The Reality of Rare Mutations

224,390 new cases of lung cancer are expected in 2016

Number of Patients Per Mutation

![Pie chart showing the distribution of patients with different mutations.]

- KRAS: 72,250
- EGFR: 25,400
- None: 22,700
- MET ex14: 6,700
- MET amp RIT1: 7,800
- ERBB2 amp MAP2K1: 7,900
- RET fusion: 7,200
- NRAS: 1,570
- HRAS: 1,790
- ALK fusion: 670
- ROS1 fusion: 1,370

There will be an estimated **19,950** cases of AML diagnosed this year.

NSCLC Somatic Mutations

- KRAS
- EGFR
- BRAF
- MET ex14
- MET amp RIT1
- ERBB2
- ROS1 fusion
- ALK fusion
- NRAS
- HRAS
- None

- Erlotinib, gefitinib, afatinib, osimertinib
- Dabrafenib, trametinib, vemurafenib
- Crizotinib or second generation ALK inhibitors

For KRAS mutations:
- Numerous clinical trials using inhibitors of MEK and other pathways in combination

For EGFR mutations:
- Chemotherapy or immunotherapy

Targeting Therapy in Lung Cancer

**BRAF**
- Mutations seen in up to 7% of NSCLC with more than half being the V600E mutation which is associated with more aggressive disease
- **Dabrafenib** and **trametinib**, or **vemurafenib**

**MET**
- Exon 14 skipping seen in 3-4% of NSCLC
- Amplification in 2-4% untreated patients and 5-20% in EGFR-mutated tumors as acquired resistance
- **Crizotinib** or **Cabozantinib**

**RET**
- RET fusions seen in about 1% of NSCLC, but may be closer to 6-19% in select never-smokers
- **Cabozantinib**, **vandetinib**, **lenvatinib** or **ponatinib**

**ERBB2**
- Mutations seen in 2-4% of NSCLC with the majority being exon 20 insertion mutations
- **Trastuzumab**, **afatinib**, or investigational **neratinib**

Patient Case #1

- CH is a 48 yo male, never smoker developed a chronic cough and shortness of breath, right pleural effusion found.
  - PET showed multiple avid areas in the lung
  - Thoracentesis was performed and cytology showed adenocarcinoma
  - An in house next generation sequencing (NGS) test was ordered on the subsequent lung biopsy

<table>
<thead>
<tr>
<th>TEST PERFORMED</th>
<th>TruSight Tumor Gene Set</th>
<th>Targeted next-generation sequencing was performed on this sample of adenocarcinoma, poorly differentiated. See under Test Details for more information.</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>RESULT SUMMARY</th>
<th>FDA Approved Therapies, Prognostic Indication, or Other Course of Action (in patient’s tumor type)</th>
<th>FDA Approved Therapies, Prognostic Indication, or Other Course of Action (in another tumor type)</th>
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</thead>
<tbody>
<tr>
<td>Variants Detected</td>
<td>BRAF p.V600E</td>
<td>✅</td>
</tr>
</tbody>
</table>
BRAF Mutations

- **Activating** BRAF mutations in NSCLC
  - V600E (50%)  
  - G469A (39%)  
  - D594G (11%)
- **Inactivating** mutations
  - G466V (7.5%)
- **Patient characteristics**
  - Current or former smokers  
  - Female  
  - No significant differences in overall survival compared with other mutations

BRAF V600E in Lung Cancer

Vemurafenib

- Histology independent, Phase 2 basket trial of BRAF V600E-mutation positive, non-melanoma cancers
  - 7 cohorts
- 20 patients with BRAF V600E positive NSCLC received vemurafenib 960 mg PO daily
  - Response rate = 42%
  - mPFS = 7.3 months

mPFS = median progression free survival

N Eng J Med. 2015;373;8:726-36

Dabrafenib + Trametinib

- Phase 2, non-randomized, open-label trial of BRAF V600E-mutation positive NSCLC patients
- 59 patients received dabrafenib 150 mg PO BID and trametinib 2 mg PO daily
  - Objective response = 63.2%
  - 2 patients had a complete response
  - 34 patients had a partial response
  - Median duration of response = 9.0 months
  - Survival data not yet mature

Lancet Oncol. 2016;17:984-93
**Patient Case #1**

- CH is a 48 yo male, never smoker developed a chronic cough and shortness of breath, right pleural effusion found.
  - PET showed multiple avid areas in the lung
  - Thoracentesis was performed and cytology showed adenocarcinoma
  - An in house next generation sequencing (NGS) test was ordered on the subsequent lung biopsy
  - She received first line therapy with carboplatin and pemetrexed and now has recurrent disease

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</table>
Question 4: Which of the following therapies would you recommend for this patient?

