The iQ&A Case-by-Case 
*interactive* Precision Cancer Intelligence Zone

Focus on the Foundational Importance of Genomic Profiling and Molecular Markers to Identify Targetable, Actionable, and Therapeutically Significant Genomic Alterations in the Setting of Lung Cancer

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Session Moderators and Distinguished Faculty

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<table>
<thead>
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<th>Name</th>
<th>Position and Affiliations</th>
</tr>
</thead>
<tbody>
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</table>
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Expert Roundtable Session #1
Case Study #1 – Expert Faculty

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Case Study #1 – Presentation

A 24 year-old woman from Brazil with a 5 pack-year history of former smoking presented with cough

• Her history includes a diagnosis of Hodgkin’s lymphoma for which she underwent radiation in the past that rendered her NED.
• A CT of the chest revealed multiple bilateral lung nodules up to 2 cm in size.
• Biopsy of a suspicious adrenal nodule revealed non-small cell carcinoma that is poorly differentiated.
• Next-generation sequencing identified an NTRK1 fusion.
Case Study #2 – Treatment Strategy

What would you do next?
• What systemic therapy would you recommend for this patient?
• Would you administer targeted therapy if available on a clinical trial?
• What targeted therapy would you recommend?
• Do you screen for NTRK fusions in your practice?
Case Study #2 – Presentation

A 52 year-old female never smoker presents with worsening back pain

• An MRI reveals multiple thoracic and lumbar lesions suspicious for metastatic disease.
• A PET scan confirms hypermetabolic osseous lesions along with a 3cm LUL hypermetabolic mass, mediastinal lymphadenopathy, and a right adrenal hypermetabolic focus.
• Biopsy of the LUL mass revealed adenocarcinoma of the lung.
• An immunohistochemical stain for ALK returns positive.
Case Study #2 – Treatment Strategy

What would you do next?
• Would you pursue further molecular profiling for this patient?
• If so, what test would you perform?
• What therapy would you recommend for this first-line patient?
• Assuming the patient first received ceritinib and developed disease progression, how would you treat the patient?
• Would you perform a repeat biopsy for molecular profiling at this point?
• Should you decide to administer cytotoxic chemotherapy, do you prefer a particular regimen for patients with ALK-rearranged cancers in patients who are chemotherapy-naïve?
A 68 year-old former heavy smoker presents with right upper quadrant pain

- An ultrasound of the liver reveals 3 discrete masses suspicious for metastases.
- Further workup identified a RLL 5 cm mass and R hilar adenopathy.
- Biopsy of a liver nodule revealed TTF1+ and p40- adenocarcinoma.
- Plasma molecular profiling of ctDNA revealed a MET exon 14 splice site mutation.
Case Study #3 – Treatment Strategy

What would you do next?

• Would you await further molecular profiling of this case in order to initiate systemic therapy?

• If tumor tissue was already prepared to be sent for molecular profiling, what type of test would you order?

• How would you approach the treatment of this patient?

• Would you administer targeted therapy in the first-line setting?

• How many patients with MET exon 14 mutations have you treated in your practice?
A 48 year-old man with a 15 pack-year history of smoking presents with shortness of breath.

- He is found to have evidence of lymphangitic carcinomatosis on a CT of the chest.
- An MRI of the brain reveals 3 small subcentimeter nodules suspicious for metastases.
- A biopsy of an area of consolidation in the lung reveals adenosquamous carcinoma.
- Molecular profiling identifies a KIF5B-RET fusion.
Case Study #4 – Treatment Strategy

What would you do next?

• How many RET-rearranged lung cancer patients have you identified in your practice?

• What systemic therapy would recommend for this treatment-naïve patient?

• What therapy would you recommend after that?

• What is your experience with the use of tyrosine kinase inhibitors for patients with RET-rearranged lung cancers?

• Are you aware of emerging approaches to the treatment of these tumors?
Case Study #5 – Expert Faculty

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Molecular Geneticist  
Chief, Molecular Diagnostics Service  
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New York, New York, USA

Julien Sage, PhD  
Professor of Pediatrics (Hematology/Oncology) and of Genetics  
Stanford University School of Medicine  
Stanford, California, USA

Case Study #5 – Presentation

75-year-old Asian man, smoker, 1 pack per day for 50 years

• He had chronic obstructive pulmonary disease in the past 20 years.
• Right upper lobe tumor was noted in chest X ray.
• CT scan of the chest showed in addition to the 3.3 cm tumor in the RUL, several mediastinal lymphnodes up to 2 cm were found.
• Bone scan showed multiple bone metastasis
• CT scan guided biopsy of the RUL tumor was performed, pathology examination showed adenocarcinoma, moderately differentiated, TTF-1 (+)
• T2N2M1 (stage IV)
Case Study #5 – Treatment

• Immunohistochemistry was performed: ALK(-), PDL1 (22C3): 1%,
  • EGFR mutation : Cobas : negative.

