AAADV-ASCO-CDDF joint workshop on global collaboration Sept 14-16, 2022

H. Kim Lyerly, M.D. AAADV Workshop

2023 CDDF Annual Conference

Disclaimer

- H. Kim Lyerly is Director of AAADV Workshop

Learning Objectives

- Describe global challenges in industry, government, and academia task in cancer drug development in 2023.
- Understand the expertise and skills required for contemporary and future eras of cancer drug development.

A Global Perspective
Development and Access

JAMA Network Open

Original Investigation | Ethics

Evaluation of Drug Trials in High-, Middle-, and Low-Income Countries and Local Commercial Availability of Newly Approved Drugs

Jennifer E. Miller, PhD; Michelle M. Mello, JD, PhD, MPhil; Joshua D. Wallach, PhD, MS; Emily M. Gudbranson, BS; Blake Bohlig, PA-C; Joseph S. Ross, MD, MHS; Cary P. Gross, MD; Peter B. Bach, MD

Abstract

IMPORTANCE Clinical research supporting US Food and Drug Administration (FDA) drug approvals is largely conducted outside the US.

OBJECTIVE To characterize where drugs were tested for FDA approval and to determine how commonly and quickly these drugs received marketing approval in the countries where they were tested, both overall and by country income level and geographical region.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional analysis of trials supporting FDA approval of novel drugs in 2012 and 2014, sponsored by large drug companies, did not involve human participants. The settings were the countries hosting trials supporting US drug approval. Data sources included Drugs@FDA, ClinicalTrials.gov, PubMed, Google Scholar, EMBASE, and drug regulatory agency websites. Data analysis was completed March through September 2020.

MAIN OUTCOMES AND MEASURES The primary outcomes were the proportion of drugs approved for marketing in the countries where they were tested for FDA approval within 1, 2, 3, 4, and 5 years of FDA approval and the proportion of countries contributing participants to trials supporting FDA approvals receiving market access to the drugs they helped test within 1, 2, 3, 4, and 5 years of FDA approval.

RESULTS In 2012 and 2014, the FDA approved 34 novel drugs sponsored by large companies, on the basis of a total of 898 trials, 563 of which had location information available. Each drug was tested in a median (interquartile range [IQR]) of 25 (18-37) unique countries, including a median (IQR) of 20 (13-25) high-income countries, 6 (4-11) upper-middle-income countries, and 1 (0-2) low-middle-income country. One drug was approved for marketing in all testing countries within 1 year of FDA approval and 15% (5 of 34 drugs) were approved in all testing countries within 5 years of FDA approval. Of the 70 countries contributing research participants for FDA drug approvals, 7% (5 countries) received market access to drugs they helped test within 1 year of FDA approval and 31% (22 countries) did so within 5 years. Access within 1 year occurred in 13% (5 of 39) of high-income countries, 0 of 22 upper-middle-income countries (0%), and 0 of 9 lower-middle-income countries (0%), whereas at 5 years access rates were 46% (18 of 39 countries), 9% (2 of 22 countries), and 22% (2 of 9 countries), respectively. Approvals were faster in high-income countries (median [IQR], 8 [0-11] months) than in upper-middle-income countries (median [IQR], 11 [5-29] months) or lower-middle-income countries (median [IQR], 17 [11-27] months) after FDA approval. Access was lowest in African countries.

(continued)

Key Points

Question How commonly are drugs commercially available in the countries where they were tested?

