Breakthrough Therapy Designation from an Oncology Perspective

NORD Rare Diseases and Orphan Products
Breakthrough Summit
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DOP2, OHOP, OND, CDER
If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.
The Benefits of Breakthrough Designation

- All the benefits of Fast Track Designation
  - Frequent interactions with review team
  - Eligibility for priority review
  - Eligibility for Rolling review

- Intensive guidance on efficient drug development

- Organizational commitment
  - Involve Senior Managers and experienced reviewers
  - Assign a cross-disciplinary project lead
Breakthrough Requests

- Not just a drug, must be for a specific disease indication
- Intended... to treat a serious or life threatening disease

<table>
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<tr>
<th>Total Requests</th>
<th>188</th>
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<tbody>
<tr>
<td>Hematology/Oncology</td>
<td>81  (43%)</td>
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<tr>
<td>All others in CDER</td>
<td>107 (57%)</td>
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Date Range: 9/1/2012 through 9/24/2014
Requests to Center for Drug Evaluation and Research (CDER)
“Transformative Therapies”
Ideal Breakthrough Request in Oncology

- Adequate sample size of patients
- Markedly higher response rate relative to available therapies
- Substantial duration of response
- An indication with no or few effective available therapies
- A novel mechanism, first-in-class, biologic plausability
- Safety profile that is as good or better than available therapies
- Early in Development provides maximum benefit of BT Designation
Analysis of BTD submissions to OHOP
For those that have been Denied:

• Inadequate magnitude of benefit

• Very small sample size
  – Preliminary clinical data, not Premature clinical data

• Post-hoc subgroup analyses for OS or PFS in randomized trials failing their primary endpoint
  – Unclear Mechanistic/biologic plausibility
  – Lack of internal consistency

• Inadequate benefit in setting of significant toxicity
Opportunities and Challenges

• Like any new program, FDA and industry will need experience with the program to identify areas for improvement.
Granting Breakthrough Therapy:

- **Opportunity:**
  - OHOP recommends an informal teleconference prior to formal submission for a preliminary assessment to sponsor

- **Challenges:**
  - What is the right threshold for granting a BT designation?
  - What constitutes available therapy?
  - How late is too late? Timing of BT designation request
Implementing Breakthrough Therapy:

– **Opportunities:**
  - “All Hands on Deck” for Transformative Therapies:
    – Aligns and Prioritizes Key FDA review teams (Clinical, Statistics, Manufacturing, Clinical Pharmacology, Toxicology, Inspections)
  - Optimizes communication between FDA and Sponsor

– **Challenges:**
  - Resource saturation for both FDA and Sponsor?
  - On what basis should we rescind a BT therapy?
  - Manufacturing timelines can be a bottleneck
Case Study of breakthrough in action: ceritinib in patients with crizotinib-refractory ALK+ metastatic lung cancer
Lung Cancer: a common malignancy comprising 100s (1000s?) of rare diseases

- Better Science
- Faster, cheaper, better molecular profiling techniques
- More rational drug discovery and drug development
Lung Cancer Pie Chart circa 2003: based predominantly on light microscopy
Lung Adenocarcinoma pie chart in 2014

- **Unknown**
- **KRAS**
- **EGFR**
- **ALK fusions**
- **PIK3CA**
- **AKT1**
- **MAP2K1**
- **NRAS**
- **ROS1 fusions**
- **KIF5B-RET**

- **Braf inhibitor?**
- **anti her2?**
- **Crizotinib**
- **Ceritinib + many in clinical development**
- **erlotinib afatinib + many in clinical development**
- **ROS1 inhibitor?**
- **RET inhibitor?**
Better science begets more rational drug development

Crizotinib in pts with ALK+ NSCLC
Kwak et al, NEJM, 2010; Yang et al Lancet 2012

Afatinib in pts with EGFRdel19 NSCLC

Kwak et al, NEJM, 2010; Yang et al Lancet 2012
1st generation ALK inhibitor: crizotinib

2nd generation ALK inhibitor: ceritinib

- **Pre clinical studies**: potent and selective ALK inhibitor to overcome intrinsic and acquired mechanisms of crizotinib resistance
- **January 2011**: First in human phase 1 initiated
- **March 2013**: Breakthrough Therapy designation
  - High/ durable ORR in early studies in ALK+ patients who progressed on crizotinib
- Frequent interactions with sponsor ensued
Ceritinib in ALK+ NSCLC (continued)

- November 2013: Rolling Submission begins
- December 2013: final component of NDA submitted
- Priority review (PDUFA date August, 2014)
- Expedited review initiated (internal target of April 2014)
- “late” in cycle, cGMP issue identified
- Meeting with senior CDER management, rapid deployment of foreign inspectors, resolved expeditiously
- April 2014: Accelerated Approval- response rate and durability in single arm study
- 3.25 years from FIH study to FDA approval
Take home/ lessons learned

• More breakthrough therapies than originally envisioned
• Appears to be another effective tool in facilitating expedited development for transformative therapies
• Challenges:
  – Manufacturing: lose years from typical clinical development to scale up and final commercial product launch
  – Clin pharm: less opportunity for pre-marketing dose optimization
  – Device: companion diagnostic development may lag behind clinical data
  – Clinical: how do you assess safety, define clinical benefit/ value with smaller trials, earlier endpoints?
Special Thanks

- Paul Kluetz
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