A New Paradigm for Oncology Drug Development:
Research, Regulation, & Policy

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Friends of Cancer Research
Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients.

A unique model to create a path to better drug development and approval through scientific, regulatory, and legislative solutions.
Research:

Novel Partnerships – Lung-MAP
Current Challenges

• Each potential new therapy is typically tested independently from other therapies seeking to treat the same condition

• For every new trial, the protocol must be reviewed by a number of oversight entities
  – new phase III trials requires an average of 36 administrative or regulatory approvals and averages more than 2 years

• Approximately 4% of adult cancer patients enroll in clinical trials
  – inability to meet accrual goals is a frequent factor causing trials to close, wasting time, money, and limited patient resources

• New therapies molecularly targeted against specific mutations may be present in only a fraction of the patient population
A groundbreaking collaborative approach to clinical trials.

- To address the issue of modernizing the process with innovative approaches and new clinical trial designs
- Leaders from FDA, NIH, NCI, academic research centers, patient advocacy organizations and the private sector to reach consensus on the design of a biomarker-driven, multi-drug, multi-arm Phase 2/3 registration trial in lung cancer.
- White paper was published by these leaders as part of the 2012 Friends of Cancer Research – Brookings Institution, Conference on Clinical Cancer Research.
- This paper served as the foundation for the protocol that became Lung-MAP.
Trial Structure

- **Primary Endpoint:** Response rate assessed at “rolling” interim analyses (no temporary closure) determine if a protocol arm proceeds to phase III portion. Each arm independently powered for PFS with OS comparison.

- **Goal:** minimum of 4 arms open at any time, to ascertain a reasonable chance for patients to be “biomarker positive”.

- Marker-negative patients enter “non-match” group treated with anti-PD-1 vs. anti-PD-1 + CTLA-4 agent to evaluate the combination and establish annotated repository
Lung-MAP Protocol Schema

Biomarker-Driven Sub-Studies

- S1400B PI3K+
- S1400C CCGA+*
- S1400D FGFR+
- S1400G HRRD+*

**Single Arm Phase II**
- GDC-0032 vs. TBD
- Palbociclib vs. TBD
- AZD4547 vs. TBD
- PARP vs. TBD

**Potential for Randomized Phase III**
- GDC-0032 vs. TBD
- Palbociclib vs. TBD
- AZD4547 vs. TBD
- PARP vs. TBD

Non-match Sub-Studies

- S1400I Checkpoint Naive
- S1400F Checkpoint Refractory

- Nivolumab/Ipilimumab vs. Nivolumab
- PD-L1 / CTLA-4 Combination

Two new sub-studies – S1400G and S1400F – added within 6 months; Additional Sub-studies expected within 6-9 month period

*CCGA = Cell Cycle Gene Alternation, HRRD = Homologous Recombinant Repair Deficiency

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Key Points:
- Patient population: Allow any histology not just squamous
- Trial with registration-intent
- All patients receive NGS
- Patients assigned to a sub-study based on biomarker results or to non-match sub-study
- Assume most patients will be immunotherapy-refractory and non-match sub-studies will be designed accordingly

Questions:
- Can this be a registration strategy for IO combos?
- How does allowing 1st line IO impact registration for Biomarker-driven sub-studies?
- Should we include non-squamous patients in the matched sub-studies?

Proposed Lung-MAP Re-Design

Stage IV Non-Small Cell Lung Cancer
(All histology)
2nd Line or higher
(Chemo or Immuno-therapy Refractory Patients)

Centralized NGS Biomarker Profiling

NGS-Matched Sub-studies
- Biomarker 1 Positive
  - Sub-study 1
    - Biomarker-driven Targeted Therapy
    - Evaluate: Investigational therapy 1
- ...Biomarker n Positive
  - ...Sub-study n
    - Biomarker-driven Targeted Therapy
    - Evaluate: Investigational therapy n

Non-NGS-Matched Sub-studies
- IO Naive
  - S1400!
    - Nivolumab + Ipilimumab vs. Nivolumab
  - Randomization
- IO Refractory
  - ...IO Sub-study m
    - IO combo m
  - Common Control
    - Dealer’s choice based on histology

Phase 2
- R vs.
- Investigational therapy 1
  - Standard of Care
- Investigational therapy n
  - Standard of Care

Phase 3
- R vs.
- IO-refractory study goals:
  - Evaluate IO combinations
  - Biomarker discovery (Immunoprofile) for evaluation in future studies
  - Follow-on studies within immuno-biomarker defined subsets may be done within this framework
Where Are We Now?