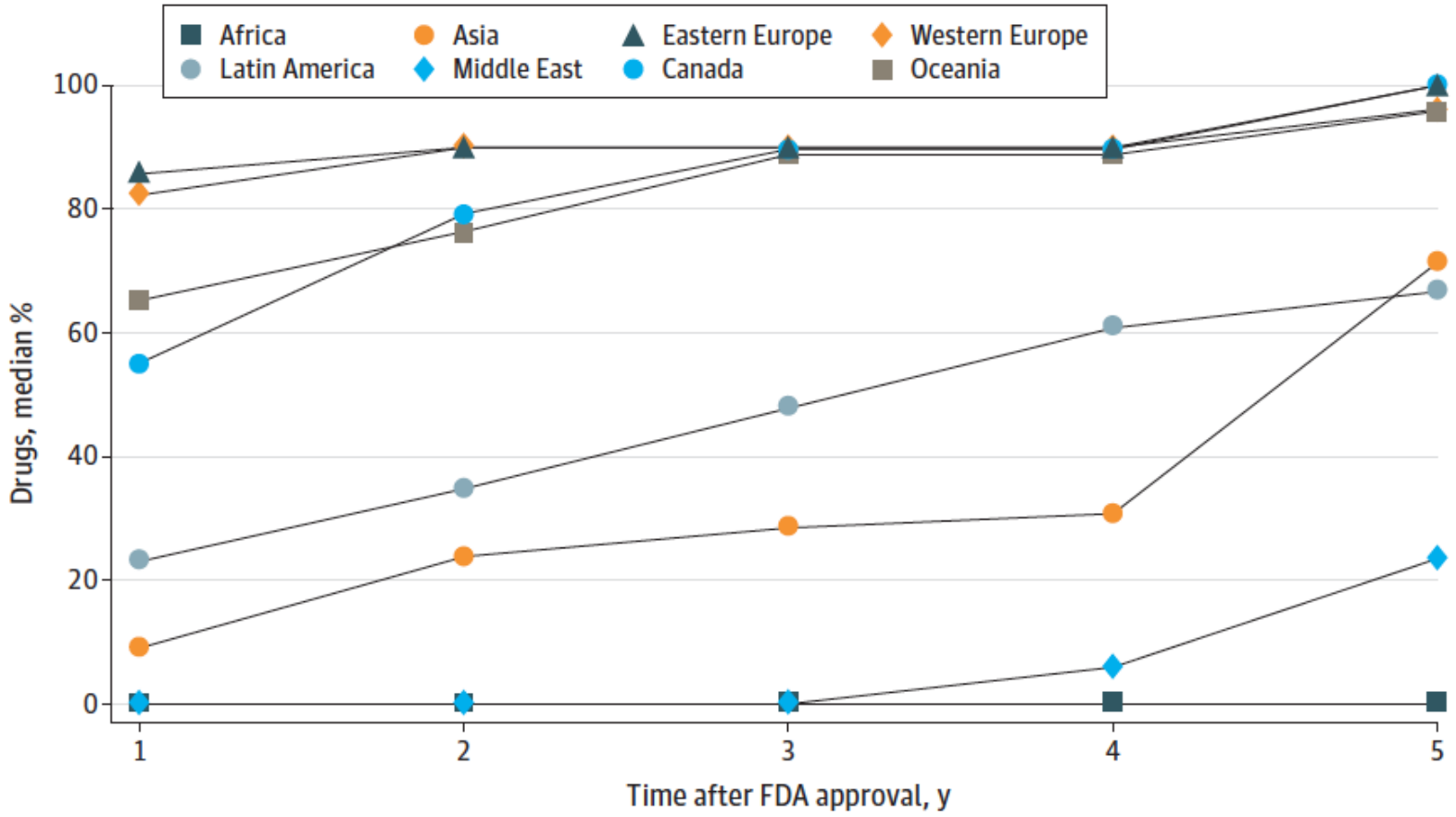
Findings This cross-sectional study found that 5 years after their approval in the US, 15% of novel drugs (5 of 34 drugs) were approved in all countries where they were tested; among 70 countries contributing research participants, 7% (5 countries) received market access to the drugs they helped test within 1 year of US approval and 31% (22 countries) did so within 5 years. Approvals were faster in high-income countries, and access was lowest in African countries.

Meaning These findings suggest that substantial gaps exist between where drugs are tested and where they become available to patients, raising concerns about the equitable distribution of research benefits.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Figure 3. Percentage of Drugs Approved for Sale in the Countries Where They Were Tested for US Food and Drug Administration (FDA) Approval, by Geographical Regions



A Recent US FDA Perspective

Background

The FDA Oncology Center of Excellence (OCE) Conversations on Cancer public panel discussion series event on July 27, 2022, will address clinical trial site selection in the context of declining U.S. patient enrollment, geo-political turmoil, and our commitment to equity and diversity in clinical trials.

Recent trends in oncology drug development have seen a shift to more international clinical trials, as rates of US patient enrollment decline. The OCE is aware of several ongoing or completed clinical trials which are multi-regional but lack US patient enrollment. Importantly, due to travel restrictions stemming either from the global pandemic or geo-political turmoil, FDA is not able to inspect certain regions of the world in which there is significant clinical trial activity. Given recent efforts to increase access to US clinical trial sites and in turn diversity, a deeper understanding of the site selection process is warranted.

