Current Topics in the Development and Regulatory Approval of Cancer Therapies

Michelle Ponpipom
Associate Director
Worldwide Regulatory Affairs
Merck & Co., Inc.

Oncology Drug Development: Dynamic & Evolving
• The paradigm for oncology drug development is changing rapidly
• The complexity of information concerning tumor genetics and signaling pathways is growing and brings greater opportunities for personalized medicine
• There is an unprecedented number of anti-cancer therapies in development and standard of care changes quickly
• Past precedent is no longer enough to predict future success
Traditional Oncology Drug Development

- Classical chemotherapy-cytotoxic mechanisms of action
- Patient populations defined by organ, histology, stage and/or line of therapy
  - **First-line** non-small cell lung cancer
  - **Metastatic** colorectal cancer
  - **Relapsed, refractory** ovarian cancer
- Efficacy evaluated in the overall population
- Clinical studies conducted in North America & Europe
- Combination therapy developed after monotherapy
  - Agents typically combined with standard of care
- IV formulations

Present & Future of Oncology Drug Development

- Targeted agents for chronic treatment
- Biomarker-driven patient populations
  - Biomarker used for prospective patient selection
  - Retrospective analysis currently used to identify & support biomarker
- Efficacy evaluated within a pre-defined subpopulation
  - Metastatic breast cancer in pts whose tumors over-express HER2
  - Kit (CD117) positive gastrointestinal stromal tumors
  - EGFR over-expressing, KRAS wild-type metastatic colorectal cancer
- Multi-national trials increasing in scope
- Development of novel combinations for multiple pathway inhibition
- Oral Formulations & Pediatric Formulations

Regulatory Affairs – Bridging the Gap

- Begin with the end in mind:
  - Patient access to clinically important therapies
- Years of preclinical and clinical development will not achieve this end goal without the execution of an effective regulatory strategy
- Regulatory strategy is developed in collaboration with in-house scientists and clinicians, external scientific leaders in the oncology community, and regulatory agencies worldwide
Current Regulatory Considerations - Oncology

• Assessment of Regulatory Opportunities
  – Accelerated Approval Paradigms
  – Priority Review Paradigms
  – Orphan Designations

• Clinical Study Development Issues
  – Endpoints, Population, Comparators, Combinations

• Oncology clinical practice changing rapidly
  – Impact of a changing clinical/regulatory standard on oncology drug development

Assessment of Regulatory Opportunities

Accelerated Development Paradigms
Accelerated Review Paradigms
Orphan Designations
## Oncology - Regulatory Interactions

- Early and ongoing dialog with key agencies is critical
  - FDA input on proposed clinical program
  - Special Protocol Assessment helpful for novel development programs
  - EU Scientific Advice from CHMP
  - Consultations with Japan’s PMDA
  - Interactions with more than 85 agencies worldwide

- Regulatory options are explored based on unmet medical need, orphan diseases, life-saving potential and/or new MOA for therapies
  - FDA Fast Track (rolling submission)
  - Accelerated approval (surrogates/unmet need) by FDA
  - Priority Review (6 months) by FDA
  - Accelerated reviews by EU, Canada, Australia
  - Orphan Designation

## US Options for Acceleration

### Fast Track Designation
- Intended for products that address an unmet medical need
- Formal mechanism to interact with FDA using approaches available to all applicants
- Benefits include:
  - Option of submitting NDA in sections rather than all components simultaneously
  - Option of requesting evaluation of studies using surrogate endpoints
  - Independent of Priority Review and Accelerated Approval.
  - Applicant may use any or all of the components of Fast Track without formal designation

### Priority Review
- Reviews for NDA/BLAs are designated as either Standard or Priority.
  - Standard designation sets target date for FDA action at 10 months
  - Priority designation sets the target date for FDA action at 6 months
- Intended for products that address an unmet medical need
- Designation granted after a marketing application has been submitted to FDA

### Accelerated Approval (AA)
- Allows for accelerated approval for life-threatening diseases based on preliminary evidence
  - Provisional approval based on surrogate marker likely to predict patient benefit
  - Commitment to complete studies to formally demonstrate patient benefit
  - AA designation does not necessarily lead to a Priority Review