• What is your recommendation?

Case Study #5 – Presentation

• Patient received pemetrexed and carboplatin for 4 cycles and pemetrexed maintenance. The response was stable.

• He had progression in the liver new tumor, 5 months after starting chemotherapy

• What is your next step?
Case Study #5 – Presentation

- Plasma cell free DNA showed no mutation in the genes below: EGFR, K-ras, B-raf, ALK fusion, ROS1 fusion, HER2,

  What is your next step?

Case Study #5 – Presentation

- Re-biopsy was performed from the liver tumor, tissue was sent to NGS targeted gene panel test:

  - Result showed
    - EGFR gene amplification
    - cMET skipping exon 14 mutation
    - P53 mutation

  What is your next step?
Case Study #5 – Presentation

- Crizotinib was given. Patient had a partial response after 2 months.
**Expert Roundtable Session #6**

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**Table 1: Overview cMET Exon 14 Skipping Patients Who Received Anti-cMET Therapy: An Overview of the Characteristics of the Patients Described Thus Far Who Presented with cMET Exon 14 Skipping and Were Treated with cMET Small Molecule Inhibitors**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Cancer Type</th>
<th>Previous Treatments</th>
<th>cMET ex14 Splice Mutation</th>
<th>Other Genetic Information</th>
<th>cMET Inhibitor</th>
<th>Response</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>Female</td>
<td>Stage IIb thryocytic squamous cell lung cancer</td>
<td>Nivolumab, pembrolizumab, erlotinib</td>
<td>cMET K630N</td>
<td>NA</td>
<td>Crizotinib</td>
<td>65%</td>
<td>4</td>
</tr>
<tr>
<td>82</td>
<td>Female</td>
<td>Stage IV lung cancer</td>
<td>Pembrolizumab, nivolumab, erlotinib</td>
<td>cMET K630N</td>
<td>NA</td>
<td>Crizotinib</td>
<td>65%</td>
<td>4</td>
</tr>
<tr>
<td>66</td>
<td>Female</td>
<td>Stage III squamous cell lung cancer</td>
<td>Nivolumab, pembrolizumab, erlotinib</td>
<td>cMET K630N</td>
<td>NA</td>
<td>Crizotinib</td>
<td>65%</td>
<td>4</td>
</tr>
</tbody>
</table>

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**References**

Nele Van Der Steen et al. JTO 2016;11(9):1423-1432
A chest X ray showed mediastinal widening.
CT scan of the chest showed multiple mediastinal lymphnodes up to 2 cm in size.
A left upper lobe tumor 2 cm in size close to left main bronchus was noted.
Examinations showed that there were not other tumor lesions in lung, liver, bone and other organs.
Bronchoscopic biopsy was performed. Pathology showed moderately differentiated adenocarcinoma. TTF-1 (+).
What is your next step?
Case Study #6 – Treatment

- Immunohistochemistry test showed ALK (-), ROS1(+), PDL1 (22C3) 0%.
- EGFR, K-Ras, HER2, B-raf hotspots mutation were negative by Sangers direct sequencing tests.

- What is your next step?

Case Study #6 – Treatment

- Concurrent chemoradiotherapy with cisplatin / VP16 +60Gy were given. She had a good partial response.

Will you give her durvalumab after CCRT?
Case Study #6 – Treatment

• She was followed for one year. Multiple lung metastasis were detected in the follow up CT scan.

• What is your next step?

Case Study #6 – Treatment

• She had a re-biopsy of the lung tumor. Pathology proved recurrence of tumor.
• She received 4 cycles of pemetrexed and cisplatin and pemetrexed maintenance. She had a partial response for 1 year. Progression in the lung nodules were noted in a regular 3 monthly CT scan.

• What will you do?
Case Study #6 – Treatment

- Her archived tissue was sent to NGS targeted gene sequence. The report showed CD74-ROS1 fusion. Tumor mutation burden low.

What is your next step?