2022 AAADV-ASCO-CDDF Global Drug Development Workshop

- *Day 1- Primer for new learners*
- **Day 2- AAADV-ASCO-CDDF Global Drug Development Workshop**
  - Multi-Regional Clinical Cancer Trials
  - Challenges and Opportunities for Dose Optimization in Oncology
- Day 3- Satellite Sessions
  - ctDNA for Cancer Detection, Prognostication and Monitoring Efficacy
  - Innovative Diagnostics Use of Computational Pathology and Proteomics for Target Quantification: Potential to Inform Decision Making in Precision Oncology
  - Therapeutic Drug Monitoring and Dose Optimization
  - Adapting to the New Normal: Clinical Trial Diversity and Challenges in Global Cancer Drug Development
  - Digital Patient Solutions: A Strategy for Decentralized Care
  - Improving Global Capacity to Develop Medicines and Improve Care: Targeting Pediatric Brain Tumors

Day 1- Primer for new learners (1)

Start	Title	Who
8:45	Welcome and Introduction	H. Kim **Lyerly**, Professor, Duke University
9:00	Keynote Address: The Cancer Medicines Forum	Denis **Lacombe**, Chief Executive Officer, European Organization for Research and Treatment of Cancer (EORTC)
10:00	Global Clinical Research Methods: Scientific Issues	Martin **Stockler**, Professor of Oncology and Clinical Epidemiology, University of Sydney, Oncology Director at the NHMRC Clinical Trials Centre
10:20	Global Clinical Research Methods: Regulatory Issues	Chitkala **Kalidas**, Vice President and Head of Global Regulatory Affairs for Oncology and In Vitro Diagnostics, Bayer
10:40	Global Clinical Research Methods: Translational Research Issues	Jian **Wang**, Head of Translational, Oncology Regulatory Science, Strategy & Excellence, AstraZeneca
11:00	Global Clinical Research Methods: Statistical Considerations	Mahesh **Parmar**, Professor of Medical Statistics and Epidemiology and Director of MRC Clinical Trials Unit at University College London and the Institute of Clinical Trials and Methodology at University College London
11:20	Global Clinical Research Methods: Trial Group Capability	Lesley **Seymour,** Professor and Medical Oncologist Queens University, Canadian Cancer Trials Group Deputy Director, and IND Program Director

Day 1- Primer for new learners (2)

Start	Title	Who
13:00	Data Supporting Regulatory Action from Academic Trials	Chitkala **Kalidas**, Vice President and Head of Global Regulatory Affairs for Oncology and In Vitro Diagnostics, Bayer
13:05	Academic Perspective	Vassilis **Golfinopoulos**, European Organization for Research and Treatment of Cancer (EORTC) Headquarters Director
13:25	Academic Perspective	Mahesh **Parmar**, Professor of Medical Statistics and Epidemiology and Director of MRC Clinical Trials Unit at University College London and the Institute of Clinical Trials and Methodology at University College London
13:45	Pharma Perspective	Serban Ghiorghiu, Vice President, Late Oncology, AstraZeneca
14:05	Academic Perspective	Lesley **Seymour**, Professor and Medical Oncologist Queens University, Canadian Cancer Trials Group Deputy Director, and IND Program Director
15:00	Supporting the Future of Global Cancer Drug Development	H. Kim **Lyerly**, Professor, Duke University
15:05	NCI's NExT Program: Supporting the next generation of global cancer therapeutics	James **Doroshow**, Deputy Director, US National Cancer Institute, National Institutes of Health
15:45	St. Jude Global: To improve survival rates of children with cancer and other life-threatening diseases around the world	Carlos **Rodriguez-Galindo**, Executive Vice President, Chair, Department of Global Pediatric Medicine, Director, St. Jude Global
16:25	Training/Education in Global Drug Development	Wendy **Clemens**, Vice President, Research and Early Development, Sr. Early Development Program Lead, Oncology, Bristol Myers Squibb

AAADV-ASCO-CDDF Workshop Agenda

- Keynote Address: *Global Cancer Drug Development: Opportunities and Value to Society*
- Plenary Sessions:
  - Learnings from Infectious Disease in Global Drug Development: COVID, HIV, Vaccines
  - Global Access to Cancer Therapies Post-Approval
  - Assessing Africa's Readiness to Participate in Global Cancer Drug Development
  - Assessing Latin America's Readiness to Participate in Global Cancer Drug Development
- Panel Discussion: *Regulatory and Health System Perspectives of Global Drug Development*
- Parallel Sessions:
  - Multi-Regional Clinical Cancer Trials
  - Challenges and Opportunities for Dose Optimization in Oncology

