FDA and the Challenges of Drug Review in the 21st Century:

Immunotherapies, Targeted Therapies, and Companion Diagnostics

Martha Donoghue, MD
Office of Hematology and Oncology Products
FDA
Disclosures and Disclaimer

• No financial relationships to disclose
• No discussion of off label or investigational use of specific products/devices
• The views expressed are those of the speaker and do not necessarily represent the opinions of the Food and Drug Administration
Breakthrough Therapy Designations for Cancer Therapeutics

Breakthrough Therapy Designation Requests

<table>
<thead>
<tr>
<th>Total</th>
<th>Granted</th>
<th>Denied</th>
<th>Pending</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>29</td>
<td>43</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

* As of 3/11/15

- Vast majority are targeted agents or immunotherapies
- FDA has granted accelerated or full approval to 12
With Breakthroughs Come Challenges

• **Shorter development timelines**
  - place pressure on manufacturing
  - can mean more limited safety data at time of approval
  - optimal dose?

• **Issues related to target patient population**
  - in vitro diagnostics
  - rare subsets

• **Feasibility of confirmatory trials**
Examples of Clinical Development Timelines

• Pembrolizumab
  – First-in human trial (FIH): December 2010
  – Breakthrough therapy designation: early 2013
  – Accelerated approval for advanced melanoma: September 2014

• Ceritinib
  – FIH: January 2011
  – Breakthrough therapy designation: early 2013
  – Approval in ALK-positive NSCLC: April 2014
Dose Finding

- Paradigm of “more is better” does not necessarily apply to targeted therapies or immunotherapies.
- Since 2001, FDA has approved ~26 small molecule kinase inhibitors for cancer indications.
  - Many of these therapies will be dosed chronically.
- Exposure/response relationship not always clearly defined.
- Dose modification for toxicities experienced beyond Cycle 1 frequently required.
- Increased number of postmarketing requirements to examine alternate dosing regimens.
  
  e.g., vandetanib
Dose Finding (cont.)

• Need to rethink 3+3 design and assumption that maximum tolerated dose is the best dose for future development

• Interdisciplinary approach to efficient dose finding throughout product development lifecycle required

• Upcoming FDA-AACR Dose Finding Workshop for Small Molecule Oncology Drugs: May 18 & 19, 2015
Oncogene-directed Therapies Typically Developed for Patient Subsets

Molecular Subsets Lung Adenocarcinoma

Percent Prevalence

- ALK 5%
- ROS1 1%
- EGFR T790M+ (20%)
- BRAF V600E (1%)

Pao W et al 2012 Nat Med
EGFR Mutations in NSCLC: Not All Equal (at least when it comes to response to afatinib)

- ~10% of U.S. NSCLC patients have somatic EGFR mutations
- Exon 19 deletion and exon 21 (L858R) substitution comprise ~ 85% of EGFR mutant NSCLC
- Rare “activating” mutations include exon 18 G719X and exon 21 L861Q
Afatinib Approval

- 1st line treatment of metastatic NSCLC with exon 19 deletions or exon 21 L8585R substitution as detected by FDA-approved test
- Companion Diagnostic: Therascreen EGFR RGQ PCR kit
- Registration trial randomization stratified by EGFR mutation status [exon 19 del (49%) vs exon 21 L858R (40%) vs ‘other’ (11%)]
- ‘Other’ contained a mix of mutations including resistant and sensitizing mutations
# Afatinib Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>GILOTRIF (N=230)</th>
<th>Pemetrexed/Cisplatin (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Deaths or Progressions, N (%)</td>
<td>152 (66.1%)</td>
<td>69 (60.0%)</td>
</tr>
<tr>
<td>Median Progression-free Survival (months)</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>(9.6, 13.6)</td>
<td>(5.4, 8.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.58 (0.43, 0.78)</td>
<td></td>
</tr>
<tr>
<td>Stratified Log-Rank Test P-value*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Deaths, N (%)</td>
<td>116 (50.4%)</td>
<td>59 (51.2%)</td>
</tr>
<tr>
<td>Median Overall Survival (months)</td>
<td>28.1</td>
<td>28.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>(24.6, 33.0)</td>
<td>(20.7, 33.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.91 (0.66, 1.25)</td>
<td></td>
</tr>
<tr>
<td>Stratified Log-Rank Test P-value*</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td><strong>Objective Response Rate (CR + PR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>116 (50.4%)</td>
<td>22 (19.1%)</td>
</tr>
<tr>
<td><strong>Response Duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>12.5</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*Stratified by EGFR mutation status and race. CR=complete response; PR=partial response
Afatinib Forest Plots in Label