A. Docetaxel and ramucirumab
B. Vemurafenib and cobimetinib
C. Dabrafenib and trametinib
D. Nivolumab
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Off Label Drug Acquisition

• Let us all pause for a moment of thanks....

• The success of getting off label drug therapy depends heavily on the patient’s insurance

• Appeal letters:
  – Explanation of the genetic mutation
  – Explanation of any human data with citations
  – Personalized Medicine Consult Notes or Genetic testing reports can be helpful
Patient Case #2

- PM is a 78 yo female, former smoker who was diagnosed with NSCLC on work up for pneumonia.
  - Biopsy showed pulmonary sarcomatoid carcinoma histology
  - Further scans showed involvement of the liver
  - A commercial next generation sequencing (NGS) test was ordered on the lung biopsy

### TUMOR TYPE: LUNG SARCOMATOID CARCINOMA

**Genomic Alterations Identified**

- **MET** exon 14 splice site (2888-30_2888-5del26)
- **IDH2** R140Q
- **KRAS** A146P - subclonal
- **JAK2** V617F
- **TET2** F1854*
- **TP53** H193L, L252fs*93, splice site 993+1G>A

**CHIP: Clonal Hematopoiesis of Indeterminate Potential?**
MET Exon 14 Mutations

- Seen in 3-4% adenocarcinoma NSCLC
  - Enriched in pulmonary sarcomatoid carcinoma
  - Older patients (median about 72 years old)
  - Females
  - Former or current
- Most commonly result in skipping of MET exon 14 during pre-mRNA splicing
  - 47 amino acid deletion of the juxtamembrane domain
  - Loss of Y1003 CBL binding site

Ex 14 = Exon 14, TKD = Tyrosine Kinase Domain

MET inhibitors in NSCLC

• Phase I trial with Crizotinib 250 mg PO BID
  – 13 patients with MET amplification (not exon 14 skipping)
  – Partial response: 4 patients
  – Median duration of response: 35 weeks

• Case report series (MET exon 14 skipping)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>MET Therapy</th>
<th>Response</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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</thead>
<tbody>
<tr>
<td>80</td>
<td>Female</td>
<td>Cabozantinib (3rd line)</td>
<td>Stable disease</td>
<td>5.1 +</td>
<td>55.1 +</td>
</tr>
<tr>
<td>80</td>
<td>Female</td>
<td>Crizotinib (3rd line)</td>
<td>Partial response</td>
<td>3.6</td>
<td>22.2</td>
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<tr>
<td>80</td>
<td>Male</td>
<td>Crizotinib (3rd line)</td>
<td>Progressive disease</td>
<td>0</td>
<td>22.2</td>
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<tr>
<td>65</td>
<td>Male</td>
<td>Crizotinib (3rd line)</td>
<td>Partial response</td>
<td>4.6 +</td>
<td>17.9 +</td>
</tr>
<tr>
<td>90</td>
<td>Female</td>
<td>Crizotinib (3rd line)</td>
<td>Partial response</td>
<td>3.1 +</td>
<td>73.3 +</td>
</tr>
</tbody>
</table>


PFS: Progression free survival
OS: overall survival
Patient Case #2

- PM is a 78 yo female, former smoker who was diagnosed with NSCLC on work up for pneumonia.
  - Biopsy showed pulmonary sarcomatoid carcinoma histology
  - Further scans showed involvement of the liver
  - A commercial next generation sequencing (NGS) test was ordered on the lung biopsy
  - She has progressed on carboplatin and pemetrexed as well as single agent docetaxel but still desires therapy

TUMOR TYPE: LUNG SARCOMATOID CARCINOMA

Genomic Alterations Identified†

*MET* exon 14 splice site (2888-30_2888-5del26)
Question 5: Which of the following therapies would you recommend for this patient?