Keynote Address: Global Cancer Drug Development: Opportunities and Value to Society

Richard Sullivan, Professor of Cancer and Global Health at King's College London, and Director of the Institute of Cancer Policy (ICP) and co-Director of the Conflict and Health Research Group

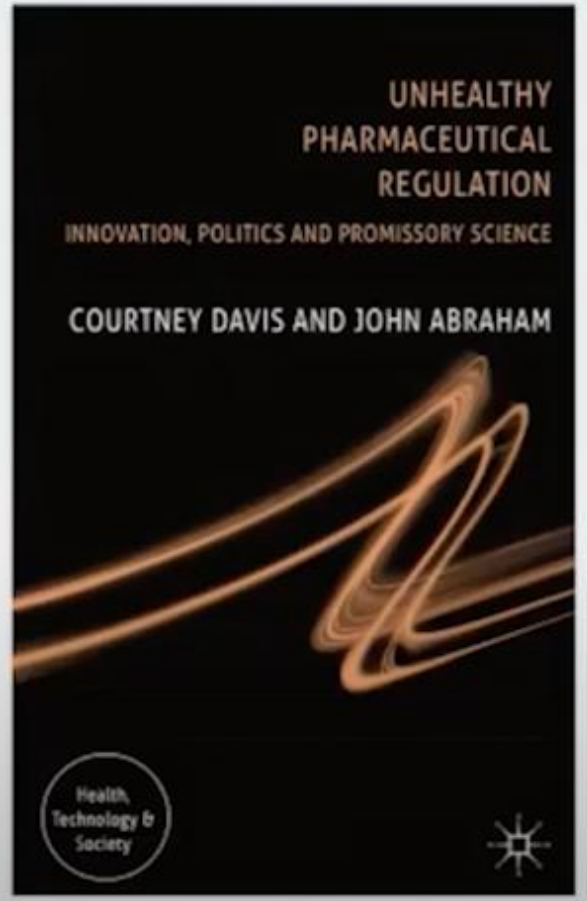
Learnings from Infectious Disease in Global Drug Development: COVID, HIV, Vaccines

Sir Richard Peto, Emeritus Professor of Medical Statistics and Epidemiology at the University of Oxford

Huge regulatory shifts

Project Orbis: the UK experience after 1 year

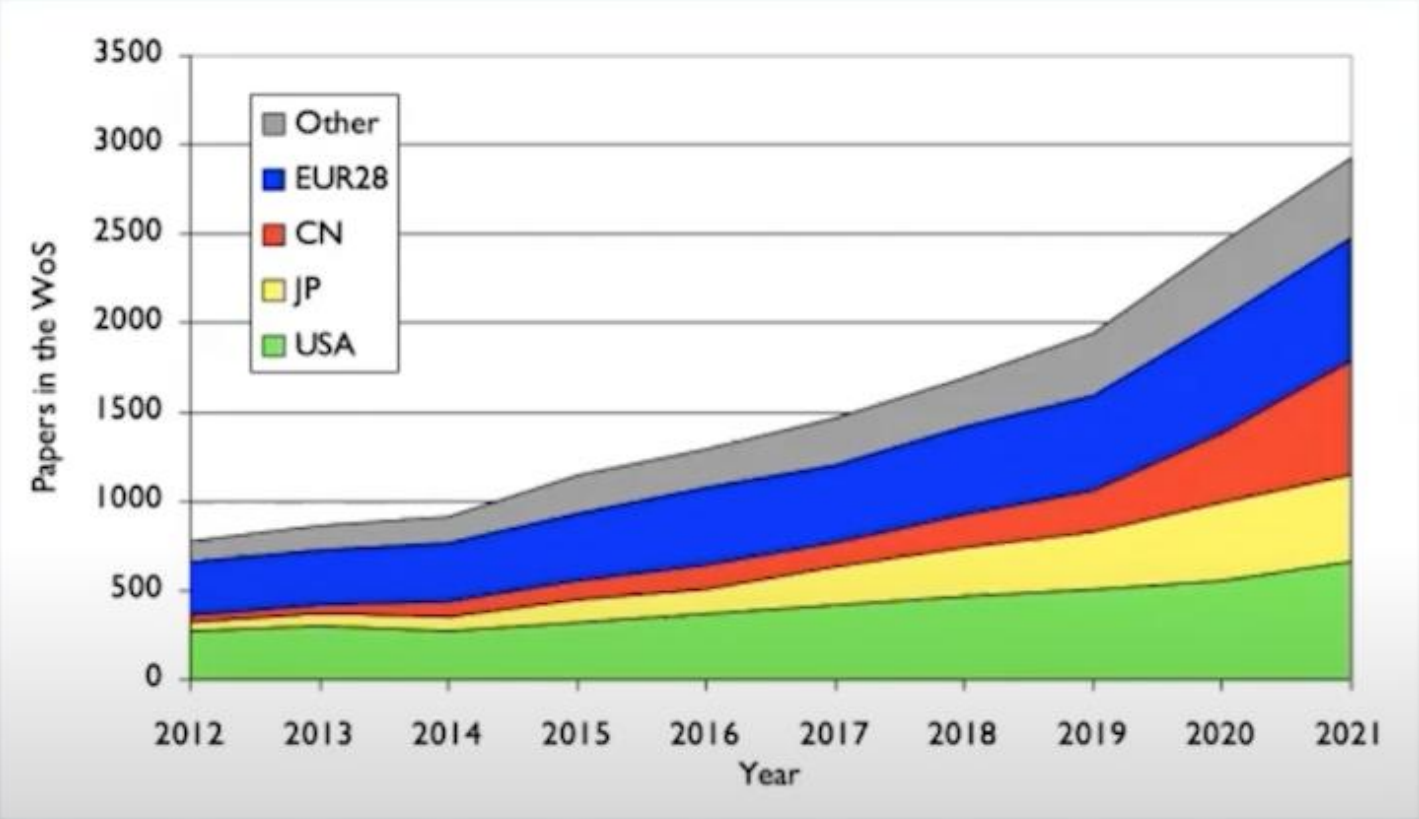
M Lythgoe, R Sullivan **Lancet Oncology** 2022, 23: 1-3