IRB Approvals:
702 sites
270 sites with at least 1 patient accrued

Patient registrations/status:
1109 patients enrolled in screening phase (51400 registrations)
730 screened at PD
379 pre-screened
824 patients notified of sub-study assignment
647 screened at PD
177 pre-screened
408 patients registered to a sub-study
Real Change, Real Benefits

- **Enrollment Efficiency**: Grouping these studies under a single trial reduces the overall failure rate for patient biomarker screening.

- **Operational Efficiency**: Single master protocol can be amended as needed as drugs enter and exit the study.

- **Consistency**: Every drug entered into the trial will be tested in the identical manner.

- **Predictability**: If pre-specified efficacy and safety criteria are met, the drug and accompanying companion diagnostic will be approved.

- **Patient Benefit**: Brings safe and effective drugs to patients sooner than they might otherwise be available.
Regulation:

FDA Oncology Center of Excellence
• **1906 Pure Food and Drugs Act** – primarily about policing fraud and label requirements
• **1938 Food Drug and Cosmetic Act** – established premarket review of safety
• **1962 Kefauver-Harris Amendments** – effectiveness had to be derived from “substantial evidence” in “adequate and well-controlled investigations”
Center for Biologics Evaluation & Research

- **1902 Biologics Control Act** – required purveyors of vaccines to be licensed with the Hygienic Laboratory
- **1930 Amendment** – authority to establish standards for vaccines
- **1944 Public Health Services Act** – expanded regulation of biologics to the products themselves, not just the bodies that manufactured them.
• **1938 Food Drug and Cosmetic Act** – provided authority for legal action against adulteration and misbranding of devices, but not the same premarket notification requirements as drugs

• **1976 Medical Device Amendments Act** – created an alternative regulatory approach that involved classifying devices according to risk
Product-Oriented Regulation

The current FDA process for a combination oncology product

Drugs (CDER)

Biologics (CBER)

Devices (CDRH)

The new FDA Oncology Center of Excellence will facilitate optimal regulation of complex medical treatments

FDA

Center of Excellence

Evaluation

Approval

Approval

Approval

Evaluation
• Included in the Cancer Moonshot and included in 21st Century Cures Initiatives
• Intended to reflect the current state of multi-modal interventions in cancer treatment
• Organize clinical aspects in a more patient-oriented approach rather than a product-oriented approach
Public Policy:

Breakthrough Therapies
Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe

ABSTRACT The US Food and Drug Administration is often criticized as inefficient compared to its European counterpart, the European Medicines Agency. This criticism is especially common in the field of oncology, where severely ill patients have few therapeutic options. We conducted a direct drug-to-drug comparison of the two regulatory agencies' approvals of new oncology drugs. We found that contrary to public assertions, the median time for approval for new cancer medicines in the United States was just six months—and that these new anticancer medicines are typically available in the United States before they are in Europe. Our findings reinforce the need for strong financial and public support of the Food and Drug Administration, so that such medicines can continue to be made available speedily to patients in need.

In recent years the scientific understanding of the basic biology of cancer has undergone a major transformation. With the advent of next-generation technologies, it is now possible to elucidate the molecular pathways involved in cancer development and to design drugs to specifically target these pathways. Examples of such breakthroughs include Herceptin (trastuzumab), which blocks the effects of a protein that transmits growth signals to breast cancer cells, and Gleevec (imatinib mesylate), which inhibits an enzyme that is active in chronic myelogenous leukemia. This new era of scientific discovery has the potential to lead to new anticancer medicines with greater efficacy and reduced toxicity, allowing patients to live longer and healthier lives.