Case Study #6 – Treatment

- She received crizotinib and had a complete response for 3 years.
Expert Roundtable Session #7

Case Study #7 – Expert Faculty

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Case Study #7 – Presentation

75-year-old Asian man, smoker, 1 pack per day for 50 years

- He had chronic obstructive pulmonary disease in the past 20 years.
- Right upper lobe tumor was noted in chest X ray.
- CT scan of the chest showed in addition to the 3.3 cm tumor in the RUL, several mediastinal lymphnodes up to 2 cm were found.
- Bone scan showed multiple bone metastasis
- CT scan guided biopsy of the RUL tumor was performed, pathology examination showed adenocarcinoma, moderately differentiated, TTF-1 (+)
- T2N2M1 (stage IV)
- What is your next step?

Case Study #7 – Treatment

- Immunohistochemistry was performed: ALK(-), PDL1 (22C3): 1%,
- EGFR mutation : Cobas : negative.

- What is your recommendation?
Case Study #7 – Presentation

• Patient received pemetrexed and carboplatin for 4 cycles and pemetrexed maintenance. The response was stable.

• He had progression in the liver new tumor, 5 months after starting chemotherapy

• What is your next step?

Case Study #7 – Presentation

• Plasma cell free DNA showed no mutation in the genes below: EGFR, K-ras, B-raf, ALK fusion, ROS1 fusion, HER2,

What is your next step?
Case Study #7 – Presentation

• Re-biopsy was performed from the liver tumor, tissue was sent to NGS targeted gene panel test:

  • Result showed
    ▪ EGFR gene amplification
    ▪ cMET skipping exon 14 mutation
    ▪ P53 mutation

  What is your next step?

Case Study #7 – Presentation

• Crizotinib was given. Patient had a partial response after 2 months.
NSCLC
cMET Skipping Exon 14 Mutation

Nele Van Der Steen et al. JTO 2016;11(9):1423-1432
Expert Roundtable Session #8

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Case #8: Large Cell NET; June 2015

• 68-year-old female; 40 pack years
• Right wrist pain
• Lost 11 kg in 2 months
• Histology: Large cell NET; KI67: 10-35%
• NGS: KRAS G12C

Large Cell NET; June 2015
Large Cell NET

What would be your treatment approach?

1) Carboplatin/Etoposide
2) Carboplatin/Pemetrexed +/- Bevacizumab
3) Sunitinib
4) Clinical trial

Large Cell NET; July-Nov 2015

- Carboplatin/Pem/Bev X 4 cycles
- Clinical PD: hoarseness and right wrist pain; PS=1
- CT/PET: Liver PD
- PD1: Low positive (Dako)
- MSI STABLE
- Mutational burden:
  - Intermediate
  - ~8 mutations per Mb
Large Cell NET; July-Nov 2015

- Carboplatin/pem/Bev X 4 cycles
- Clinical PD: hoarseness and right wrist pain; PS=1
- CT/PET: Liver PD
- PD1: Low positive
- MSI Stable;
- Intermediate mutational burden

**September, 2015**
- Nivolumab 3 mg/kg q2w
- Spine MRI:
  - PR in L2 (was radiated)
  - PD in S1
  - Gain weight and PS=1

Large Cell NET; January 2016

- Continue Nivolumab q2w
- PS=0, no wrist pain

**January, 2017**
- Reduced PS
- Weakness
- CT-PET: NED
- Hypothyroidism
- Continue Nivo through today
• PD1 is efficient also in large cell NET
• TMB is an important predictive biomarker
• Would this patient be treated differently today?
  ▪ Yes, combo chemo-IO as 1st line
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Case #9: August, 2016
A 63-Year-Old Woman Who Has Never Smoked

- PS=0
- Cough and PAF
- RUL SOL
- EBB: Squamous CC NSCLC
- CT-PET: Liver 14 mm
- Brain MRI: Normal
- PDL1 not available
- EGFR (-)
- Pathology revision:
  - Pure squamous CC
  - Minimal tissue left
Question: what is your next step (August, 2016) ?