- Improvements in the curability of cancer have been limited thus far.
- Less than one-third of the approvals are supported by unequivocal evidence of prolonged OS and only 29% met threshold for substantial benefit
- In a radical departure from the past history of FDA approvals, 58 (36%) of the 161 approvals in 2017–2021 were based on data derived from single-arm studies evaluating ORR and DoR

- Very limited socio-economic and QoL data
- Drug development strategies geared towards speed, but is this the right policy for patients and society?

The rise of China in cancer drug development: case of IO



The state of lung cancer research: a global analysis. **J Thoracic Oncology** 2016 11(7): 1040-1050.

Assessing Africa's Readiness to Participate in Global Cancer Drug Development

Bello Abubakar, Immediate Past President, African Organization for Research and Training in Cancer (AORTIC)

Assessing Latin America's Readiness to Participate in Global Cancer Drug Development

Gustavo Werutsky, Chairman, Latin American Cooperative Oncology Group (LACOG)

Global Access to Cancer Therapies Post-Approval

Cary Adams, Chief Executive Officer, Union for International Cancer Control (UICC)

Q and A, and Discussion

Julie Gralow, Thomas Fleming, Sir Richard Peto, Bello Abubakar, Gustavo Werutsky, Invited Discussant Gilberto Lopes

Regulatory and Health System Perspectives of Global Drug Development- A Panel Discussion

Agnes Saint-Raymond, Iordanis Gravainis, Reiko Yanagihara,
Beeta Bak, Mojisola Adeyeye , Andre Ilbawi , Stephen O'Brien

Session Summary: Key Barriers to Global Cancer Drug Development

Key Barriers	Details
Lack of diagnostic services and human resources	• Limited pathology and radiology services • Lack of trained personal (physicians, nursing, surgeons and supportive staff) • Weak health systems infrastructure • Centralized services creating geospatial barriers to access for patients
Drug accessibility and affordability	• Unstable drug supply chains • Unaffordable drug pricing for LMICs • Lack of public funding for cancer drugs (not included in national health coverage plans) • Failure to prioritize cancer drugs on national drug lists • Lack of value-based pricing
Research infrastructure, Regulatory and authorization challenges	• Insufficient research infrastructure to support trial development • Clinical trials asking questions that are not relevant to clinicians in LMICs • Competing time requirements for patient care driven by inadequate staffing and resources. • Un-necessarily complex regulatory process for drug development and policy

In Preparation: Global Cancer Drug Development – A Report the 2022 Accelerating Anti-Cancer Agent Development and Validation Meeting

