FoundationOne®

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Presentation Outline

• Precision Medicine: Improving Patients Outcomes in 2017
• Targetable Alterations
• Why Do Conventional Molecular Diagnostic Assays Miss Alterations?
• Immunotherapy Markers
• In Conclusion
Precision Medicine: Improving Patient Outcomes in 2017
The use of Molecularly-Targeted Therapies has Revolutionized the Cancer Therapeutic Landscape

**Trastuzumab in HER2 positive breast cancer**


**Gefitinib in EGFR-mutated NSCLC**

Baseline

6 weeks


**Vemurafenib in BRAF V600E mutated melanoma**

Baseline

15 days


**Capmatinib in MET Exon 14-mutated in Lung Cancer**

Baseline

5 months

Rapid Market Growth in Targeted Drugs Will Increase the Use of Precision Medicine in the Clinic

- Up to 87% of oncology drugs in pharma pipelines are targeted therapies
- >850 targeted compounds in development
- >3200 active clinical trials supporting new drug development
- Over 500 BioPharma companies are developing targeted therapies
- Over twenty tumor types are being treated with new medicines that have been launched in the past five years

Source: 2016 IMS Institute Global Oncology Report
Studies Support the use of Personalized Medicine in Cancer Care

<table>
<thead>
<tr>
<th>Study Description</th>
<th>RR</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM arm</td>
<td>Non-PM arm</td>
</tr>
<tr>
<td><strong>Meta-analysis of 570 Phase II single agent studies published between 2010-2012</strong></td>
<td>31%*</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>Meta-analysis of 112 registration trials leading to FDA approval from 1998-2013</strong></td>
<td>48%*</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Followed patients with genomic profiling that subsequently enrolled in clinical trials</strong></td>
<td>19%*</td>
<td>9%</td>
</tr>
</tbody>
</table>

* p $\geq$ .05, PM: Personalized Medicine, RR: Response Rate, OS: Overall Survival,

Standard Molecular Diagnostic Tests Can Miss Oncogenic Alterations

Up to 50% of the genomic alterations described in NCCN guidelines for NSCLC can be missed using hot spot panels without supplemental FISH assays.¹

35% of targetable ALK fusions in NSCLC are missed using FISH.²

17% of targetable classical EGFR exon19 del and 83% of C-helical EGFR exon19 del were missed by standard focused molecular testing.³

As a result, potentially effective targeted therapies may not be identified.

Why Do Conventional Molecular Diagnostic Assays Miss Alterations?
### Three Different Approaches to Genomic Marker Assessment and Analysis

**Type 1 Tests: Single Gene Markers**
- In general, only single gene assessed (*e.g.*, immunohistochemistry, PCR, and FISH)
- Only genes commonly altered in a specific disease are tested
- Technical limitations such that rare and novel alterations will be missed

**Type 2 Tests: Hot-Spot Panels**
- Hot spot panels are designed to identify only pre-specified mutations in very limited areas of genes of interests
- Does not interrogate the entire coding region of genes
- May not detect all classes of genomic alterations
- Technical limitations such that rare and novel alterations will not be identified

**Type 3 Tests: Comprehensive Genomic Profiling via NGS**
- Sequences the entire coding region of genes relevant in human cancer (not limited to the high probability 'hot-spot' regions)
- Detects all four classes of genomic alterations: base pair substitutions, small insertions/deletions, copy number alterations (amplification and homozygous gene deletion), rearrangements/fusions
- High degree of accuracy (high positive predictive value)
- Simultaneous interrogation of all genes and alteration types conserves limited tissue
Next Generation Sequencing Panels Can Provide Comprehensive Genomic Profiling

• Comprehensive next-generation sequencing (NGS), or high-throughput sequencing:
  – Utilizes fragmented DNA libraries to simultaneously sequence hundreds of millions of DNA molecules
  – Comprehensively and accurately analyzes small quantities of DNA to identify rare and common variants
  – Used by Foundation Medicine for comprehensive genomic profiling
Type 2: Hot Spot NGS Panels

Gene 1

Exon 1  Exon 2  Exon 3  Exon 4

Can identify:
- Select base substitutions
- Short insertions/deletions
- Few copy number alterations
- No rearrangements

Hot spot approach
Only sequences select regions of a gene

= Clinically relevant alteration

Not for distribution
MKT-0029-01
Type 3: Comprehensive Genomic Profiling (CGP)

Comprehensive Genomic Profiling*
Sequences entire coding regions of genes
* = FoundationOne® test

Can identify:
- **Select** base substitutions
- **Short** insertions/deletions
- **Few** copy number alterations
- **No** rearrangements

Gene 1

Exon 1
Exon 2
Exon 3
Exon 4

Gene 1 = Clinically relevant alteration

**Hot spot approach**
Only sequences select regions of a gene

Can identify:
- **ALL** base substitutions
- **ALL** insertions/deletions
- **ALL** copy number alterations
- **Select** rearrangements

**Exon 1**
**Exon 2**
**Exon 3**
**Exon 4**
Comprehensive Genomic Profiling Detects Alterations Missed by Other Assays

- **Single Gene Testing** misses up to 35% of ALK$^1$ and 17% of EGFR$^2$ alterations.