1) Chemo-RT with liver SBRT
2) Systemic chemo
3) Perform liquid next generation sequencing
4) Clinical study

Next Step (August, 2016)

1) Chemo-RT with liver SBRT
2) Systemic chemo
3) Perform next generation sequencing (NGS)
4) Clinical study (MEDI-TREMI arm)
Case Continues Into October, 2016:

- MEDI-TREMI 2 cycles
- Pleural effusion → positive for cytology
- Right groin pain
Next Generation Sequencing in Squamous Cell Carcinoma

NCCN Guidelines Version 7.2017 Updates
Non-Small Cell Lung Cancer

NSCL-17
• Testing added for ROS1 and PD-L1.
• Squamous cell carcinoma: “Consider EGFR mutation testing and ALK testing especially in never smokers or small biopsy specimens, or mixed histology.”
• Footnote “I” added: “If repeat biopsy is not feasible, plasma biopsy should be considered.”
• Footnote “II” modified: “The NCCN NSCLC Guidelines Panel strongly endorses-advises broader molecular profiling…”
• Footnote “IX” added: “PD-L1 expression levels of ≥50% are a positive test for first-line pembrolizumab therapy.”
—Footnote removed since the content was added to the algorithm: Consider ROS1 testing; if positive, may treat with crizotinib.

Comprehensive Genomic Characterization of Squamous Cell Lung Cancers

Figure 1: Significantly mutated genes in squamous cell lung cancer.

From:
Comprehensive genomic characterization of squamous cell lung cancers
The Cancer Genome Atlas Research Network
Nature 2014; 518:423-434 | doi 10.1038/nature14144

Significantly mutated genes (Q-value < 0.1) identified by exome sequencing are listed vertically by Q-value. The percentage of lung SQCC samples with a mutation detected by exome sequencing is listed at the left. Samples displayed as columns, with the overall number of mutations plotted at the top, and samples are arranged to emphasize isolated exome-mutation signatures. Syn, synonymous.

(https://www.nature.com/nature/journal/v489/n7417/full/nature11404.html)
SCC in never smoker
ROS1 in SCC
1. Continue MEDI-TREMI
2. Switch to Chemo
3. Xalkori
Next Step (October, 2016)

SCC in never smoker
ROS1 in SCC

1) Continue MEDI-TREMI
2) Switch to Chemo
3) Xalkori

Case Continued (November, 2016)

• Xalkori 250 mg BID
• Fast resolution of pain
• No FDG uptake

• Last update 8/2017
Take Home Message

• ROS1 in SCC 0.8% at FMI database
• 0.8% is 100% here !!!!!!!
• Information is powerful

Expert Roundtable Session #10
Case Study #10 – Expert Faculty

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Yonsei Cancer Center
Yonsei University College of Medicine
JE-UK Laboratory of Molecular Cancer Therapeutics
Seoul, Korea

Case #10: 50 y; Non Smoking Woman
EGFR ex19 del

- October, 2013:
  - Stage 3B ADC → ChemoRT
  - Brain SRS for a single lesion
- April, 2014: Liver + Brain + Bone
  - WBRT
  - Gefitinib 250 mg X1
- April, 2015: Systemic PD
  - Seeking for T790M
  - Liver Biopsy:
    - EGFR ex19
    - Negative for T790M
  - ctDNA T790M pos

Peled N et al. JTO 2017
Biomarker Analysis: ctDNA (Guardant)

Peled N et al. JTO 2017

Response Rate in T790M Positive Cohorts
AZD9191 (Osimertinib)

Peled N et al. JTO 2017
ctDNA Guided Therapy
AZ291 (Osimertinib); 2 wks

Peled N et al. JTO 2017

Peled N et al. JTO 2017
Liver Biopsy for Next Generation Sequencing

Peled N et al. JTO 2017

Distribution of EGFR Mutations

Deletions 46%
Duplications/insertions (9%)
L858R (39%)
G724S Blockade by Afatinib (NovellusDx)

A Month After Adding Afatinib (October, 2015)

Peled N et al. JTO 2017
50 y; Non Smoking Woman; EGFR ex19 del

**Take Home Message**

- ctDNA support uncovering resistance clones
- ctDNA may direct therapy
- ctDNA may quantify disease burden
**66y Never Smoker; Tamponade**

### About the Test:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

#### Patient Results

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>Therapies Associated with Potential Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR exon 19 deletion (E746-A750del)</td>
<td>Gefitinib, Osimertinib</td>
</tr>
<tr>
<td><strong>BRAF</strong> V600E</td>
<td>None</td>
</tr>
<tr>
<td><strong>LRP1B</strong> G2651R</td>
<td>None</td>
</tr>
</tbody>
</table>

#### Tumor Type: Lung Non-Small Cell Lung Carcinoma (NSCLC)

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA-Approved Therapies (for patient's tumor type)</th>
<th>FDA-Approved Therapies (for another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong> V600E</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>LRP1B</strong> G2651R</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Tough Decisions

