

**Current Topics in the
Development and Regulatory
Approval of Cancer Therapies**

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**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

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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

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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

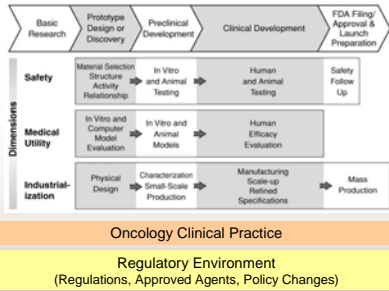
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Regulatory Affairs – Bridging the Gap

- 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

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Regulatory Affairs: Working in Multiple Dimensions



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


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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


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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


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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