**Median PFS (months)**

<table>
<thead>
<tr>
<th>EGFR mutation category</th>
<th>HR</th>
<th>GILOTRIF</th>
<th>Pem/Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del19/L858R (Common; N=308)</td>
<td>0.47</td>
<td>13.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Del19 (n=170)</td>
<td>0.28</td>
<td>13.7</td>
<td>5.6</td>
</tr>
<tr>
<td>L858R (n=138)</td>
<td>0.73</td>
<td>10.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Other (Uncommon; N=37)</td>
<td>1.89</td>
<td>2.8</td>
<td>9.9</td>
</tr>
</tbody>
</table>

**Median OS (months)**

<table>
<thead>
<tr>
<th>EGFR mutation category</th>
<th>HR</th>
<th>GILOTRIF</th>
<th>Pem/Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del19/L858R (Common; N=308)</td>
<td>0.82</td>
<td>30.3</td>
<td>26.2</td>
</tr>
<tr>
<td>Del19 (n=170)</td>
<td>0.55</td>
<td>31.6</td>
<td>21.1</td>
</tr>
<tr>
<td>L858R (n=138)</td>
<td>1.30</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td>Other (Uncommon; N=37)</td>
<td>3.08</td>
<td>15.9</td>
<td>NE</td>
</tr>
</tbody>
</table>

NE=Not estimable
26 patients treated with afatinib had “other” uncommon EGFR mutations with 9 unique mutation patterns. 0/26 achieved a CR; 4 achieved a PR. No responses seen with the following mutations: T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (n=1), exon 20 insertion (n=6), and L861Q alone (n=3).
How to Develop Multiple Agents Targeting Same Molecular Aberration?

- May not be feasible to run multiple separate trials in small patient populations

- Example: Second generation ALK inhibitors in ALK+ NSCLC

- Potential solution: Master protocol with shared control arm.
Master Protocols

“Umbrella”
Test impact of different drugs on different mutations in a single type of cancer
• BATTLE
• I-SPY2
• SWOG Squamous Lung Master (LUNG-MAP)

“Basket”
Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types
• Imatinib Basket
• BRAF+
• NCI MATCH
Evolving Development Paradigm

- Single drug/single test/all comers clinical trial model may be suboptimal for developing targeted therapies
- Biomarker-driven, but more complex clinical trials require substantial upfront preparation but offer efficiencies
  - FDA partnership with industry/cooperative groups crucial throughout the process
  - Co-development of in vitro diagnostic(s) critical - biomarker assays need to have adequate performance characteristics capable of rapid turnaround for timely treatment assignment or randomization
In Vitro Diagnostics

- An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

- Without knowledge of the test performance, drug review is compromised and drug cannot be adequately labeled.

- When IVD used for patient selection in clinical trials, an investigational device exemption (IDE) may be required:
  - Close collaboration between OHOP and CDRH routine during IND review process
  - Pre-submission meeting for risk determination is often recommended.
In Vitro Diagnostics

• Contemporaneous approval of therapeutic and companion diagnostic is required, with certain exceptions
  – Benefit/risk determination when therapy is for serious or life threatening disease with no alternative treatment

• Labeling of therapeutic product points to a type of approved or cleared IVD companion diagnostic, not generally a specific test name, although test used in trials may be mentioned in certain sections

• Potential issues with interchangeable use of IVDs to select therapies in the “real world” – need for uniform analytic standards.
Large Response Rates: When is Clinical Equipoise Lost?