- **Hot Spot NGS** 50% of targetable alterations can be missed without supplemental FISH$^3$.

- **Comprehensive Genomic Profiling** detects all classes of NSCLC clinically relevant alterations$^3$.

Frequency of selected drivers across 6,832 cases of NSCLC:

- ALK: 4.1%
- EGFR: 20.0%
- BRAF: 5.7%
- ERBB2: 6.0%
- RET: 2.4%
- MET: 5.6%
- ROS1: 1.5%
- KRAS: 32.0%

Note: Some KRAS mutations can be detected by hot spot assays, however they are not targetable.

Comprehensive Genomic Profiling Detects Novel, Unpredictable Alterations

Approximately 4-5% of patients with BRCA-mutated Breast, Ovarian, Pancreatic or Prostate cancer develop secondary resistance mutations that are unpredictable in nature and vary widely from patient to patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Original BRCA mutation</th>
<th>Acquired BRCA Resistance Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>S1982fs*22</td>
<td>S1971_S1989del</td>
</tr>
<tr>
<td>Patient 2</td>
<td>S1982fs*22</td>
<td>C1975_S1985del, K1735_E2004del</td>
</tr>
<tr>
<td>Patient 3</td>
<td>S1982fs*22</td>
<td>N1878_N1995del, S1882_K2244del, S1901_S2186&gt;L</td>
</tr>
<tr>
<td>Patient 4</td>
<td>S1982fs*22</td>
<td>D1754_S2072del</td>
</tr>
<tr>
<td>Patient 5</td>
<td>S1982fs*22</td>
<td>Q1987fs*7</td>
</tr>
<tr>
<td>Patient 6</td>
<td>S1982fs*22</td>
<td>splice site 6304_6841+12del550 (Exon 11)</td>
</tr>
<tr>
<td>Patient 7</td>
<td>S1982fs*22</td>
<td>splice site 5679_6841+194del1357 (Exon 11)</td>
</tr>
<tr>
<td>Patient 8</td>
<td>S1982fs*22</td>
<td>Exon 11-12 Deletion</td>
</tr>
<tr>
<td>Patient 9</td>
<td>S1982fs*22</td>
<td>Exon 11 Deletion</td>
</tr>
</tbody>
</table>

Presented at ASCO 2017
The NCCN NSCLC Guidelines Panel “strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials.”
Conventional Technologies Present Several Key Barriers to the Comprehensive Identification of Genomic Alterations

- Conventional approaches require multiple tests to cover all types of genomic alterations
  - Inefficient use of time
  - Wastes precious tissue samples

- Conventional approaches test only for individual genomic alterations

- Even “hot spot” and “tumor type” panels, which test for many mutations at once, can only identify mutations known prospectively

- Less invasive needle biopsies produce less tissue available for testing

- Therefore, there is a need for a single, comprehensive genomic test that can identify all types of genomic alterations of known cancer genes from a modest amount of tumor tissue.
Predicting Responses to Immune Checkpoint Inhibitors
The Immunotherapy Landscape is Increasingly Complex with an Unmet Need for Predictive Biomarkers

- Many patients do not respond to novel immuno-oncology therapies.
- Immune therapies can be expensive and some are associated with severe side effects.

Therefore Biomarkers that accurately stratify patients provide significant clinical benefit.

Adapted from: Batlevi et al. *Nat Rev Clin Onc*, 2015

Three Assays to Detect Biomarkers that Predict Response to Immune Checkpoint Inhibitors

**PD-1/PD-L1 IHC**
- PD-1/PD-L1 interaction can prevent the immune system from attacking cancer cells.
- IHC: Immunohistochemistry to detect expression levels of PD-1 and PD-L1
- NGS: Amplification of CD274 (PD-L1) detected by CGP correlates with PD-L1 positive IHC
- **PD-1 and/or PD-L1 IHC can be ordered concurrent with FoundationOne or separately**