Brooke E Wilson[1,2], Richard Sullivan[3,4], Richard Peto[5], Bello Abubakar[6], Christopher Booth[1,2], Gustavo Werutsky[7], Cary Adams[8], Agnes Saint-Raymond[9], Tom Fleming[10], Kim Lyerly[11], Julie R Gralow[12]

1. Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Kingston, Canada
2. Department of Oncology, Queens University, Kingston, Ontario, Canada
3. Institute of Cancer Policy, King's College London, London, United Kingdom
4. Department of Oncology, Guy's & St Thomas' NHS Trust, London, United Kingdom
5. Department of Medical Statistics and Epidemiology, University of Oxford, England
6. Department of Radiotherapy and Oncology, National Hospital Abuja, Nigeria
7. Department of Medical Oncology, Hospital São Lucas, Porto Alegre, Brazil
8. Union for International Cancer Control, Geneva, Switzerland
9. Former Head of International Affairs Division European Medicines Agency
10. University of Washington
11. Departments of Surgery, Pathology, and Immunology, Duke University School of Medicine, Durham, North Carolina
12. American Society of Clinical Oncology, Alexandria, Virginia, USA

Corresponding Author

Julie R. Gralow, M.D.
American Society of Clinical Oncology
2318 Mill Road, Suite 800
Alexandria, Virginia 22314
Julie.gralow@asco.org
1-571-483-1650

Multi-Regional Clinical Cancer Trials: Introduction

Renzo Canetta (BMS), Jaap Verweij (CDDF)

Multi-Regional Clinical Cancer Trials

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Industry Challenges of MRCT

Andrew Lee, Senior Vice President, Head of Global Clinical Trial Operations at Merck

Regulatory Implications of MRCT

Fergus Sweeney

Multi-Regional Clinical Cancer Trials: Introduction

Renzo Canetta (BMS), Jaap Verweij (CDDF)

Current Models of MRCT- PedAL

Gwen Nichols, Chief Medical Officer, Leukemia and Lymphoma Society (LLS)

Practical Implementation of MRCT

Patricia Keegan, Chief Medical Officer, TopAlliance

Q and A, Discussion

Renzo Canetta and Jaap Verweij, Gwen Nichols, Andrew Lee, Patricia Keegan, Fergus Sweeney, Renzo Canetta, Jaap Verweij

Regulatory perspectives of MRCT

(Fergus Sweeney, former Head, Clinical Studies and Manufacturing Taskforce, EMA)

- MRCT can address shortcomings of many trials that are small, underpowered and poorly designed. Well-designed, large RCT, run multi-nationally, deliver better information for regulatory ad healthcare decision making.
- ICH E17 provides guidance on general principles for planning and design of MRCTs
- MRCT provide advantages for oncology trials
  - Enable recruitment of sufficient number of trial participants in reasonable timeframe
  - Evaluating consistency of treatment effects across regions; understanding of how treatment effects can vary between populations; may explain reasons for differences
  - Simultaneous availability to patients by addressing requirements of different HAs
  - Engagement with regulators is important to facilitate launch, maintain feasibility and scientific integrity
  - More efficient development of drugs, facilitates concurrent approval across regions

Multiregional Cancer Clinical Trials (MRCT)
(Patricia Keegan, former FDA, CMO, TopAlliance)

- FDA OCE position on MRCT appears to be
  - MRCT generally required except in exceptional circumstances
  - Extrapolation to US population by other means (bridging, popPK modeling) will not overcome lack of direct assessment in "diverse" US population
  - New "requirement" for comparative efficacy against US-approved drug products to demonstrate applicability to US practice-limits all but first approval to a non-inferiority (NI) trial design
  - Single region trials may be acceptable to support US approval if
    - Diseases occurring predominantly in other regions for which US enrollment would be low
    - Neglected drug development for that indication in the US
  - Trials in US may be necessary to support US approval based on differences in international standards of care
    - Recent change of SOC due to drug approval
    - Differences in chemotherapeutic regimens of choice by region
    - Differences in treatment approach, e.g., surgical approach/expertise, complementary therapy (TACE in HCC)
  - Dr Keegan also discussed challenges in MRCTs
    - **Other than parallel scientific advice (FDA-EMA), there is no clear mechanism for achieving simultaneous advice across regional authorities on trial design issues; in order to work, this cannot be a sequential process**