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

<table>
<thead>
<tr>
<th>PATIENT RESULTS</th>
<th>TUMOR TYPE: LUNG ADENOCARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 genomic alterations</td>
<td>ERBB2: G776+V777D</td>
</tr>
<tr>
<td>4 therapies associated with potential clinical benefit</td>
<td>ARID1A: Q788*</td>
</tr>
<tr>
<td>1 therapy associated with lack of response</td>
<td>CTNNB1: S33A</td>
</tr>
<tr>
<td>30 clinical trials</td>
<td>TP53: Q192*</td>
</tr>
<tr>
<td></td>
<td>WTT: Q308*</td>
</tr>
</tbody>
</table>

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

<table>
<thead>
<tr>
<th>PATIENT RESULTS</th>
<th>TUMOR TYPE: LUNG SQUAMOUS CELL CARCINOMA (SCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 genomic alterations</td>
<td>Genomic Alterations Identified¹</td>
</tr>
<tr>
<td>10 therapies associated with potential clinical benefit</td>
<td>EGFR amplification – equivocal⁶</td>
</tr>
<tr>
<td>0 therapies associated with lack of response</td>
<td>HGF amplification – equivocal³</td>
</tr>
<tr>
<td>30 clinical trials</td>
<td>MET exon 14 splice site (3028+1G&gt;A)</td>
</tr>
<tr>
<td></td>
<td>BRC42 B1982fs*22</td>
</tr>
<tr>
<td></td>
<td>CCND1 amplification – equivocal⁶</td>
</tr>
<tr>
<td></td>
<td>MDM2 amplification</td>
</tr>
<tr>
<td></td>
<td>APC11357K</td>
</tr>
<tr>
<td></td>
<td>ATXN1 R533_H534insQV1H</td>
</tr>
<tr>
<td></td>
<td>FRS2 amplification</td>
</tr>
<tr>
<td></td>
<td>RET truncation intron 11</td>
</tr>
</tbody>
</table>

Conclusion

- Expect the unexpected
- Go wide as much as possible without QA compromise
- Clinical decisions are always required
- Cross technologies in uncommon cases
Expert Roundtable Session #11

Case Study #11 – Expert Faculty

**Professor Nir Peled, MD, PhD, FCCP**
iQ&A Case by Case Program Chair
Head of The Cancer Institute
Soroka Medical Center & Ben-Gurion University

**Prof. Reinhard Buettner, MD**
Professor and Chairman
Institute for Pathology
University Hospital Cologne
Cologne, Germany

**Professor Caroline Dive, PhD**
Deputy Director and Senior Group Leader
Cancer Research
UK Manchester Institute
Manchester, England

**Roy S. Herbst, MD, PhD**
Ensign Professor of Medicine (Medical Oncology)
Professor of Pharmacology
Chief of Medical Oncology
Yale Cancer Center and Smilow Cancer Hospital
Associate Director for Translational Research
Yale Cancer Center
Disease Aligned Research Team (DART) Leader
Thoracic Oncology Program, Yale Cancer Center
New Haven, Connecticut, USA
Case #11: 50 y; Non Smoking Woman
EGFR ex19 del

- October, 2013:
  - Stage 3B ADC → ChemoRT
  - Brain SRS for a single lesion
- April, 2014: Liver + Brain + Bone
  - WBRT
  - Gefitinib 250 mg X1
- April, 2015: Systemic PD
  - Seeking for T790M
  - Liver Biopsy:
    - EGFR ex19
    - Negative for T790M
  - ctDNA T790M pos

Peled N et al. JTO 2017

Biomarker Analysis: ctDNA (Guardant)

Peled N et al. JTO 2017
Response Rate in T790M Positive Cohorts
AZD9191 (Osimertinib)

*Imputed values for patients who died within 1.1-3.5 weeks (85 days) of start of treatment and had no evaluable tumor lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease


ctDNA Guided Therapy
AZ291 (Osimertinib); 2 wks

Peled N et al. JTO 2017
Liver Biopsy for Next Generation Sequencing

Peled N et al. JTO 2017
Distribution of EGFR Mutations

G724S Blockade by Afatinib (NovellusDx)
50 y; Non Smoking Woman; EGFR ex19 del

Peled N et al. JTO 2017
Take Home Message

• ctDNA support uncovering resistance clones
• ctDNA may direct therapy
• ctDNA may quantify disease burden