Despite these breakthroughs, some critics argue that given the advances in basic science, we should be able to develop new oncology drugs more quickly than we do. One reason cited for the slower-than-desired pace is a regulatory environment that is not sufficiently equipped with the resources and scientific foundation needed to evaluate new approaches to cancer treatment. Some critics specifically have characterized the Food and Drug Administration (FDA) as slow and inefficient at reviewing drugs in comparison to its European counterpart, the European Medicines Agency (EMA). Furthermore, some have claimed that the FDA has become so risk-averse, it is increasingly difficult to obtain approval for effective drugs in the United States.

To examine these claims as they pertain to new anticancer medicines, we analyzed new oncology drug approvals by the FDA and the EMA. We describe our methods and results below.

Study Data And Methods
We compared review times at the FDA and the EMA for new oncology drugs in the period 2003-10. Our data came from the publicly available drug databases on the FDA and EMA websites; they represent only initial approvals, not supplemental applications. In addition, we investigated only active treatment drugs, not drugs for supportive care, such as pain relievers or antiemetics.

For each new drug in the United States, we collected the date of the first New Drug Application or Biologics License Application submission.
Approved NMEs in Oncology 2003-2010
FDA vs EMA
“But critics of the trials argue that the new science behind the drugs has eclipsed the old rules — and ethics — of testing them. They say that in some cases, drugs under development, PLX4032 among them, may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering.”
Developing Standards for Breakthrough Therapy Designation

Charles L. Sawyers, Chair, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center; Investigator, Howard Hughes Medical Institute
Daniel A. Haber, Director, Cancer Center, Massachusetts General Hospital; Investigator

Development Paths for New Drugs with Large Treatment Effects Seen Early

Thomas Fleming, Professor, Biostatistics, University of Washington
Mikael Sekeres, Director, Leukemia Program, Associate Professor of Medicine, Cleveland Clinic
Grazyna Lieberman, Director, Biostatistics, Genentech
Edward Korn, Mathematical Statistician, Biometric Research Branch, National Cancer Institute
Wyndham Wilson, Senior Investigator, Chief, Lymphoma Therapeutics Section, NCI
Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. FDA
Rajeshwar Sridhara, Director, Division of Biostatistics V, CDER, U.S. FDA
Jane Perlmuter, President and Founder, Gemini Group

To provide for the expedited development and evaluation of drugs designated as breakthrough drugs.

IN THE SENATE OF THE UNITED STATES
MARCH 26, 2012
Mr. Bensure (for himself, Mr. Hatch, and Mr. Burr) introduced the following bill, which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

A BILL
To provide for the expedited development and evaluation of drugs designated as breakthrough drugs.

BE IT ENACTED BY THE SENATE AND HOUSE OF REPRESENTATIVES OF THE UNITED STATES OF AMERICA IN CONGRESS ASSEMBLED,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Advancing Breakthrough Therapies for Patients Act of 2012”.

SEC. 2. BREAKTHROUGH THERAPIES AND FAST TRACK PRODUCTS.
Getting Breakthrough Therapies to Patients

Goals of Breakthrough Therapy Designation

Goal 1: Expedite drug development process for products that show remarkable clinical activity early

Goal 2: Minimize the number of patients exposed to a potentially less efficacious treatment

“(a) Designation of a Drug as a Breakthrough Therapy.—
“(1) IN GENERAL.—The Secretary shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.
Current Breakthrough Therapies

Breakthrough Therapy by the Numbers
• 464 Applications for Designation
• 158 Designations Granted
• 52 Approvals of Breakthrough Drugs
A scientific series to address challenging aspects to the efficient development of a Breakthrough Designated Drug:

- 2013 - A Risk-based Approach for In Vitro Companion Diagnostic Device FDA Approval Process Associated with Therapies that have a Breakthrough Designation

- 2014 – A Blueprint for Drug/Diagnostic Co-Development: Next-Generation Sequencing (NGS) in Oncology