CDDF Annual Conference 2023

Day 2 - Sept. 15 2022 Track B

Challenges & Opportunities for Dose Optimization in Oncology: Introduction

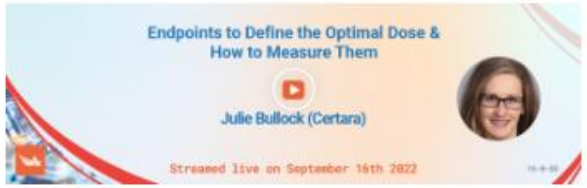
Donald Harvey (Emory University)

Challenges & Opportunities for Dose Optimization in Oncology

Mark Ratain (University of Chicago)

Designing More Efficient First in Human Dose-Finding Studies

Lillian Siu (University of Toronto)



Endpoints to Define the Optimal Dose & How to Measure Them

Julie Bullock (Certara)

Panel Discussion

Donald Harvey, Mark Ratain, Lilian Siu & Julie Bullock

Patient Heterogeneity & Defining the Optimal Dose: Introduction

Richard Schilsky (University of Chicago)

Patient Heterogeneity & Defining the Optimal Dose: Introduction

Peter O'Donnell (University of Chicago)

Randomized Dose Finding Studies

Elizabeth Garrett-Mayer (CENTRA & ASCO)

Patient Reported Outcomes to Define Tolerance vs Toxicity & Impact on Adherence

Lori Minasian (NIH)

Panel Discussion: Patient Heterogeneity & Defining the Optimal Dose

Richard Schilsky, Peter O'Donnell, Elizabeth Garrett-Mayer, Lori Minasian

Challenges and Opportunities for Dose Optimization in Oncology (Mark Ratain, MD, University of Chicago)

- US senate recognized that dose optimization studies can and should be done. In context of the appropriations bill for the FDA, there is a whole paragraph on dose optimization studies, emphasizing that FDA is strongly encouraged to organize clinical trials, in collaboration with academic medical centers and other federal agencies, of marketed cancer drugs and biologics to assess whether dosing and frequency adjustments may decrease the cost of care and/or toxicities of treatment without compromising efficacy.
- More is not better: Potential Benefits of using an accurate lower dose
  - Reduction in the frequency and/or severity of adverse events
  - Improvement in efficacy
    - Reduced treatment interruption for adverse events
    - Better patient adherence
  - Reduction in costs
    - Indirect cost of adverse events
    - Direct cost of drugs (in post market setting only)
- Phase 1-2 strategy
  - Primary objective of “phase 1” is to determine a range of doses for a randomized dose-ranging “phase 2” study
  - Upper bound constrained by toxicity
  - Lower bound ideally identified based on tumor-related biomarkers (e.g., radiographic size, ctDNA, serum biomarkers)
  - Optimal dose based on global assessment of dose/exposure-efficacy/toxicity relationship in randomized dose-ranging studies, with a focus on accuracy rather than precision.

Day 3- Satellite Sessions

- ctDNA for Cancer Detection, Prognostication and Monitoring Efficacy
- Innovative Diagnostics Use of Computational Pathology and Proteomics for Target Quantification: Potential to Inform Decision Making in Precision Oncology
- Therapeutic Drug Monitoring and Dose Optimization
- Adapting to the New Normal: Clinical Trial Diversity and Challenges in Global Cancer Drug Development
- Digital Patient Solutions: A Strategy for Decentralized Care
- Improving Global Capacity to Develop Medicines and Improve Care: Targeting Pediatric Brain Tumors

Martin Stockler (NHMRC)

ctDNA for Cancer Detection, Prognostication & Monitoring Efficacy: Introduction

Axeil Glassmacher (Jacques)

Patient Advocate Perspective

Mark Stewart (FOCR)

Academic Perspective

Aadel Chaudhuri (Assistant Professor WUSTL)

Industry Perspective

Megan Hall (Vice President, Medical Affairs, Grail)

Regulatory Perspective

Carla Herberts (European Medicines Agency)

Q & A, Discussion

Axel Glasmacher & Jacques Mascaro, Megan Hall, Carla Herberts Invited Discussant: Scott Patterson, Gilead Sciences

Innovative Diagnostics Use of Computational Pathology & Proteomics for Target Quantification: Potential to Inform Decision Making in Precision Oncology

Carl Barrett, AstraZeneca, Rich Schilsky

Digital/Computational Pathology- Academic Perspective

Jochen Lennerz (Massachusetts General Hospital)

Digital/Computational Pathology- Industry Perspective

Joseph Oakley (Medical Director for Biomarker Development, Paige)