A. Erlotinib
B. Crizotinib
C. Cabozantinib
D. Nivolumab
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Patient Case #3

• LT is a 65 yo male, never smoker who was diagnosed who was found to have a right pleural effusion
  - Pleurocentesis analysis showed adenocarcinoma likely of lung origin
  - Further scans showed adrenal and bone involvement
  - A commercial cell free DNA (cfDNA) assay was ordered from blood sample given the difficulty of obtaining a biopsy

<table>
<thead>
<tr>
<th>Alteration</th>
<th>% cfDNA</th>
<th>cfDNA Amplification</th>
<th>FDA Approved in Indication</th>
<th>Available for Use in Other Indications</th>
<th>Clinical Drug Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>0.1</td>
<td>None</td>
<td></td>
<td>Cabozantinib, Lenvatinib, Ponatinib, Regorafenib, Sorafenib, More drugs available</td>
<td>Trials Available</td>
</tr>
<tr>
<td>ARID1A</td>
<td>G827G†</td>
<td>0.1</td>
<td>There is no change in the amino acid at this position and it is not likely to be a therapeutic target. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>D230D†</td>
<td>0.1</td>
<td>There is no change in the amino acid at this position and it is not likely to be a therapeutic target. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### RET Fusions in NSCLC

#### Diagram:
- **KIF3B-RET fusion**
- **Exon 15**
- **Kinase**
- **5’**
- **3’**

#### Text:
- Occur in 1-2% of NSCLC, most commonly in never-smokers with adenocarcinoma and no other molecular abnormalities.
- Other fusion partners include CCDC6, NCOA4, and TRIM33.

#### Table: Drug Targets and IC50 Values

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tyrosine Kinase Targets</th>
<th>Anti-RET IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>VEGFR 2, KIT, RET, MET, FLT-1/3/4, TIE-2, AXL</td>
<td>5-10 nM</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>VEGFR 1-3, FGFR 1-4, PDGFR, KIT, RET</td>
<td>1.5 nM</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>BCR-ABL, VEGFR, PDGFR, FGFR, KIT, RET, TIE2, FLT3</td>
<td>25.8 nM</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR 1/2, KIT, RET, CRAF, BRAF</td>
<td>6-47 nM</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR 2, KIT, RET, PDGFRα</td>
<td>220-1300 nM</td>
</tr>
<tr>
<td>Vandetinib</td>
<td>VEGFR 2/3, EGFR, RET</td>
<td>100 nM</td>
</tr>
</tbody>
</table>

*J Med Chem. 2015;58:3672-81*
RET Inhibitors in NSCLC

- Cabozantinib has the most case report data in NSCLC
  - Of 3 patients with NSCLC adenocarcinoma:
    - 1 patient had a confirmed PR of 66% tumor decrease and remained progression free for at least 5 months,
    - 1 patient had a confirmed PR of 32% tumor decrease and remained progression free for at least 4 months
    - 1 patient had stable disease after 4 weeks and lasting at least 8 months
  - Second case series of 3 patients:
    - All 3 experienced a PR after 4 weeks of therapy
  - Dosing: 60 mg PO daily rather than FDA approved dosing of 140 mg PO daily
  - Numerous ongoing trials including with apatinib, cabozantinib, vandetinib, ponatinib, and lenvatinib

RET Inhibitors in NSCLC: ASCO 2016

- Global registry of RET-rearranged NSCLC
  - 132 patients, 62% never-smokers, 97% adenocarcinoma
  - 31% of the patients received therapy off protocol with a RET inhibitor, mostly 3rd line

- RET inhibitor results:
  - Cabozantinib (n=14): 1 CR, 3 PR, 4 SD
  - Vandetinib (n=11): 2 PR, 3 SD
  - Sunitinib (n=10): 2 PR, 3 SD
  - Sorafenib (n=2): 2 SD

J Clin Oncol 34, 2016 (suppl; abstr 9014)
Patient Case #3

- LT is a 65 yo male, never smoker who was diagnosed with Stage IV NSCLC with adenocarcinoma histology.
  - A commercial cell free DNA (cfDNA) assay was ordered from blood sample given the difficulty of obtaining a biopsy.
  - She received first line therapy with carboplatin and pemetrexed and then docetaxel and ramucirumab second line. She now has progressive disease.
Question 6: Which of the following therapies would you recommend for this patient?