## Orphan Drug Designations

- **Orphan Drug**: A drug developed to treat rare diseases
- **Orphan Drug Designation (ODD)**: Agency approval of a specific product for a specific rare disease based on non-clinical, clinical, and epidemiological data
- **Orphan Drug Designation is not** a marketing authorization
- **Criteria for Orphan Drugs** are country-specific
  - **US**: Diseases affecting <200,000 people
- **Development generally follows** the same path as non-orphan programs
- **Advantages of orphan designation** include special protocol assistance, evaluation of marketing applications, fee reductions, enhanced marketing exclusivity (broader, longer), and possibly tax credits
Clinical Development Issues
Endpoints, Population, Comparators, Combinations

Endpoints

• Overall Survival
  - Global, gold standard
  - Accurate for event and date; Not subject to investigator bias
  - Requires larger sample size and longer follow-up
  - Crossover and secondary therapy may obscure the results
• Progression Free Survival (PFS)
  - Shorter follow-up
  - Results not obscured by secondary therapy
  - Potential for bias due to sensitivity to timing of the assessment
  - Regulatory acceptability is in part dependent upon tumor type.
• Time to progression (TTP)
  - Acceptable only if demonstrated to be a reliable surrogate for clinical benefit
  - Most applicable to cytostatic agents; does not require tumor size reductions.
• Overall Response Rate (ORR)
  - Reliability of response rate to predict survival varies by tumor type.
  - ORR alone is more likely to support accelerated approval than full approval.
• Quality of Life (QOL)/Patient Reported Outcomes (PRO)
  - Accepted when prospectively defined in a blinded, controlled trial
  - QOL/PRO instruments are expected to be validated
  - Changes in QOL scores must be correlated with clinically meaningful changes

Personalized Medicine – Biomarkers Opportunities

• Advances in understanding the molecular basis of disease have led to identification of specific targets for intervention which may be reflected by biomarkers
• Biomarkers (BMX) are the key to the realization of Personalized Medicine
  - The right drug at the dose for the right patient at the right time
• Targeting therapy at patients most likely to benefit
  - Enrollment of ‘all comers’ may result in a negative study if therapy is only active in BMX+ population
  - Patients not likely to benefit will be exposed to toxicity of investigational therapy
Personalized Medicine–
Biomarker Challenges

• Prospectively identifying BMX likely to predict response
• Availability of a validated in vitro diagnostic (IVD) for patient selection (and likely labeling)
  – Issues relating to CLIA Certification vs CDE registration
• Potential need to evaluate efficacy in both BMX+ and BMX- patients
  – Large trial size for powering on BMX+ while enrolling all comers
  – Inclusion of patients in study who are not likely to receive maximum benefit or only experience toxicity
• Rapidly evolving field; identification of new biomarkers can have a tremendous impact on ongoing clinical trials
  – e.g., KRAS and colorectal cancer trials

Multinational Trials

• Multinational trials are increasing in frequency & scope
  – Large number of investigational therapies creates competition for patients
  – Best supportive care comparisons are difficult to enroll in US
  – Many Asian countries require local clinical data for registration
• US population may represent only a portion of the total patient database for registration trials
• Regional differences in standard of care (approved agents, clinical practice, dose) may complicate trial design
• Careful evaluation of ethnic sensitivity of compound is necessary to ensure generalizability of data
  – Difference in medical practice
    • Treatment differences, especially prior lines of therapy
    • Differences in diagnosis
    • Reporting of AEs
  – Cultural differences in metabolism (e.g., genetic polymorphism)

New Paradigm: Development of Therapies in Combination

• Combination therapy targeting complementary pathways may have synergistic effects compared to monotherapy
  – Compensatory mechanisms may exist in tumors that overcome inhibition of one pathway
• Development of two new molecular entities represents a new paradigm in oncology
  – Determination of monotherapy activity at the same time as combination activity
  – Contribution of each agent vs combination of two
• Selection of optimal targets is complex
Oncology Regulatory Affairs – Today

- Regulatory Affairs applies the core disciplines of pharmacy education.
- The goal of regulatory affairs is to provide patients with access to safe and effective therapies that address clinically important indications, based upon sound clinical, preclinical & manufacturing data.
- As the field of oncology changes rapidly, the role of regulatory affairs is to ensure that drug development starts and proceeds with the end in mind.
- Regulatory affairs is a liaison role; integrating the internal drug development with the external environment of the regulatory agencies and medical practice.
  - Building upon past precedent, understanding current environment and anticipating future directions.