Straight Forward Reports
66y Never Smoker; Tamponade

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS
- 7 genomic alterations
- 2 therapies associated with potential clinical benefit

TUMOR TYPE: LUNG NON-SMALL CELL LUNG CARCINOMA (NSCLC)

Genomic Alterations Identified:
- BRAF V600E
- LRP1B G2663R

THERAPEUTIC IMPLICATIONS

<table>
<thead>
<tr>
<th>Genomic Alteration Detected</th>
<th>FDA-Approved Therapies in Patient’s Tumor Type</th>
<th>FDA-Approved Therapies in Another Tumor Type</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
<td>None</td>
<td>Cobimetinib</td>
<td>Yes, see clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dabrafenib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regorafenib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trametinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venetasib</td>
<td></td>
</tr>
<tr>
<td>LRP1B G2663R</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

RABIN MEDICAL CENTER RENAL + HASHARON

Tough Decisions

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS
- 5 genomic alterations
- 4 therapies associated with potential clinical benefit
- 1 therapy associated with lack of response

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS
- 10 genomic alterations
- 10 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 30 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified:
- ERBB2/3/78, Y777Y=V777
- ARID1A Q735
- CTNNB1 S33A
- TP53 Q292
- WTI Q308

TUMOR TYPE: LUNG squamous cell CARCINOMA (SCC)

Genomic Alterations Identified:
- EGFR amplification – equivocal
- HGF amplification – equivocal
- MET exon 14 splice site (3028+1G>A)
- BRC42 E1692F
- CCND1 amplification – equivocal
- MDM2 amplification
- APC 1137K
- AXR1 R533_H534insQVH
- FRS2 amplification
- RET truncation intron 11
Conclusion

• Expect the unexpected
• Go wide as much as possible without QA compromise
• Clinical decisions are always required
• Cross technologies in uncommon cases

Expert Roundtable Session #12
Case Study #12 – Expert Faculty

Professor Nir Peled, MD, PhD, FCCP
iQ&A Case by Case Program Chair
Head of The Cancer Institute
Soroka Medical Center & Ben-Gurion University

Professor Reinhard Buettner, MD
Professor and Chairman
Institute for Pathology
University Hospital Cologne
Cologne, Germany

Professor Rolf Stahel, MD
Professor
Oncology Clinic
University Hospital
Zurich, Switzerland

Case #12: August, 2016
A 63-Year-Old Woman Who Has Never Smoked

- PS=0
- Cough and PAF
- RUL SOL
- EBB: Squamous CC NSCLC
- CT-PET: Liver 14 mm
- Brain MRI: Normal
- PDL1 not available
- EGFR (-)
- Pathology revision:
  - Pure squamous CC
  - Minimal tissue left
A 63-Year-Old Woman Who Has Never Smoked; August, 2016

Question: what is your next step (August, 2016)?

1) Chemo-RT with liver SBRT
2) Systemic chemo
3) Perform liquid next generation sequencing
4) Clinical study

Next Step (August, 2016)

1) Chemo-RT with liver SBRT
2) Systemic chemo
3) Perform next generation sequencing (NGS)
4) Clinical study (MEDI-TREMI arm)
Case Continues Into October, 2016:

- MEDI-TREMI 2 cycles
- Pleural effusion → positive for cytology
- Right groin pain
Next Generation Sequencing in Squamous Cell Carcinoma

NCCN Guidelines Version 7.2017 Updates
Non-Small Cell Lung Cancer

NSCL-17

• Testing added for ROS1 and PD-L1.
  • Squamous cell carcinoma: “Consider EGFR mutation testing and ALK testing especially in never smokers or small biopsy specimens, or mixed histology.”
  • Footnote “I” added: “If repeat biopsy is not feasible, plasma biopsy should be considered.”
  • Footnote “gq” modified: “The NCCN NSCLC Guidelines Panel strongly endorses advises broader molecular profiling...”
  • Footnote “ik” added: “PD-L1 expression levels of ≥50% are a positive test for first-line pembrolizumab therapy.”
  • Footnote removed since the content was added to the algorithm: Consider ROS1 testing; if positive, may treat with crizotinib.

Comprehensive Genomic Characterization of Squamous Cell Lung Cancers

Figure 1: Significantly mutated genes in lung SQCC.

From:
Comprehensive genomic characterization of squamous cell lung cancers
The Cancer Genome Atlas Network
https://www.nature.com/nature/journal/v489/n7417/full/nature11404.html

(https://www.nature.com/nature/journal/v489/n7417/full/nature11404.html)
What is Your Next Step (1October, 2016)?