**TMB Analysis**
- The TMB score represents the total number of coding somatic base substitution and indel mutations in a tumor specimen, per Mb of coding genome assessed.
- Tumors with more mutations are more likely to respond to immunotherapies given the increased likelihood they will have neoantigens that can be targeted by the immune system.
- **TMB analysis is included in the FoundationOne report**

**MSI Analysis**
- Microsatellite instability is caused by defects in DNA mismatch repair genes and results in greatly increased insertion/deletion mutation rate in microsatellite repeat genome regions.
- MSI is associated with positive prognosis and increased likelihood of response to immunotherapy.
- Pembrolizumab is an FDA-approved therapy for patients with high levels of MSI or dMMR, irrespective of cancer type.
- **MSI analysis is included in the FoundationOne report**
FoundationOne Overview

• Comprehensive genomic profiling (CGP) in a single assay utilizing next generation sequencing (NGS) to simultaneously detect all clinically relevant classes of genomic alterations for all solid tumors

• Focused on the entire coding region* of 315 genes and select intronic regions in 28 genes known to be clinically & biologically relevant

• Validated high accuracy achieved by high, uniform coverage: >99.5% of exons covered >250 times

• Requires only the small amounts of tissue routinely encountered in FFPE samples, including needle biopsies (≥50 ng of DNA)

• Provides a suite of patient-centric services to overcome potential financial barriers to testing

*only the promoter region is sequenced in TERT
FoundationOne Identifies at Least One CRGA in 86.4% of Samples

**Proven clinical utility**

<table>
<thead>
<tr>
<th><strong>% of genes with an alteration reported</strong></th>
<th>99.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% of samples with at least one clinically relevant alteration</strong></td>
<td>86.4%</td>
</tr>
<tr>
<td><strong>Mean/median number of alterations per sample</strong></td>
<td>5.1/4.0 (range 0-106)</td>
</tr>
<tr>
<td><strong>Mean number of clinically relevant alterations per sample</strong></td>
<td>2.2/2.0 (range 0-42)</td>
</tr>
<tr>
<td><strong>Median depth of coverage (unique DNA fragments)</strong></td>
<td>533x</td>
</tr>
</tbody>
</table>

**Clinical relevance defined as associated with:**
- FDA approved targeted therapy in tumor type
- FDA approved targeted therapy in another tumor type
- Open clinical trial of therapy relating to alteration in gene
FoundationOne has Experience in a Wide Range of Tumor Types and Alterations in over 100,000 Patients

**TYPES OF ALTERATIONS**
- **Base Substitutions**: 47%
- **Copy Number Alterations**: 3%
- **Insertions/Deletions**: 16%
- **Rearrangements**: 34%

**TUMOR TYPES**
- **Lung**: 23%
- **Unknown**: 13%
- **Breast**: 12%
- **Colon**: 10%
- **Ovarian**: 6%
- **Brain**: 6%
- **Pancreatic**: 4%
- **Uterine**: 2%
- **Hepatic**: 2%
- **Other**: 10%

Foundation Medicine, data on file
More information, less tissue

• Sample requirements

Can be run on small samples of routinely available tissue

≥ 40 μm tissue, of which a minimum of 20% is of malignant origin, on 10 unstained slides (optimal surface area: 25 mm²) or in an FFPE block.
FoundationOne is suggested for these clinical scenarios:

**Newly-Diagnosed**
- Stage IV NSCLC
- Carcinoma of unknown primary origin
- Stage IV rare or uncommon solid tumor
- Aggressive Stage IV solid tumor

**Insufficient Biopsy**
- FNA
- Thorac/paracentesis
- Endobronchial ultrasound

**Stage IV solid tumors**
- Limited response to standard of care
- High prevalence of clinically-relevant genomic alterations
FoundationOne Report Summarizes Results

**TUMOR TYPE: LUNG ADENOCARCINOMA**

**Genomic Alterations Identified***
- **EGFR** amplification, L858R, T790M
- **AKT2** amplification
- **CCNE1** amplification
- **CDKN2A/B** loss
- **TP53** splice site 376–1G>A

**Additional Biomarkers***
- Microsatellite status MSI – High
- Tumor Mutational Burden TMB – High 25 Mutations/Mb

**Additional Disease-relevant Genes with no Reportable Alterations Identified***
- **KRAS**
- **ALK**
- **BRAF**
- **MET**
- **RET**
- **ERBB2**
- **ROS1**

*For a complete list of the genes assayed and performance specifications, please refer to the Appendix.

