Role of Molecular Profiling in Tumors & Identifying Targets for Therapeutic Intervention in Patients with Advanced Cancers

Joshua H. Bilenker, MD
Chief Executive Officer, Loxo Oncology
Two Trends, One Triage Decision

Precision Medicine

Immuno-Oncology

NGS Profiling

Actionable Genomic Alterations

MSI and TMB
FDA Approved Drugs/ Validated Biomarkers

- BRAF
- BRCA1/BRCA2
- EGFR
- FLT3
- HER2
- IDH2
- KIT
- KRAS
- MSI/dMMR
- ROS1
- ALK
- PDGFRA/PDGFRB

- Melanoma
- Ovarian
- Lung
- AML
- Breast
- GIST
- CRC
- Tissue Agnostic
- MDS/MPD
Clinically actionable alterations in cancer

Patient samples (%)

1,579 unique gene alterations
N=2,112 patients tested

All Cancers Are Rare Cancers: The Story of the “Long Tail”

Testing the “Long Tail”

RESEARCH ARTICLE
High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial


843 pts tested → 199 received matched therapy
The “Long Tail” Matters Clinically

- Patients should do worse with each line of therapy
- Many did better
- Negative bias by excluding FDA approved matched therapies

The Rise of the Tissue-Aagnostic Drug

FDA Approves Merck’s KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

MAY 23, 2017

Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children
Advantages of Biomarker-Selected PD1 Use

- MSI-H

- TMB and other emerging biomarkers:
  - Inform risk: benefit decision
  - Differentiate competing drugs
  - Identify patients for combos

- Adverse events are biomarker-agnostic

- Emerging concerns over accelerated progression after stopping PD-1

- Financial toxicity

1. Pembrolizumab package insert
2. Nivolumab package insert
Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

Efficacy Regardless of Tumor Type

ETV6-NTRK3 breast cancer patient

14F, prior therapy: 4 lines of chemotherapy and repeated resections
Treated with larotrectinib under expanded access
TRK fusions are found in diverse cancer histologies. TRK Fusions are distributed widely but rarely; NGS is the most rational screening strategy.
A Scientific Tipping Point for NGS?

• The actionable target list is growing
  – FDA-approved
  – Trial referral

• Tissue-agnostic drug approvals argue for testing everybody, for both targeted therapy and IO

• May lead to better use of anti-PD1 therapies
  – TMB
  – MSI-H
But the Complexity!

Your waiting room:

Your lab director:

SHOW ME THE MONEY!!!!!!

Biopsy tissue requirements:

Logistics:
“Dining Out” for NGS

- It’s less work than cooking at home
- It’s more expensive
- Sometimes the service is slow
- You don’t know what goes on in the kitchen
- We often save it for special occasions
For a Long Time, Someone Else Picked Up the Check!
Today’s Patchwork of NGS

100,000-150,000 patients tested/yr, but 1 million new cases

Why?
...BUT NEW REIMBURSEMENT AND NEW TEST KITS PROMISE TO CHANGE THESE BEHAVIORS...
New Clarity On Reimbursement: CMS NCD Decision

CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients

- Reimbursement path established for any and all FDA-approved/cleared companion diagnostics
- Local MACs continue to govern local lab developed NGS tests
Easy-to-Use Kits Will Democratize NGS

TST170

Oncomine
Off the Shelf Kits Offer Cutting Edge Technology

- Their panels cover most relevant, actionable genes

- They cover amplifications and gene fusions
  - DNA + RNA

- They have manageable tissue requirements and can be performed locally
In-House Testing Reduces Overall Testing Costs

FMI buys custom reagents

Lab/hospital buys kit

+ Sales, Marketing, R&D spend, Overhead $$$

+ labor $
Local Testing: Near-Term Opportunities

- Illumina TST170 and various Thermo Fisher Oncomine versions can be purchased and validated locally as lab developed tests (LDTs).

- CMS decision acknowledges reimbursement pathway through local MACs:
  - Palmetto MolDX program (and other local MACs) had provided local coverage determinations on an indication-by-indication basis.

- May require dialogue with MAC medical director, especially as volumes increase.

- Commercial insurers will lag CMS, but can be expected to follow.
Local Testing: End Game

• Ion Torrent and Illumina earn FDA approval in 1-2 years

• Tests fall under CMS NCD

• Universal testing for all cancer patients, with test ordered at first diagnosis/ first availability of tissue specimen

• Reimbursement expected to be meaningful, and provide a healthy operating margin for the lab
Lung Cancer As Case Study

Biomarker Profile of Adenocarcinoma

Frequency of driver mutations in NSCLC

<table>
<thead>
<tr>
<th>Driver</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>3–7%</td>
</tr>
<tr>
<td>BRAF</td>
<td>1–3%</td>
</tr>
<tr>
<td>EGFR</td>
<td>10–35%</td>
</tr>
<tr>
<td>HER2</td>
<td>2–4%</td>
</tr>
<tr>
<td>KRAS</td>
<td>15–25%</td>
</tr>
<tr>
<td>MEK1</td>
<td>1%</td>
</tr>
<tr>
<td>MET</td>
<td>4%</td>
</tr>
<tr>
<td>NRAS</td>
<td>1%</td>
</tr>
<tr>
<td>NTRK1</td>
<td>1–3%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1–3%</td>
</tr>
<tr>
<td>RET</td>
<td>1–2%</td>
</tr>
<tr>
<td>ROS1</td>
<td>1–2%</td>
</tr>
</tbody>
</table>
Loxo Oncology Pipeline
LOXO-292

• A highly selective and well-absorbed drug that inhibits RET signaling deeply, i.e. > IC90 coverage

• RET fusion testing in lung cancer is already included in NCCN lung cancer guidelines

• Other activating RET alterations can be found in patients with thyroid, colon, breast and other cancers

• Enrolling since May 2017

• Upcoming Phase 1 update
LOXO-292 Patient Case: Systemic and Intracranial Tumor Response

Pre-treatment

LOXO-292 at 2 mo.

Pre-treatment

LOXO-292 at 2 mo.

Drilon et al. IASLC 2017. Abstract 10955. September 27, 2017 data cut-off date
Conclusions and Predictions

• We (oncologists) have become the first molecular subspecialty!

• Technology, cost and reimbursement barriers to NGS are rapidly falling away

• Comprehensive testing will democratize, no longer affecting patient referral/self-referral

• NGS will put money back into the healthcare system through the rational use of targeted therapies and IO