- 2015 - Examining Manufacturing Readiness for Breakthrough Drug Development

- 2016 – Exploring the Utility of Real-world Evidence
Public Policy:

21st Century Cures Act
Key Provisions

– Sec. 3001. Patient experience data
– Sec. 3002. Patient focused drug development guidance
– Sec. 3011. Qualification of drug development tools
– Sec. 3031. Summary level review
– Sec. 3072. Hiring authority for scientific, technical, and professional personnel
– Sec. 3073. Establishment of Food and Drug Administration Intercenter Institutes
Critical Resources

• Additional funding to be supplied outside the traditional budget and appropriations process
• Protects investments from being subject to budget caps and sequestration
• Supports high-risk/high-reward projects & young investigators
• NIH – NIH Innovation Fund
  – $4.8B over 5 years - $1.8B to Cancer Moonshot
• FDA – FDA Innovation Fund
  – $500M over 9 years
Public Policy:

Prescription Drug User Fee Act
Prescription Drug User Fee Act

- First signed into law in 1992, PDUFA, was passed to address growing concern among drug developers, regulators, and patients that the FDA review and approval process was taking too long due to insufficient funding.

- In 1992, the FDA took 27 months on average to review a new drug.

- The law supplements FDA funding by requiring developers to pay user fees when they submit drugs for review. In return, the FDA sets target completion times for drug review:
  - 12 months for standard review
  - 8 months for priority review
User Fee Supported Programs Regularly Expand

Activities supported by PDUFA

|-------------|--------------|----------------|---------------|--------------|---------------|

- **Post-approval safety activities for 3 years**
- **Good Review Management Practices**
- **Improved performance management**
- **Rolling applications**
- **Standards for scheduling meetings**
- **Additional review guidance**

**Review Goals:**
- 12 months Standard
- 10 months Standard
- 6 months Priority

**NME Review Goals:**
- 12 months Standard
- 8 months Priority

**Regulatory Science enhancements, including:**
- Patient-Focused Drug Development
- Biomarkers
- Rare Diseases
- Benefit Risk
- Patient Reported Outcomes

**Risk Evaluation and Mitigation Strategies**
- Procedures to analyze drug safety data
- Enhancement of safety surveillance
- Mandatory advisory committees

**NME Review Model**

FRIGENTS of CANCER RESEARCH

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PDUFA VI Goals Letter Overview

1. Preserves Current Drug Review Timelines
2. Integration of the Patient Voice
3. Assessing the Benefits and Risks
4. Biomarkers
5. Review of Combination Products
6. Breakthrough Therapy Program
7. Innovative Clinical Trial Designs
8. Model-Informed Drug Development
9. Real-world Evidence
10. Post-Market Safety
11. FDA Hiring
# PDUFA VI Timeline

## SEP 2015 – MAR 2016
**FDA-Industry Discussions**
- **5/13/15** Federal Register notice for initial public meeting
- **7/15/15** Public meeting
- **8/15/15** Docket closes; analyze comments
- **SEP 2015** Initiation of FDA/Industry technical negotiations and FDA/Stakeholder consultation meetings
- **MAR 2016** Finalization of draft PDUFA VI Performance Goals Letter

## APR 2016 – JUL 2016
**Clearance Process**
- **APR 2016** Submit draft PDUFA VI Performance Goals Letter for HHS and OMB clearance
- **JULY 2016** HHS and OMB clearance
- **7/15/16** Federal Register notice for final public meeting

## AUG 2016 – SEP 2017
**Legislative Process**
- **8/15/16** Final public meeting
- **1/15/17** Deadline for Administration to Transmit Proposed PDUFA VI Legislation (along with the Performance Goals Letter) to Congress
- **9/30/17** PDUFA V Expires

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**A New Paradigm for Oncology Drug Development: Research, Regulation, & Policy**

- **Jan 3** – New Congress
- **Jan 20** – Inauguration
- **??** – New Commissioner
“For the loved ones we’ve all lost, for the family we can still save, let’s make America the country that cures cancer once and for all.”

- President Barack Obama

State of the Union
January 12, 2016