Giant Cell Tumor of Bone

Before denosumab

After 2 months

- Demirsoy U et al. 2014 J Pediatr Hematol Oncol
Immunotherapies: Unique Patterns of Response and Unique Toxicities

• Concept of “pseudoprogresion” prior to response
  – Exception (~5%), not rule
  – Criteria for treatment beyond RECIST progression should be clearly defined

• RECIST vs. Immune-related Response Criteria (IrRC)
  – RECIST remains most appropriate standard for regulatory decision making
  – Allows comparisons to available therapy
Challenges

• For PD1/PDL1 inhibitors, questions remain regarding whether PDL1 will be a necessary predictive/selection biomarker, how PDL1 assays will be used in the clinic, whether there are better predictive biomarkers than PDL1, etc.

• Characterization of immune-mediated adverse events (such as colitis, pneumonitis, endocrine disorders, renal dysfunction, neurologic disorders, rash) important but requires careful, pre-specified data collection
  – Concomitant medications (corticosteroids)
  – Dose discontinuation and delays
  – Exclusion of alternative etiologies
  – Re-challenge
Patient-Centered Outcomes

- Data from clinical outcome assessments (COAs) rarely incorporated into patient labeling for hematology/oncology products
  - Exceptions: e.g., ruxolitinib (demonstrated improvement in total symptom score over placebo in myelofibrosis), abiraterone (delayed median time to opiate use for prostate cancer pain compared to placebo and delay in patient reported pain progression)

- Issues related to rarity of double blind, randomized controlled trials in oncology, missing data, typical absence of symptoms related to cancer at baseline, lack of validated instruments
Patient-Centered Outcomes

• OHOP recognizes need for inclusion of COA data into product labeling and importance of not “sacrificing the good for the perfect”

• In collaboration with Study Endpoints and Labeling Development Team (SEALD) and as part of an ongoing effort across CDER, OHOP is working to:
  – Encourage use of clinical outcomes assessment tools in oncology trials and standardize advice to stakeholders
  – Develop approaches to careful review of COA data as part of the overall benefit:risk determination of a regulatory submission
  – Include high quality data from COAs into product labeling, when appropriate
Expanded Access in the News

Twitter storm forces Chimerix's hand in compassionate use request

Texas woman with cancer pressuring experimental drug maker for "compassionate" access

Using experimental drugs and vaccines against Ebola is ethical, WHO panel says

Push to Get Experimental Drugs With Social Media Pressure on the Rise

Colorado first state to pass ‘Right to Try,’ or the ‘Dallas Buyers’ Club’ law
Expanded Access Programs (EAPs) Requirements under 21 CFR 312.305

- Serious or immediately life threatening illness/condition
- No comparable or satisfactory alternative therapy
- Therapy cannot be obtained under another IND or protocol
- Potential benefit justifies the potential risks
  - risks are acceptable in the context of the disease
- Providing expanded access will not interfere with its clinical development for marketing approval
EAP Implementation

Doctor

Commercial Sponsor

Patient

FDA

IRB
Pros and Cons EAPs

Pros

• Provides access to potentially lifesaving therapies
• Bridges gap between late stage development and FDA approval
• Can provide clinical data to support development

Cons

• Limited safety and efficacy information
• Potential for overestimation of benefit and underestimation of risks
• Can circumvent clinical trial process
• May be limited by drug supply
• Paperwork/Requires resources!
Potential Barriers to Expanded Access

• Variable understanding regarding EAP process in community
• Variable time and monetary resources to devote to expanded access (physician, patient, manufacturer)
• Limited supply of investigational therapy
• Requirement for IRB approval
• Concerns over liability, inconsistent approach to determining who gains access to therapy
Potential Ways to Harmonize Goals of Expanded Access and Drug Development

- Timely creation of intermediate access and treatment INDs to facilitate aggregation of data

- Encourage examination of eligibility criteria for registration trials
  - Are they too stringent??
  - Opportunities for expanding patient base?

- House single patient EAPs within the commercial sponsor IND when possible
  - Facilitates analysis of clinical data that can support marketing application
  - Particularly important for rare diseases
  - May assist with identification of “ultra responders” in oncology
Thank you for your attention!
Acknowledgements

• Much thanks to Gideon Blumenthal, Sean Khozin, Geoff Kim, Paul Kluetz, and Marc Theoret for their support and input.