Session 2: What is the status of the technologies of "precision medicine"?

- Gideon Blumenthal, MD, Clinical Team Leader, Thoracic and Head/Neck Oncology, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration
Oncology Drug Development in the Era of Precision Medicine: FDA Perspective

Gideon Blumenthal, MD
Clinical Team Leader
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Disclosure Information

• I have no financial relationships to disclose
Expedited programs
Approval Pathways for Drugs and Biologics

**Traditional (Regular) Approval**

Based on improvement in a *direct measure of clinical benefit*: Longer life, better life, or established surrogate

**Accelerated Approval**

Initiated in 1992 (HIV crisis- using viral load as surrogate)

Based on improvement in *surrogate endpoint reasonably likely to predict clinical benefit* over available therapy

Need post-marketing studies to confirm benefit

Used frequently in Oncology
If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.
Breakthrough therapy designation

• Signed into law in 2012 (FDASIA)
• For serious life threatening disease, a drug, based on preliminary clinical evidence, has substantial improvement over available therapy
• About 40% of BT requests across drug center have been in Oncology
  • About a third of these have been granted
• Of 9 oncology new molecular entities approved in 2014, 5 were breakthrough designated
• Pace of breakthrough therapy designations in oncology has continued throughout 2015
Breakthrough Therapy: Opportunities and Challenges

• 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:
  • What is the right threshold for granting a BT designation?
  • What constitutes available therapy?
  • How late is too late? Timing of BT designation request
  • Resource saturation for both FDA and Sponsor?
  • On what basis should we rescind a BT therapy?
  • Manufacturing timelines can be a bottleneck
Examples of Breakthrough therapies granted and subsequently approved in NSCLC

- Ceritinib for crizotinib-refractory ALK+ NSCLC based on expansion cohort in Phase 1
  - First in human to Accelerated approval 3.25 years
  - Expeditious resolution of “late” in cycle cGMP issue
- Pembrolizumab for PDL1 positive 2nd line NSCLC based on expansion cohort “validation set” in Phase 1
- Nivolumab for non-squamous NSCLC- 3.5 month review
- Osimertinib for T790M EGFR mutation NSCLC after progression on EGFR TKI
  - First in Human to Accelerated Approval 2.5 years
Next generation trials
**Traditional drug development paradigm**

*Linear, sequential, drugs and companion diagnostic development*

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**Pharmaceutical R&D process and decision points**

- **Research ~7yrs**
  - New Medicines Proposal
  - Target Validation
  - Lead Identification
  - Lead Optimization

- **Development ~8yrs**
  - EIH Enabling Pre-clinical safety
  - Phase I Early clinical safety
  - Phase II Proof of concept
  - Phase IIb Early clinical efficacy
  - Phase III Key registration trials
  - Lifecycle management (phase IV)

**Diagnostic development process and milestones**

- **Pre-clinical assay development ~2yrs**
  - Biomarker Discovery
    - BM Dx candidate identified
  - Analytical Development
    - Translation of assay onto a clinical diagnostic platform
  - Replication
    - Confirm markers and reproducibility of assay

- **Clinical Phase ~3yrs**
  - Phase I Sensitivity & specificity
  - Phase II PPV and NPV
  - Phase III Clinical benefit and Cost effectiveness
  - Registration
    - Clinical impact
    - Clinical utility
    - Clinical validation

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R&D = Research & Development; BM = Biomarker; PPV = Positive predictive value; NPV = Negative predictive value
Vision for drug development in Oncology

New Drug Candidate

Exploratory Human Trials (POM, POE)

Surrogate Endpoints

Limited Approval

Exploratory Biomarkers

Companion Diagnostics

Fail Early

Additional Approvals

New Hypotheses

Companion Diagnostics

Exploratory Biomarkers

Post-Marketing Surveillance

Translational Research

POM = Proof of mechanism; POE = Proof of efficacy

Kapil Dhingra Annals of Oncology, September 2015
Challenges with “old paradigm”

- **MET**
- **ROS1**
- **KRAS**
- **p53**
- **EGFR**
- **ALK**

Platinum doublet

\[ N=800-1200 \]

- Platinum doublet + drug X
- HIGH RISK PHASE 3 FAILURE OR CLINICALLY SMALL EFFECT

Challenges with “new paradigm”

- **ALK**

Targeted Therapy

\[ N=100-200 \]

Large, Clinically Meaningful Effect

- 1% Prevalence of even common tumors: Number needed to screen > 100 patients → need to reduce screen failure rate
- 1 drug/1 biomarker per trial unsustainable → Need common multi-analyte platform(s)
- Need Rapid Learning/Failure/Confirmation
Rare is common and the “long tail” phenomenon

Patients with TARGET Gene events by category (%)


Master Protocols

**Umbrella**
Test impact of different drugs on different mutations in a **single type of cancer**
- BATTLE
- I-SPY2
- 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
Public-Private Partnership: Novel Collaboration in Oncology Clinical Research
Future Lung-MAP Trial Schema (Reflecting Revisions # 3 & 4)

Matched Sub-studies
- PI3K
- CDK4/6
- FGFR
- HRD

Non-match Sub-studies
- Checkpoint Naive
  - Nivo/Ipi
  - Nivolumab
- Checkpoint Refractory
  - MEDI4736/Treme

GDC-0032 | Palbociclib | AZD4547 | BMN 673

1 Revision #3: Expected late October 2015
2 Revision #4: Expected December 2015/January 2016

NOTE: S1400A (MEDI4736) Open arm sub-study is expected to complete accrual by Oct/Nov
Incorporating the patient voice
Traditional Oncology Endpoints

**Direct Clinical Benefit**

- **PRO**
  - Measures symptoms/function
  - Challenges include missing data, un-blinding

- **PFS**
  - Accounts for stable disease
  - Ascertainment bias/Informed censoring
  - Magnitude important!!
  - Can not be assessed in single arm trials

- **ORR**
  - Smaller/quicker
  - Binary
  - No stable disease
  - Can be assessed in single arm trials

- **OS**
  - Bigger and longer studies
  - Confounded by cross-over and subsequent therapies
  - Can not be assessed in single arm trials

**Surrogate**

- **Subjective**
- **Objective**
Efforts to incorporate patient voice

• Validating lung cancer specific patient reported outcome (PRO) as a drug development tool

• Patient focused drug development meeting
  • June, 28, 2013

• Lung cancer twitter chat
Its been a busy time in lung cancer....
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