SCC in never smoker
ROS1 in SCC

1. Continue MEDI-TREMI
2. Switch to Chemo
3. Xalkori
Next Step (October, 2016)

SCC in never smoker
ROS1 in SCC

1) Continue MEDI-TREMI
2) Switch to Chemo
3) Xalkori

Case Continued (November, 2016)

- Xalkori 250 mg BID
- Fast resolution of pain
- No FDG uptake
- Last update 8/2017
Take Home Message

• ROS1 in SCC 0.8% at FMI database
• 0.8% is 100% here !!!!!!!

• Information is powerful

Expert Roundtable Session #13
Case Study #13 – Expert Faculty

Professor Nir Peled, MD, PhD, FCCP
iQ&A Case by Case Program Chair
Head of The Cancer Institute
Soroka Medical Center & Ben-Gurion University

D. Ross Camidge, MD, PhD
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Faculty, Developmental Therapeutics Program
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Naiyer A. Rizvi, MD
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Director of Immunotherapeutics
Division of Hematology and Oncology
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Martin Filipits, MD
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Institute of Cancer Research
Medical University of Vienna
Vienna, Austria

Case #13: Patient Characteristics

4/2017:
• 57 y 30 PY
• LUL lesion & Bone mets
• EGFR/ALK/ROS – Negative
• PDL1 > 75%
• ctDNA : BRAF P751S
How would you treat?

- Pembro 1\textsuperscript{st} line
- Combo Chemo+Pembro
- Chemo ±Bevacizumab
- Dabrafinitib+Trametinib

Case continued

- Pembro 3 cycles
- PS=1 & general improvement
- After 4\textsuperscript{th} cycle
  - Right Pelvic pain
  - CT RLL new lesions
What would you do next?

• Continue Pembro and wait
• Switch to 2\textsuperscript{nd} line (chemo without Pembro)
• Continue Pembro and add Chemo

What would you do next?

• Continue Pembro and wait
• Switch to 2\textsuperscript{nd} line (chemo without Pembro)
• Continue Pembro and add Chemo
  • With fast clinical improvement
• 1st line combo although PDL>75%
  • Higher ORR with combo
  • Very high PDL1 does not promise a Response
• Continue Pembro and add Chemo
• Payer’s perspective vs. combo first
Case Study #14 – Expert Faculty

Professor Nir Peled, MD, PhD, FCCP  
iQ&A Case by Case Program Chair  
Head of The Cancer Institute  
Soroka Medical Center & Ben-Gurion University

Prof. Solange Peters, MD, PhD, PD-MER  
Professor of Medicine  
Department of Oncology  
University of Lausanne  
Head, Thoracic Clinic  
University Hospital  
Lausanne, Switzerland

Yasushi Goto, MD  
Division of Internal Medicine and Thoracic Oncology  
National Cancer Center Hospital  
Chuo-ku, Tokyo, Japan  
Department of Pulmonary and Critical Care Medicine  
Mayo Clinic Minnesota  
Rochester, Minnesota, USA

Case #14: Patient Characteristics

4/2017:  
• 57 y 30 PY  
• LUL lesion & Bone mets  
• EGFR/ALK/ROS – Negative  
• PDL1 > 75%  
• ctDNA : BRAF P751S
How would you treat?

- Pembro 1\textsuperscript{st} line
- Combo Chemo+Pembro
- Chemo ±Bevacizumab
- Dabrafinib+Trametinib

Case continued

- Pembro 3 cycles
- PS=1 & general improvement
- After 4\textsuperscript{th} cycle
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  - CT RLL new lesions
What would you do next?

- Continue Pembro and wait
- Switch to 2\textsuperscript{nd} line (chemo without Pembro)
- Continue Pembro and add Chemo

What would you do next?

- Continue Pembro and wait
- Switch to 2\textsuperscript{nd} line (chemo without Pembro)
  - Continue Pembro and add Chemo
    - With fast clinical improvement
Discussion

• 1st line combo although PDL>75%
  • Higher ORR with combo
  • Very high PDL1 does not promise a Response
• Continue Pembro and add Chemo
• Payer’s perspective vs. combo first
Case Study #15 – Expert Faculty

Professor Nir Peled, MD, PhD, FCCP
iQ&A Case by Case Program Chair
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Pasi A. Jänne, MD, PhD
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Harvard Medical School
Lowe Center for Thoracic Oncology
Dana-Farber Cancer Institute
Boston, MA, USA

Heather Wakelee, MD
Professor of Medicine (Oncology)
Stanford University Medical Center
Stanford, CA

Case #15: 60y male, ex smoker (-30y; 10 PY)

OCT 2013:
• Low Back Pain
• Bone Mets for RLL lesion
• NSCLC Adenocarcinoma
• EGFR PCR – Technical failure
What would you do?