A. Erlotinib
B. Lenvatinib
C. Nivolumab
D. Cabozantinib
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Turning tumor genetic sequencing into standard clinical practice

The value of the Molecular Tumor Board
Tumor Genome Analysis Workflow

- What is the goal of the test?
- What test should be ordered?
- What tissue is available?
Cell Free DNA (cfDNA) Assays

- Tissue biopsies are not always feasible
- Enables serial monitoring over time to assess for resistance mutations and changes in frequency
- May better represent tumor heterogeneity
- Value of cell free DNA (cfDNA) and serial sampling
  - Plasma derived assays
    - Best concordance when higher number of metastatic sites, lower albumin, higher number of prior therapies
    - Site of disease also showed correlation
  - Cerebral Spinal Fluid (CSF)
    - Somatic alterations found in 63% of CNS metastases from solid tumors and 50% of primary brain tumors

Tumor Genome Analysis Workflow

- What is the goal of the test?
- What test should be ordered?
- What tissue is available?

- What type of variants will be assessed?
  - Lower limit of quantitation, number of reads, etc

- How is actionability determined?
  - Priority given to multiple actionable variants?
  - How to handle variants of unknown or almost known significance?
  - Germline variants?
Clinical Actionability

• Genetic alteration predicts response to a particular therapy
  – Benefit or resistance to a particular therapy
  – FDA approved therapy in the patient’s tumor or another type of tumor
  – Clinical trial for the particular alteration or reasonable based on molecular biology

• Genetic alteration provides diagnostic or prognostic information

• Clinically relevant germline alteration that informs disease risk or pharmacokinetic or pharmacodynamics
**Actionability and Levels of Evidence**

**Clinical Actionability**
- FDA approved therapy in patient’s tumor type
- FDA approved therapy in different tumor type
- Clinical trial based on specific mutation
- Clinical trial based on application of pathway biology
- Prognostic information
- Not clinically actionable at this time

**Supporting Data**
- Comparative trial with biomarker selection/stratification (patient’s tumor type or different tumor type)
- Retrospective cohort or case-control trials
- Biomarker association with response less robust (secondary endpoint)
- Case study or case series
- Preclinical data only (in vitro or in vivo models)
Variants of Almost Known Significance

- Variation found in clinically significant gene in area of known tyrosine kinase binding or other known relevant area
  - Specific alteration itself is unknown
  - Example: EGFR N771Y
    - Located in the EGFR tyrosine kinase domain in exon 20 but has not been previously reported in COSMIC or other sources

- Value of functional based assays
- Importance of data sharing, especially regarding relevant clinical outcomes
Tumor Genome Analysis Workflow

- Tumor Genome Testing
  - What is the goal of the test?
  - What test should be ordered?
  - What tissue is available?

- Identification of Variants
  - What type of variants will be assessed?
  - Lower limit of quantitation, number of reads, etc.

- Clinical Interpretation
  - How is actionability determined?
  - Priority given to multiple actionable variants?
  - How to handle variants of unknown or almost known significance?
  - Germline variants?

- Patient – Oncologist Decision
  - Ability to qualify and travel for a clinical trial?
  - Ability to acquire off label therapy?
  - Other patient factors to consider?
Translating Recommendations into Clinical Decision Making

• Researching and presenting available data to facilitate the decision making process

• Considering the interaction of all the mutations together
  – Cyclin D pathway alteration + RB1 loss

• Consideration of each patient’s unique characteristics
  – Desire for a clinical trial and ability to travel
  – Availability and ability to qualify for a clinical trial
  – Sequencing of treatment options
  – Insurance coverage and ability to afford off label therapy
  – Patient preference on treatment options
  – Where patient is in his/her treatment course
Personalized Medicine Clinical Service (PMCS) and Clinical Genomics Action Committee (CGAC)

**Tumor Genome Analysis Workflow**

1. Tumor genetic testing ordered and results returned
2. Personalized Medicine Clinical Service discussion and review
3. Expedited consult communicated to ordering clinician
4. Consult report generated and documented in EHR
5. Discussion with oncologist and patient
6. Assistance with acquisition of off-label therapy if needed