Proteomics- Academic Perspective

Amanda Paulovich (Fred Hutchinson Cancer Center)

Innovative Diagnostics Use of Computational Pathology & Proteomics for Target Quantification: Potential to Inform Decision Making in Precision Oncology

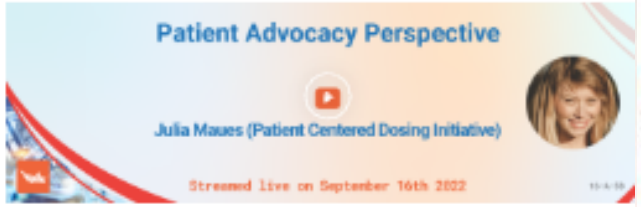
Matthew Ellis (AstraZeneca)

Q & A, Discussion

Richard Schilsky & Carl Barrett, Jochen Lennerz, Joseph Oakley, Amanda Paulovich, Matthew Ellis

Dose Optimization to Improve Risk/Benefit Profiles | Therapeutic Drug Monitoring: Introduction

Sarah Oliver (Gilead Sciences)



Patient Advocacy Perspective

Julia Maues (Patient Centered Dosing Initiative)

Industry Perspective

Divya Samieni (Genentech)

Q & A, Discussion Dose Optimization to Improve Risk/Benefit Profiles

Sarah Oliver, Julia Maues, Divya Samineni

Therapeutic Drug Monitoring

Donald Harvey (Emory University)

Therapeutic Drug Monitoring & Dose Optimization

Jan Beumer (University of Pittsburgh)

Academic Perspective

Steffie Groenland (Netherlands Cancer Institute)

Q & A, Discussion

Donald Harvey, Jan Beumer, Steffie Groenland

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Challenges in clinical trial performance

6 - 8 February 2023

Day 2 - Sept. 16 2022 Track B

Adapting to the New Normal:: Introduction

Martin Stockler, Patty Spears

Clinical Trial Diversity & Challenges in Global Cancer Drug Development

Patricia Keegan (TopAlliance)

Academic Perspective

Janet Dancey (Canadian Cancer Trials Group)

Industry Perspective

Ke Liu (Marengo Therapeutics)

Patient Advocate Perspective

Judy Needham, Rinata Haidinger, Leslie Gilham, Eva Schumacher

Q & A, Discussion

Martin Stockler, Patty Spears, Patricia Keegan, Janet Dancey, Ke Liu, Vernal Branch

Digital Patient Solutions: A Strategy for Decentralized Care

Alicyn Campbell (AstraZeneca)

Digital Patient Solutions A Strategy for Decentralized Care

Sean Connolly (Medable)

Academic Perspective

Adam Dicker (Thomas Jefferson University)

Industry Perspective

Matt Bryant (Gilead Sciences)

Q & A, Discussion

Alicyn Campbell, Sean Connolly, Adam Dicker, Matt Bryant

Global Develop Medicines & Care: Targeting Pediatric Brain Tumors

KP Haresh (AIIMS) & Jeff Buchsbaum (NCI)

Patient Advocacy Perspective

David Aarons (NBTS)

Academic Perspective

Daniel Landi (Duke University)

Industry Perspective

Chitkala Kalidas (Bayer)

Improving Patient Care Using Digital Twins in Neurooncology

Kenneth Buetow (National Biomarker Development Alliance)

Q & A, Discussion

K.P. Haresh, Jeff Buchsbaum, David Arons, Daniel Landi, Chitkala Kalidas, Kenneth Buetow

CDDF Annual Conference 2023

BAYER

Our collaboration with the Global Pediatric Brain Tumor Network, a multi-stakeholder partnership involving Duke University and the National Brain Tumor Society, will help create an equitable ecosystem of care for pediatric brain cancer patients.

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Challenges in clinical trial performance

6 - 8 February 2023

Take Home Message

- Modern cancer drug development involved basic science, clinical science, and an interplay between patient needs and regulatory trajectories in multiple agencies.
- From Dr Keegan also discussed challenges in MRCTs
  - **Other than parallel scientific advice (FDA-EMA), there is no clear mechanism for achieving simultaneous advice across regional authorities on trial design issues; in order to work, this cannot be a sequential process.**

Save the date: 2023 AAADV Workshop

September 13-15, 2023

Virtual (possible in person)

Focus on:

Global cancer drug development

Patient directed drug development

Cancer prevention

Contact: Kim.Lyerly@duke.edu or AAADV.org