1. Cis/Pem/Bev
2. Carboplatin/Paclitaxel/Bev
3. Repeat Biopsy for further diagnosis
4. Repeat biopsy on progression

What would you do?

1. Cis/Pem/Bev
2. Carboplatin/Paclitaxel/Bev
3. Repeat Biopsy for further diagnosis
4. Repeat biopsy on progression
Next Generation Sequence

What would you do?

1. Erlotinib
2. Gefitinib
3. Afatinib
4. EGFR TKI + BRAF blockade
What would you do?

1. Erlotinib since 12/2013 + RT to sacral area
2. Gefitinib
3. Afatinib
4. EGFR TKI + BRAF blockade

Case cont. Feb 2014

Feb 2014:
- Skin rash
- Nausea & Vomiting
- AST & ALT elevation X 20
- Switch to gefitinib
- LFTs normalized within 3 weeks
Case cont. March 2014

March 2014:

![Images of chest CT scans]

Case cont. April 2015

April 2015:
- Visual disturbances and walking instability
- Brain MRI: Leptomeningeal spread
- CT/PET: Complete response

Your advise is:
1. WBRT
2. Pulse dose gefitinib
3. Afatinib
4. Osimertinib
Case cont. July 2015

- Post WBRT
- Cont. gefitinib
- Clinical improvement
- MRI progress
- Systemic Dexamethasone
- Steroid induced SAEs

Case cont.

**September 2015**
- Bevacizumab q 3wks
- Reduced brain edema
- Clinical stability till March 2016

**April 2016**
- Clinical PD
- Shift to Gefitinib
- Exitus 2 months later
Expert Roundtable Session #16

Case Study #16 – Expert Faculty

Professor Nir Peled, MD, PhD, FCCP
iQ&A Case by Case Program Chair
Head of The Cancer Institute
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Haiying Cheng, MD, PhD
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Sylvia Hassenfeld Chair in Lung Cancer Research
Co-Director, Drukenmiller Center for Lung Cancer Research
Professor of Medicine, WCMC
Memorial Sloan Kettering Cancer Center
New York, New York, USA
Case #16: 60y male, ex smoker (-30y; 10 PY)

**OCT 2013:**
- Low back pain
- Bone mets for RLL lesion
- NSCLC adenocarcinoma
- EGFR PCR – technical failure

**What would you do?**

1. Cis/Pem/Bev
2. Carboplatin/Paclitaxel/Bev
3. Repeat Biopsy for further diagnosis
4. Repeat biopsy on progression
What would you do?

1. Cis/Pem/Bev
2. Carboplatin/Paclitaxel/Bev
3. Repeat Biopsy for further diagnosis
4. Repeat biopsy on progression

Next Generation Sequence
What would you do?

1. Erlotinib
2. Gefitinib
3. Afatinib
4. EGFR TKI + BRAF blockade

What would you do?

1. Erlotinib since 12/2013 + RT to sacral area
2. Gefitinib
3. Afatinib
4. EGFR TKI + BRAF blockade
Case cont. Feb 2014

**Feb 2014:**
- Skin rash
- Nausea & Vomiting
- AST & ALT elevation X 20
- Switch to gefitinib
- LFTs normalized within 3 weeks

Case cont. March 2014

**March 2014:**

![Images of chest CT scans]
Case cont. April 2015

April 2015:
• Visual disturbances and walking instability
• Brain MRI: Leptomeningeal spread
• CT/PET: Complete response

Your advise is:
1. WBRT
2. Pulse dose gefitinib
3. Afatinib
4. Osimertinib

Case cont. July 2015

• Post WBRT
• Cont. gefitinib
• Clinical improvement
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April 2016
- Clinical PD
- Shift to Gefitinib
- Exitus 2 months later

The iQ&A Case-by-Case
*interactive* Precision Cancer Intelligence Zone

Focus on the Foundational Importance of Genomic Profiling and Molecular Markers to Identify Targetable, Actionable, and Therapeutically Significant Genomic Alterations in the Setting of Lung Cancer