**Clinical Genomics Action Committee (CGAC)**

- Breast
- Thoracic
- Genetic Couns
- Medical Gen.
- PCM Fellow
- Leukemia
- Bioinformatics
- Myeloma
- Heme Pathology
- GU
- Pharmacy
- Hem/onc fellow
- Mol Pathology
- Sarcoma
List of Findings for patient (FoundationOne Heme)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Mutation</th>
<th>Significant</th>
<th>CNA</th>
<th>MAF</th>
<th>In EVS</th>
<th>Protein Domain</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP300</td>
<td>22q13.2</td>
<td>R095P</td>
<td>NO</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFE3</td>
<td>17p13.1</td>
<td>R337C</td>
<td>YES</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUP93</td>
<td>16q13</td>
<td>A72V</td>
<td>NO</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB1</td>
<td>13q14.2</td>
<td>L331fs*1</td>
<td>YES</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC7</td>
<td>12q13.1</td>
<td>R156H</td>
<td>NO</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>12q12</td>
<td>Q923H</td>
<td>YES</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>12p12.1</td>
<td>C180T</td>
<td>YES</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUX1</td>
<td>7q22.1</td>
<td>S1134C</td>
<td>NO</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP3K1</td>
<td>5q11.2</td>
<td>A19S</td>
<td>NO</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOTCH2</td>
<td>1p13-p11</td>
<td>P618*27</td>
<td>YES</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMSL3</td>
<td>T23M</td>
<td></td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>EGF</td>
<td></td>
</tr>
</tbody>
</table>

Add Gene and Mutation

Gene: [dropdown]
Mutation (Change): [text]
Significant: [dropdown]
CNA: [text]
CGAC Database

Gene Information

Symbol: ATM
ID: 472
Alias: AT1 ATA ATC ATD ATDC ATE TEL1 TEO1
Description: ataxia telangiectasia mutated

3. Mutation Frequency in TCC Samples

Tumor Samples vs. Normal Samples

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Protein</th>
<th>Sample with Mutation</th>
<th>Total Samples</th>
<th>Frequency(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>G2023R</td>
<td>1</td>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>G2023R</td>
<td>1</td>
<td>44</td>
<td>2.27%</td>
</tr>
<tr>
<td>HEME-CLL</td>
<td>G2023R</td>
<td>2</td>
<td>94</td>
<td>2.12%</td>
</tr>
<tr>
<td>Kidney</td>
<td>G2023R</td>
<td>1</td>
<td>243</td>
<td>0.11%</td>
</tr>
<tr>
<td>Lung</td>
<td>G2023R</td>
<td>1</td>
<td>603</td>
<td>0.16%</td>
</tr>
</tbody>
</table>

Mutation Frequency of ATM(G2023R)
# Clinically Important Genetic Resources

<table>
<thead>
<tr>
<th>Category</th>
<th>Resource</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variants of Unknown Significance</td>
<td>1000 Genomes Project (<a href="http://www.1000genomes.org/">http://www.1000genomes.org/</a>)</td>
<td>Provide a probability of the variant being germline</td>
</tr>
<tr>
<td></td>
<td>Exome Variant Server (<a href="http://evs.gs.washington.edu/EVS/">http://evs.gs.washington.edu/EVS/</a>)</td>
<td>Provide a probability of the variant being germline</td>
</tr>
<tr>
<td></td>
<td>HCI Breast Cancer Gene Prior Probabilities (<a href="http://priors.hci.utah.edu/PRIORS">http://priors.hci.utah.edu/PRIORS</a>)</td>
<td>Data on all possible single nucleotide substitutions in BRCA1/2</td>
</tr>
<tr>
<td></td>
<td>American College for Clinical Genetics (ACMG)</td>
<td>Association of a variant with an inherited disease</td>
</tr>
</tbody>
</table>

## Clinically Important Genetic Resources

<table>
<thead>
<tr>
<th>Category</th>
<th>Resource</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variants from across Cancer Types</strong></td>
<td>cBioPortal (<a href="http://www.cbioportal.org/">http://www.cbioportal.org/</a>)</td>
<td>The frequency of a variant across cancer types and the location of the variant in the functional domains of the gene</td>
</tr>
<tr>
<td></td>
<td>Catalogue of Somatic Mutations in Cancer (COSMIC) (<a href="http://cancer.sanger.ac.uk/cosmic">http://cancer.sanger.ac.uk/cosmic</a>)</td>
<td>The frequency of a variant across cancer types</td>
</tr>
<tr>
<td><strong>Therapeutic Association</strong></td>
<td>MyCancerGenome (<a href="http://www.mycancergenome.org/">http://www.mycancergenome.org/</a>)</td>
<td>Association of mutation with tumorigenesis, related therapeutic implications and available clinical trials</td>
</tr>
<tr>
<td></td>
<td>PharmGKB (<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>)</td>
<td>Interactive tool for researchers investigating how genetic variation effects drug response</td>
</tr>
<tr>
<td></td>
<td>Personalized Cancer Therapy Knowledge Base for Precision Oncology (<a href="https://pct.mdanderson.org">https://pct.mdanderson.org</a>)</td>
<td>Knowledge base resource for the implementation of personalized cancer therapy and integrating information about tumor DNA, RNA, protein and metabolomics profiles with predicted therapy response</td>
</tr>
</tbody>
</table>