**Clinically relevant genomic alterations detected**

**Checkpoint inhibitor response biomarkers**

**Additional alterations not detected**

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**PATIENT’S RESULTS***

- 7 genomic alterations
- 7 therapies associated with potential clinical benefit
- 2 therapies associated with lack of response
- 22 clinical trials

*Reduced sensitivity due to sample quality—See Appendix: Performance Specifications for details.
## THERAPEUTIC IMPLICATIONS

<table>
<thead>
<tr>
<th>Genomic Alterations 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><strong>EGFR</strong> amplification, L858R, T790M</td>
<td>Osimertinib</td>
<td>Cetuximab</td>
<td>Yes, see clinical trials sections</td>
</tr>
<tr>
<td></td>
<td>(−) Erlotinib</td>
<td>(−) Gefitinib</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Mutational Burden</strong></td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
<td>Yes, see clinical trials sections</td>
</tr>
<tr>
<td>TMB – High 25 Mutations/Mb</td>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microsatellite status</strong></td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI – High</td>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AKT2</strong> amplifications</td>
<td>None</td>
<td>Everolimus</td>
<td>Yes, see clinical trials sections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temsirolimus</td>
<td></td>
</tr>
</tbody>
</table>

* (−) Patient may be resistant to therapy
### FoundationOne Report: Genomic Alteration Description

#### GENOMIC ALTERATIONS

<table>
<thead>
<tr>
<th>GENE ALTERATION</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsatellite status MSH-High</td>
<td>Gene and Alteration: Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome. It generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2. The tumor seen here has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in &gt;30% of microsatellite markers and typically correlates with loss of expression of at least one, and often two, MMR family proteins, including MLH1. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes, which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC). Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers and has an estimated prevalence in the general population ranging from 1:600 to 1:2,000. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended. Frequency and Prognosis: MSI-H has been reported in 1.6–19.7% of ovarian cancer samples, including 3.8% (1/26) ovarian endometrioid adenocarcinomas, 10.0% (6/60) ovarian clear cell carcinoma (CCOC) (Strickland et al., 2016; ASCO Abstract 5514) and 84.6% (11/13) of ovarian cystadenocarcinomas. MSI-H was also frequently observed in ovarian cystadenomas (60.0% /6/10) and normal ovary tissue (78.6%; 11/14). No association of MSI-H with stage or survival was found. However, increased PD-1 expression and tumor-infiltrating lymphocytes were reported in MSI-H CCOC (Strickland et al., 2016; ASCO Abstract 5514). Potential Treatment Strategies: On the basis of emerging clinical evidence, MSI and associated increased mutational burden may predict sensitivity to anti-PD-1 immune checkpoint inhibitors, including the approved therapies nivolumab (Overman et al., 2016; ASCO Abstract 3501) and pembrolizumab. Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-H colorectal cancer (CRC) compared with MSS CRC (40% vs. 0%). Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with tumors with high MSI than those without (Overman et al., 2016; ASCO Abstract 3501). An earlier case study reported that nivolumab therapy resulted in a complete response in a patient with MSI-H CRC. In the Phase 1b KEYNOTE-012 trial, 4 patients with MSI-H gastric cancer, 2 patients reported partial responses, and 2 experienced progressive disease in response to pembrolizumab. The efficacy of immunotherapies in other MSI-H solid tumors is currently under investigation in clinical trials.</td>
</tr>
</tbody>
</table>

The Genomic Alterations section provides an interpretive statement for each genomic alteration, including:

- frequency of alteration
- its biological implication
- what it may mean for the specific patient
The therapies section provides details on approved therapies to which the patient’s cancer may be sensitive or resistant to based on their genomic profile.
The clinical trials section provides details on currently available clinical trials for which the patient may be eligible.
FoundationOne Report: Variants of Unknown Significance (VUS)

APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

Note: One or more variants of unknown significance (VUS) were detected in this patient’s tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

- Alterations or biomarkers that have either not been adequately characterized in the scientific literature and/or that are of unclear significance based upon genomic context
- Included for completeness should these alterations become clinically meaningful in the future
The appendix lists all reference information for studies used in curating the report.
FoundationOne: Concluding Remarks

• Broad, hybrid capture-based platform that interrogates entire DNA coding regions of 315 genes and select intronic regions of 28 genes known to be clinically & biologically relevant in solid tumors
• Offers comprehensive genomic profiling with identification of clinically relevant alterations that may be missed using traditional assays
• Validated high accuracy achieved by high, uniform coverage: >99.5% of exons with >250-fold coverage
• Requires only the small amounts of tissue routinely encountered in FFPE samples, including needle biopsies (≥50 ng of DNA)
• Provides genomic information that informs prognosis, and/or targeted therapeutic selection or avoidance, thereby impacting clinical management and patient outcome across all categories of solid tumors.