Genomics at FDA: 2018 Year-in-Review

PGRN Meeting
December 7, 2018

Mike Pacanowski
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
## Medical Products and Biomarkers
### Notable CY18 Approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease or Condition</th>
<th>Biomarker</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patisiran*, Inotersen*</td>
<td>polyneuropathy of hereditary transthyretin-mediated amyloidosis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tezacaftor* + ivacaftor</td>
<td>cystic fibrosis</td>
<td>responsive CFTR variant</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Migalastat*</td>
<td>Fabry disease</td>
<td>amenable GLA variant</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Ivosidenib*</td>
<td>relapsed or refractory AML</td>
<td>susceptible IDH1 mutation</td>
<td>Patient Selection</td>
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<tr>
<td>Binimetinib*, encorafenib*</td>
<td>metastatic melanoma</td>
<td>BRAF V600E/K mutation</td>
<td>Patient Selection</td>
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<tr>
<td>Dacomitinib*</td>
<td>metastatic NCSLC</td>
<td>EGFR exon 19 deletion or L858R substitution</td>
<td>Patient Selection</td>
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<tr>
<td>Larotrectinib*</td>
<td>solid tumors</td>
<td>NTRK gene fusion</td>
<td>Patient Selection</td>
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<tr>
<td>Gileritinib*</td>
<td>relapsed or refractory AML</td>
<td>FLT3 mutation</td>
<td>Patient Selection</td>
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<td>Lorlatinib*</td>
<td>metastatic NCSLC</td>
<td>ALK gene rearrangement</td>
<td>Patient Selection</td>
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<tr>
<td>Talazoparib*</td>
<td>advanced or metastatic breast cancer</td>
<td>Germline BRCA mutation</td>
<td>Patient Selection</td>
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<td>Afatinib</td>
<td>metastatic NCSLC</td>
<td>Non-resistant EGFR mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Amifampridine*</td>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>NAT2 genotype</td>
<td>Dosing</td>
</tr>
<tr>
<td>6-MP/TG</td>
<td>ALL/acute nonlymphocytic leukemia</td>
<td>TPMT/NUDT15 genotype</td>
<td>Dosing</td>
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<td>Avatrombopag*</td>
<td>thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>FVL</td>
<td>Warning</td>
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<tr>
<td>Lofexidene*</td>
<td>opioid withdrawal symptoms</td>
<td>CYP2D6 genotype</td>
<td>Informational</td>
</tr>
<tr>
<td>Elagolix*</td>
<td>severe pain associated with endometriosis</td>
<td>SLCO1B1 genotype</td>
<td>Informational</td>
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</table>

* New molecular entity
Medical Products and Biomarkers

• CDRH/in vitro diagnostic devices
  – 23andme Personal Genome Service Pharmacogenetic Reports authorized
  – ClinGen Expert Curated Human Variant Data recognized as source to support clinical validity

• Biomarker Qualification
  – Critical Path Institute/FNIH urinary nephrotoxicity biomarker panel (CLU, CysC, KIM-1, NAG, NGAL, OPN) to aid in detection of kidney tubular injury in phase 1 trials in healthy subjects
Guidance and Policy

Pharmacogenomic Data Submissions
Co-Development Concept Paper*
ICH E15 Definitions
Pharmacogenomic Data Submission - Companion*
Pharmacogenomic and Heritable Marker Tests
ICH E16 Qualification Submissions
Qualification Process for Drug Development Tools
ICH E16 Qualification Submissions
Clinical Trial Enrichment Strategies*
Clinical Pharmacogenomics
Drug-diagnostic labeling procedures
in vitro Companion Diagnostic Devices
Orphan Subsets Rule
Class Labeling for Companion Dx*
Adaptive Trial Designs*
IVD Risk in Oncology Trials*
Low-frequency Subsets
IVDs in Clinical Trials*
Laboratory-developed Tests*
Codevelopment*
Analytical Standards for NGS-Based IVDs
Public Databases to Support Clinical Validity for NGS IVDs
Single-gene Defects*
Pharmaceuticals in Clinical Trials*
Master Protocols*
Expansion Cohorts*
ICH E18 Genomic Sampling
Analytical Standards for NGS-Based IVDs
Public Databases to Support Clinical Validity for NGS IVDs
Single-gene Defects*
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Research*

• Systems biology and genomic approaches to predict target-mediated adverse events
• Strengthening safety signals through population pharmacogenomics
• Utility of early-phase biomarker investigations in detecting significant safety issues
• Cost drivers for biomarkers in drug development
• Drug development practices
  – Clinical development of synthetic oligonucleotides
  – Dose-ranging and titration
  – Racial/ethnic composition of clinical trials

* Reflects selected projects being led out of Genomics and Targeted Therapy Group in CDER’s Office of Clinical Pharmacology; many additional research projects related to genomics and precision medicine across FDA
Outreach

- Public Workshop on Weighing the Evidence: Variant Classification and Interpretation in Precision Oncology
- FDA/OCE Public Meeting on Relevant Molecular Targets in Pediatric Cancers: Applicability to Therapeutic Investigation FDARA 2017
- Public Workshop on Tissue Agnostic Therapies: Regulatory Considerations for Orphan Drug Designation
- Public Meeting on Drug Development Tool Process under the 21st Century Cures Act and PDUFA VI (upcoming – December 11, 2018)

- PrecisionFDA challenges: https://precision.fda.gov/challenges

OCE: Oncology Center of Excellence