Germline Challenges
Patient Case #4

• PH is a 56 yo male former smoker who is diagnosed with squamous cell NSCLC.
• Work up and staging reveal several spinal metastases, but brain MRI is clear
• He is initially treated with carboplatin and gemcitabine x 4 cycles and has a near complete response for 5 months
• His most recent scan shows progressive disease with new adrenal involvement confirmed on biopsy
  – Tissue from the adrenal biopsy is sent for genetic analysis and reveals FGFR3 amplification and an FGFR3 S249C mutation
Question 7:
Which of the following would provide the best information regarding whether the **FGFR3 S249C** mutation has been previously reported in lung or another cancer?

A. 1000 Genomes Project  
B. MyCancerGenome  
C. ClinVar  
D. cBioPortal
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**FGFR3 S249C**

- In vitro bladder cancer cell data supports this mutation induced phosphorylation of PLCγ1, FRS2 and ERK1/2. Differences were seen between different FGFR3 mutations and different cell types.
- Pazopanib was shown in vitro to inhibit FGFR3 activating mutations at an IC50 of 100nM-1μM and one SqCC head and neck cancer patient with an FGFR2 P253R mutation had a response to pazopanib.
- 67 yo woman with metastatic papillary urothelial carcinoma s/p several chemotherapy agents found to have FGFR3 amp and **S249C** (58%), treated with **pazopanib** and had a PR > 6 months.
- **AZD4547** is part of the NCI-MATCH trial expanded arms
  - Subprotocol W (FGFR1-3 amplifications, mutations or translocations)

CBioPortal July 2016, Oncogene 2009;28:4306-16
European Urology. 2015;68:167-170
Mutation Load and Immunotherapy

• **Exciting therapy, but not everyone has a response**
  – Durable responses to anti-PD1 therapy were seen in:
    – 31-44% of melanoma
    – 19-20% of lung cancer
    – 22-25% of renal cell carcinoma
  – Potential biomarkers:
    – Density of CD8+ T cells in tumors
    – Expression of PDL1 on tumors
    – **Mutation burden and microsatellite instability:** now being reported by some molecular testing companies for individual patients

**Example:** MSI: Stable
Mutation Burden: **High**, 25 mutations per megabase

Mutation Load and Immunotherapy

**Number of Mutations**
- Improved *overall survival* with CTLA4-inhibitors in melanoma patients with >100 mutations (p=0.04)
  - 64 patients treated with ipilimumab or tremelimumab
  - Neoantigen response signature developed
- Improved **mPFS** in lung cancer patients treated with pembrolizumab with high mutation burden
  - Patients with durable responses had a median of 302 mutations vs. 148 in those without a durable response (p=0.02)

**Microsatellite Instability**
- 41 patients with MMR-deficient colorectal cancer, 9 patients with other MMR-deficient cancer and 21 MMR-intact colorectal cancer patients
  - All treated with pembrolizumab
- Whole exome sequencing mean number of somatic mutations per tumor
  - MMR-deficient: 1782 mutations
  - MMR-intact: 73 mutations
  - Higher somatic tumor burden = improved mPFS

Science. 2015;348:124-128
Future of Somatic Genomics

• What are the optimal mutational profiling approaches?

• How do we translate these findings into clinical practice for the average oncologist?
  – Defining “clinically actionable”
  – Handling “variants of unknown significance”
  – Facilitating patient discussions
  – Ethics on germline findings

• What clinical trials should we be doing?
  – Novel trial design like “Basket Studies”

Ongoing Challenges

- Identify, interrogate and validate the correct biomarkers for targeted and immunotherapies
- Utilize novel clinical trial designs to assess outcomes across tumor types and mutations
  - Basket trials
  - Genetic-guided Registry trials
    - Targeted Agent and Profiling Utilization Registry (TAPUR)
      - Goal: To learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target or to predict sensitivity to a drug
      - Currently open at 4 sites with many more planned, 15 arms
      - NCT02693535
Optimizing Targeted Therapy

- Translate our understanding of cancer biology crosstalk and feedback signaling into rationale drug combinations
- Modify the immune environment to improve tumor identification and destruction
- Improve biomarker identification and validation to target the right genetic drivers

Questions?